STATISTICAL ANALYSIS PLAN ADDENDUM

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPENLABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – Rilonacept inHibition of interleukin-1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes stuDY (RHAPSODY)

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Study Drug:	Rilonacept (KPL-914)
Protocol Number:	KPL-914-C002
SAP Version:	2.0
Date of SAP Addendum:	21JUL2022
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Contents

1. INTRODUCTION

The final version (version 2.0) of Statistical Analysis Plan (SAP) for KPL-914-C002 study, based on the Protocol version 3.0 Amendment #2 dated 10MAR2020, was signed off on 16JUN2020. The statistical rules, efficacy and safety endpoints for long-term extension (LTE) period have been specified in SAP version 2.0. As a supplemental document, this addendum only summarizes key additional analyses, analyses planned but not conducted for LTE period in SAP V2.0 due to changes in business or scientific interests, or due to data availability.

2. ADDITIONAL ANALYSES

2.1 LTE 18-Month

LTE 18-month is the visit at 18 months after their most recent recurrence, (i.e., the qualifying episode for their original study enrollment prior to enrolling in the RI period or a recurrence in RW which was treated with bailout rilonacept, whichever is the later).

If LTE 18-month visits are collected in CRF, those visits in CRF will be used for analyses. Otherwise, LTE 18-month visits will be mapped based on the visit date on LTE 18-month disposition with 60 days window. The closest assessments will be mapped. If two visits have the same distance, the later one will be used.

In addition to treatment disposition and study disposition, disposition of LTE 18-month will be summarized as well:

- Continue treatment with open-label KPL-914
- Continue in study off-treatment for observation (with option to re-initiate open-label KPL-914 on-study if there is a pericarditis recurrence)
- Discontinue from the LTE
    - Patient decision
    - Investigator’s decision
    - No inflammation on MRI
    - Other

For subjects who decided to continue in study off-treatment for observation, the following parameters will be summarized:

- Time on observation: defined as minimum (first dose date after observation-1, EOS date) – disposition date of off-treatment for observation +1.
- Days on treatment before entering observation, defined as: (disposition date of off-treatment for observation-1) - first dose date of LTE period +1.
- Days on treatment after observation for subjects who entered observation and later resumed treatment: minimum (last dose date after observation +6, EOS date) - first dose date after observation + 1.

For the subgroups of subjects who decided to continue in study off-treatment for observation and subjects continue treatment with open-label KPL-914, additional analyses will be conducted.

- Time to recurrence from LTE 18-month will be defined from LTE 18-month disposition date to recurrence or censored at last assessment before treatment resumed or end of study whichever is first.
- Annualized incidence of recurrence after LTE 18-month visit will be defined as number of recurrences for all patients divided by sum of subject-years for all patients within each subgroup. Denominator will be calculated as below:

  For subjects who decided to continue in study off-treatment for observation

  - If subjects resumed treatment, first dose date after observation period – LTE 18-month disposition date
  - If subjects never resumed treatment, EOS date – LTE 18-month disposition date +1

  For subjects who continued treatment with open-label KPL-914,

  - EOS date – LTE 18-month disposition date +1.

  The 95% CI will be calculated using an exact method with Poisson distribution.
- Line plots of PGIPS, PGAPA, CRP over time will be provided as well.

For all subjects treated in LTE period, annualized incidence of recurrence from LTE baseline to LTE 18-month will be summarized. Denominator of subject years will be summarized from LTE first dose date to the minimum of End of study date, , LTE 18-month date-1.

2.2 Adverse Events

Two additional summaries of adverse events will be conducted:

- In addition to summarizing treatment-emergent adverse events, post-treatment adverse events will also be summarized. Post-treatment adverse events are defined as adverse events that started after the last dose of study drug in LTE period + 6 weeks.
- Upper respiratory infection adverse events will be summarized. Upper respiratory infection will be identified by the following preferred terms: Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Rhinitis, Sinusitis, Upper respiratory tract infection and Viral upper respiratory tract infection.

3. CHANGES TO THE PLANNED ANALYSES

3.1 Efficacy Endpoints

Changes to the analyses for the LTE Efficacy endpoints specified in SAP version 2.0 (section 5.3.2.3) are listed below:

Efficacy endpoints	Changes	Reason

2.Proportion of subjects with Clinical Response (rilonacept monotherapy + CRP≤0.5 mg/dL + NRS≤2) at each CRP assessment (weeks 12 and 24). The pain NRS at the visit when CRP was assessed will be used. subjects randomized to KPL-914 utilizing pooled data in RW and LTE periods and there will be no hypothesis testing.	Not done	NRS scores were collected only upon pericarditis recurrence.
4. Change over time in pericarditis pain NRS.	Not done	NRS were collected only upon pericarditis recurrence.
14. Corticosteroid use over time. For subjects who are on corticosteroid at RI baseline, the proportion of subjects using corticosteroid at LTE will be summarized. The denominator will be the number of subjects using corticosteroid at RI and entering the LTE. The average daily dose of corticosteroid (mg/day) will be summarized.	Not done	Only limited data available as corticosteroid use is allowed only as rescue medication

3.2 Safety Endpoints

Summaries of safety endpoints are conducted by study period (RI, RW, and LTE period) only.

16.1.9 Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPENLABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – Rilonacept inHibition of interleukin-1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes stuDY (RHAPSODY)

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Study Drug:	Rilonacept (KPL-914)
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History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	02 April 2020	Original document

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
CEC	Clinical Endpoint Committee
CMH	Cochran–Mantel–Haenszel
CRO	Contract Research Organization
CRP	C-reactive protein
CS	corticosteroids
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiography; echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EORW	End of Randomized Withdrawal (visit)

Abbreviation	Definition
EOT	End of Treatment (visit)
EQ-5D-5L	5-level EuroQoL-5D
ESR	erythrocyte sedimentation rate
FDA	US Food and Drug Administration
GI	gastrointestinal
HDL	High density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ISI	Insomnia Severity Index
ISR	injection site reaction
ITT	intent to treat
IV	intravenous(ly)
IWRS	interactive web response system
KM	Kaplan-Meier
KPL-914	rilonacept
LDL	Low density lipoprotein
LTE	Long Term Extension Treatment Period
MedDRA	Medical Dictionary for Regulatory Activities
cMRI	cardiac magnetic resonance imaging
MRI	magnetic resonance imaging
NMSC	Non Melanoma Skin Cancer
NSAID	nonsteroidal anti-inflammatory drug
NRS	Numerical Rating Scale
ORT	Oral Rescue Therapy
PGA-PA	Physician Global Assessment of Pericarditis Activity

Abbreviation	Definition
PGIPS	Patient Global Impression of Pericarditis Severity
PK	pharmacokinetic(s)
POC	point of care
RE	Role participation with emotional health problems in SF-6D
RI	Run-In (period)
RP	Role participation with physical health problems in SF-6D
RW	Randomized Withdrawal (period)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	subcutaneous(ly)
SF-36	36-Item Short Form Health Survey
SFU	safety follow up
SOC	standard of care
TEAE	Treatment emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

1. STUDY OBJECTIVES

1.1. Study Objectives

1.1.1. Primary Objective

The primary objective of this study is to assess the efficacy of rilonacept treatment in subjects with recurrent pericarditis.

1.1.2. Secondary Objectives

The secondary objective of this study is to assess the safety of rilonacept treatment in subjects with recurrent pericarditis.

2. STUDY DESIGN

2.1. Design Overview

This study has the following periods:

- **Screening period**, during which assessment of disease characteristics, baseline therapy, and the pretreatment workup is completed (up to 4 weeks).
- **Single-blind Run-In (RI) period** (12 weeks), during which blinded rilonacept is administered subcutaneously (SC) once weekly in all subjects after the loading dose of double injections. The RI period includes the following:
  - 1-week Stabilization period, during which blinded rilonacept is administered in addition to standard of care (SOC) pericarditis therapy and the ongoing pericarditis episode is treated.
  - 9-week Weaning period, during which subjects are weaned off background SOC pericarditis therapy, as applicable, while treatment with blinded rilonacept continues.
  - 2-week Monotherapy period during which subjects who have successfully weaned off background SOC pericarditis therapy will continue to receive blinded rilonacept.

In the single blind RI period (subjects are blinded regarding the time of transition from the single- blind to the double- blind- period), adult subjects ≥18 years old will receive rilonacept as an initial loading dose of 320 mg (2 SC injections of 160 mg each) at the RI baseline visit (2 × 2 mL), followed by a 160 mg (2 ml) SC dose once weekly throughout the RI period. Pediatric subjects ((≥12 and <18 years old) will receive an initial loading dose of rilonacept 4.4 mg/kg (2 SC injections of 2.2 mg/kg each) at the RI baseline visit (maximum 2 × 2 mL), and then 2.2 mg/kg (maximum 2 mL) SC once weekly throughout RI period.

Subjects who achieve clinical response at RI Week 12 defined as stopping background pericarditis therapy no later than Week 10 and weekly average of daily pericarditis pain score ≤2.0 on the 11-point Numerical Rating Scale (NRS) within the 7 days prior to and including the day of randomization on RI Week 12/Randomization Withdrawal (RW) baseline and a C-reactive protein (CRP) level ≤0.5 mg/dL at the RI Week 12/RW baseline visit, will proceed into the double-blind placebo-controlled RW period.

Subjects who do not achieve clinical response at RI Week 12/RW baseline on rilonacept monotherapy will be discontinued from study drug, transitioned to SOC pericarditis therapy at the Investigator's discretion and followed through the end of the RW period.

Additionally, after the randomized withdrawal period has been closed when at least 22 confirmed recurrent pericarditis events have been accrued, subjects who have not yet completed the full 12 weeks of RI period at that time will be allowed to continue tapering of concomitant meds in the RI period; those subjects who achieved clinical response by Week 12 will be given the option to receive open-label rilonacept in the Long-term Extension Treatment period (LTE) without having to proceed through the RW period.

- **Double-blind placebo-controlled RW period** (pericarditis recurrence event-driven duration), during which subjects who were able to stop background SOC pericarditis therapy and who achieve clinical response at RI Week 12/RW baseline are randomized in a double-blind manner at a 1:1 ratio to the following:
  - Rilonacept 160 mg (2.2 mg/kg in pediatric subjects) SC injections once weekly
  - Matching placebo SC injections once weekly

Pericarditis Recurrence in the RW Period

Pericarditis recurrence is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis. Upon pericarditis recurrence, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11point NRS and have 1 CRP value ≥1 mg/dL (either on the same day or separated by no more than 7 days) will receive bailout rilonacept (2 open-label injections of 160 mg rilonacept [or 4.4 mg/kg for pediatric subjects] followed by once weekly open-label rilonacept SC injections of 160 mg [or 2.2 mg/kg for pediatric subjects]) irrespective of randomized treatment assignment and as soon as at least 5 days have passed since the last study drug injection. Sequential oral rescue therapy (ORT), i.e., analgesics first, then NSAIDs, and then colchicine, can be added if needed at the discretion of the Investigator, as outlined in the protocol and Pharmacy Manual.

Subjects with pericarditis recurrence and who do not meet the protocol criteria for bailout rilonacept will continue blinded study drug until the protocol criteria for bailout rilonacept are met or through the end of the RW period. For those subjects, sequential ORT can be added to blinded study drug at the discretion of the Investigator, as outlined in the protocol and Pharmacy Manual.

All suspected pericarditis recurrence events in the RW period will be formally adjudicated by the Clinical Endpoint Committee (CEC), and only events that are confirmed by the CEC as pericarditis recurrences will be used in the Primary Endpoint analysis.

- **Long-term Extension Treatment period (LTE)** (variable, up to 24 months), during which all subjects in the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) and subjects who are in the Run-In period after closure of the RW period, will have an option to receive up to 24 months of open-label rilonacept 160 mg (or 2.2 mg/kg for pediatric subjects) SC injections once weekly based on their clinical status and at the discretion of the Investigator, after signing LTE informed consent.

  Subjects will be reviewed at 18 months after their most recent recurrence, (i.e., the qualifying episode for their original study enrollment prior to enrolling in the RI

period or a recurrence in RW which was treated with bailout rilonacept, whichever is the later). During this month visit, the Investigator and subject will decide whether to continue treatment with open-label rilonacept, to continue in the study off-treatment for observation and rilonacept bailout upon subsequent recurrence, or discontinuation from the LTE. This review may be supplemented by:

- cMRI and/or echocardiogram and/or additional diagnostic testing as determined by the Investigator.
- subjects may be unblinded at that time (if available) at the request of the Investigator per procedures outlined in the Unblinding Plan to assist in clinical decision-making.

Safety data will be reviewed throughout the LTE by the Data Monitoring Committee.

2.2. Schedule of Assessments

The schedule of assessments is in Section 13.1.

2.3. Sample Size Calculation and Randomization

2.3.1. Sample Size Calculation

Sample size calculation is based on the primary endpoint, time to pericarditis recurrence defined as the time from randomization to the date of the first pericarditis recurrence for each subject. Time to pericarditis recurrence is assumed to follow an exponential distribution. An event of interest is defined as a subject's first adjudicated recurrence of pericarditis. The following assumptions are used in the sample size calculation using EAST 6.4.1:

- 1-sided significance level: 2.5%
- Power: 90%
- Median time to event (in weeks) in placebo: 8
- Hazard ratio (rilonacept/placebo): 0.244
- Percentage of subjects in the RI period that will not reach RW: 10%.

Given these assumptions, a total of 22 adjudicated pericarditis recurrence events is required to achieve the power. About 25 subjects per arm (a total of 50 subjects) or more will be randomized. Considering 10% of subjects in the RI period that will not reach the RW period, approximately 56 subjects will be enrolled in this study.

Subject enrollment and the pericarditis recurrence event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion during the RW period. If the number of subjects randomized is less than 50 and/or the time anticipated for the number of events required for the analysis of primary efficacy endpoint significantly exceeds the projected timeline, additional subjects may be enrolled and/or randomized at Kiniksa Pharmaceutical's discretion. However, at this time it is anticipated that no more than 100 subjects will be enrolled into this study.

2.3.2. Randomization

Subjects who achieve clinical response at RI Week 12 (Section 2.1) will proceed into the double-blind placebo controlled RW period. An interactive web response system (IWRS) will be used to administer the randomization schedule. CRO Biostatistics will generate the

randomization schedule using SAS® software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for the IWRS, which will link sequential subject randomization numbers to treatment codes. The randomization schedule will be stratified by 2 factors:

- Oral CS use at baseline (RI baseline, i.e., beginning of RI period): yes or no
- Diagnosis of recurrent idiopathic pericarditis (RI baseline): yes or no

2.4. Timing of Analysis

The data cutoff for the primary analysis will be the end of RW period. When at least 22 adjudicated pericarditis recurrence events have occurred, end of RW period will be announced. The sites will have their subjects return to the site for the end-of-RW assessment (EORW). Data cutoff will occur after all subjects have completed this assessment. All data for this cutoff will be used in the primary analysis for efficacy and safety.

After the RW period, there will be a Long-term Extension Treatment period. An analysis will also be conducted after the end of the study. Since the data cutoff for the primary analysis will be done by the end of RW period, summary for LTE period will not be included in the primary analysis.

No interim analysis for claiming efficacy is planned. Interim safety review will be conducted by a Data Monitoring Committee (DMC). The analysis will be performed by a designated CRO. Details are in DMC charter and DMC Statistical Analysis Plan (SAP).

2.5. Responsibilities

The statistical analysis for the study will be performed by Kiniksa Biostatistics or its designated CROs.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. General Methods

Statistical analysis will be performed using SAS® software Version 9.4 or later. Continuous variables will be summarized using the mean, the standard deviation, median, minimum value, and maximum value. Time-to-event variables will be summarized using percent censored, event rate, and 25^{th}, 50^{th}, and 75^{th} percentiles with 95% CI, if estimable. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

At RI, RW, and LTE periods, baseline will be the last value before the first dose of study drug within each individual period unless otherwise specified. For change-over-time endpoints in the RW period, by-visit analysis will be performed at each scheduled visit for at least 24 weeks.

When weekly average of NRS is used, it will be calculated based on every 7 days starting on the day after the first injection in each period. If there are missing values during the 7- day period, the average will be calculated based on the non-missing values. If 50% or more values (≥4 days) are missing, the average value will be set to missing.

By-visit analyses will be based on nominal visits and observed data, with unscheduled visits excluded.

3.2. Stratified Analysis

There are two stratification variables for randomization: oral CS use at baseline (yes or no), and diagnosis of recurrent idiopathic pericarditis at RI baseline (yes or no). When an analysis is to be stratified by these variables and a stratum has ≤5 events of interest in a log-rank test or the same response in all subjects in a CMH test, the strata for diagnosis of recurrent idiopathic pericarditis will be pooled. If the same situation still exists, the analysis will be done without stratification.

3.3. Testing Hypotheses and Multiplicity Adjustment

All statistical tests for the treatment comparison of efficacy endpoints in the RW period will be based on a 1-sided α=0.025. For each endpoint, the null hypothesis is that the effects of rilonacept and placebo are the same. The alternative hypothesis is that rilonacept is better than the placebo.

In order to control the overall 1-sided type I error rate at the 0.025 level, a gatekeeping procedure in combination with Hochberg's procedure will be applied to testing the primary and major secondary endpoints. If the 1-sided p-value for testing the primary endpoint is ≤0.025, a significant treatment effect on the primary endpoint will be claimed.

Section 5.2.2.1 provides the order of major secondary endpoints. If the primary endpoint is significant, the first major secondary endpoint, i.e., proportion of subjects who maintained clinical response at Week 16 of RW period will be tested at 1-sided α=0.025. A significant treatment effect on this major secondary endpoint will be claimed if the 1-sided p-value is ≤0.025. If the treatment effect is not significant on the primary endpoint, significance on this major secondary endpoint cannot be claimed regardless of the result.

If both primary and first major secondary endpoints are significant following the above procedure, the second and third major secondary endpoints defined in Section 5.2.2.1 will be tested with Hochberg's procedure at overall 1-sided α=0.025. If both 1-sided unadjusted p-values are ≤0.025, claim significance of rilonacept for both endpoints. If the larger 1-sided p-value is >0.025, compare the smaller 1-sided p-value with 0.0125. If the smaller 1-sided p-value is ≤0.0125, claim significance of rilonacept on this endpoint.

3.4. Subgroups to be Analyzed

Subgroup analyses for the primary efficacy endpoint will be performed by the following variables for the RW period:

- Oral CS use at baseline (RI baseline, i.e., beginning of RI period): yes or no
- Diagnosis of recurrent idiopathic pericarditis (RI baseline): yes or no
- Type of pericarditis: idiopathic, post pericardiotomy syndrome, Dressler's syndrome, and Still's disease. Other type will not be included in the subgroup analysis due to the small sample size.
- Age group: 12 - <18, 18 - <65, and 65 – (maximum age in ITT analysis set) [Analysis for the pediatric group (12- <18) may not be performed if the sample size is too small.]
- Gender: males vs. females
- Race: Caucasian vs. non-Caucasian

- Region: USA vs. non-USA
- Number of pericarditis episodes at enrollment (including index and qualifying episodes): <5 vs. ≥5
- ADA status: ADA positive at any assessment, ADA positive with neutralizing antibody at any assessment, and ADA negative at every assessment.

P-values and summary statistics will be generated following Section 5.2 , with the understanding that the sample size is likely too small to have an adequate power. The forest plot with 95% CI will be provided for the primary efficacy endpoint.

3.5. Handling of Missing Data

To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study. Unless otherwise specified, missing data will not be imputed and only the observed data will be used in the analyses.

Additional rules for missing data imputation are provided in Section 13.2.

4. ANALYSIS SETS

4.1. Intent-to-Treat (ITT) Analysis Set

All subjects who are randomized in the RW period will be included in the Intent-to-Treat (ITT) analysis set. The primary analysis for efficacy endpoints in the RW period will be based on the ITT analysis set unless otherwise specified. Treatment comparisons for all analyses will be based on each subject's treatment assignment from randomization.

The following analysis sets are defined for the analysis of secondary endpoints:

- ITT Week 24 analysis set: All subjects randomized at least 24 weeks before data cutoff will be included. This analysis set will be used for secondary efficacy endpoints measured at week 24 in the RW period.
- ITT Week 16 analysis set: All subjects randomized at least 16 weeks before data cutoff will be included. This analysis set will be used for secondary efficacy endpoints measured at week 16 in the RW period.
- ITT Week 8 analysis set: All subjects randomized at least 8 weeks before data cutoff will be included. This analysis set will be used for secondary efficacy endpoints measured at week 8 in the RW period.

4.2. Safety Analysis Set (SS)

All subjects who take at least 1 dose of study drug in the RI period will be included in the Safety Analysis set (SS). Safety analyses will be based on the actual treatment a subject received.

4.3. Run-in Analysis Set (RIS)

All subjects who received at least 1 dose of study drug in the RI period will be included in the RI analysis set (RIS).

In addition, the following analysis set will be used for secondary efficacy endpoints measured at Week 12 in the RI period:

- Run-in Week 12 Analysis Set: All subjects who received the first dose in the RI period at least 12 weeks before data cutoff.

4.4. Long Term Extension Analysis Set (LTES)

All subjects who received at least 1 dose of study drug in the LTE will be included in the Long-term Extension Analysis set (LTES).

4.5. Per Protocol (PP) Analysis Set

The Per Protocol Analysis set (PP) is a subset of the ITT analysis set with the exclusion of subjects with important protocol violations or violations that may potentially bias statistical analyses or the ethical conduct of the study. The criteria of these violations will be determined prior to unblinding. This analysis set may be used for sensitivity analyses for efficacy endpoints in the RW period.

4.6. Pharmacokinetics Analysis Set

The Pharmacokinetic (PK) Analysis set includes subjects who receive at least 1 dose of study drug and have at least 1 post-baseline PK sample. The PK analysis set will be used for all PK analyses.

4.7. Verification of Analysis Sets

A blinded review to verify all defined analysis sets excluding LTES will be conducted before database lock of primary analysis. The results will be documented. The document will list subjects excluded from each analysis set with reason(s).

5. STATISTICAL METHODOLOGY

5.1. Population Characteristics

5.1.1. Study Subjects Disposition

Subject disposition will be summarized as follows.

- RI period
  - Screened Subjects (Signed Informed Consent)
    - Enrolled
    - Subjects treated in RI period
    - Subjects completed RI treatment
    - Subjects with early treatment discontinuation and reasons for treatment termination
    - Subjects with treatment ongoing at end of RI period
- RW Period
  - Number of subjects randomized, by arm
    - Subjects treated in RW period

  - Subjects who completed RW period
  - Subjects who discontinued study drug before end of RW period with reason of discontinuation
  - Subjects with treatment ongoing at end of RW period
- Number of subjects who consented to the LTE period
- LTE
  - Subjects who completed the Treatment Period
  - Subjects who discontinued study drug with reasons for treatment discontinuation
- Study disposition
  - Subjects who completed
  - Subjects who terminated early and reasons for early termination
  - Subjects with study ongoing at data cutoff

5.1.2. Baseline Demographic

Frequency counts (n) and percentages (%) will be presented for sex, race, ethnicity, and age group (i.e., 12-17 years, 18-64 years, and 65 years to the maximum age in the ITT analysis set). Descriptive statistics such as number of subjects (n), mean, standard deviation, median, minimum and maximum will be presented for age (years), weight (kg), Height (cm), and body mass index (BMI) kg/m^2.

5.1.3. Baseline Disease Characteristics

Baseline disease characteristics include the following:

- Oral corticosteroid use at RI Baseline (yes/no)
- Diagnosis of recurrent idiopathic pericarditis at RI (yes/no)
- Type of recurrent Pericarditis
  - Idiopathic
  - Pericardiotomy syndrome
  - Dressler's syndrome
  - Still's disease
  - Other
- Duration of disease from first episode to the date of inform consent
- Total number of pericarditis episodes, total number of episodes in the past year until first injection in the RI period, and annualized number of episodes per year,
- Time since beginning of qualifying episode in days
- Baseline central CRP value and weekly pain NRS score
- Baseline pericardial rub, effusion, tamponade, electrocardiogram (ECG) findings (widespread ST-elevation and PR-Depression), ECG interpretation

- Pericarditis treatment at baseline
  - Non-opioid analgesics
  - Opioid analgesics
  - Aspirin
  - nonsteroidal anti-inflammatory drug (NSAIDs)
  - Colchicine
  - Oral corticosteroids
  - IM/IV corticosteroids
  - Other

Disease characteristics for the qualifying episode, including the following:

- Number and proportion of subjects with presence of pericarditis pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, new or worsening in pericardial effusion, and pericardial inflammation on magnetic resonance imaging (MRI).
- Values of pain level, CRP (mg/dL), fever (Celsius), white blood cell (WBC; 10^3/uL), and erythrocyte sedimentation rate (ESR) (mm/hr).
- Treatment for the qualifying episode
  - Non-opioid analgesics
  - Opioid analgesics
  - Aspirin
  - NSAIDs
  - Colchicine
  - Oral corticosteroids
  - IM/IV corticosteroids

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using n, mean, median, standard deviation, and range (minimum, maximum). Summaries will be presented for the RI, RW, and LTE periods.

Baseline disease characteristics will also be summarized for subjects who are on corticosteroid at RI baseline. In addition to those specified above, the following baseline data will be summarized:

- Duration (in weeks) of using oral prednisone prior to enrollment
- Average dose (mg/day) of oral prednisone prior to enrollment
- Cumulative dose (mg) of oral prednisone prior to enrollment

5.1.4. Medical/Surgical History

Medical/Surgical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA; v21.1) 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 electronic case report form (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.

5.1.5. 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 treatment period which is from the date of first dose to the date of last dose plus 6 weeks.

Additionally, the medications will be considered concomitant if the start date of the medication is missing.

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 coded using World Health Organization (WHO) Drug (version March 2018). Medications will be summarized by ATC level 2 code and preferred term. Summary will be done by periods (i.e., RI, RW, and LTE) and by treatment (KPL-914 vs placebo) for RW period. One subject will be counted once within one preferred term and one ATC class. The medication information will be presented in a by-subject listing with ATC class (level 2) and WHO Drug Dictionary preferred term, start and stop date, dosage, route, frequency and indication.

Concomitant pericarditis treatment will be summarized by period and by treatment for RW period using the following categories:

- non-opioids
- opioid analgesics
- aspirin, NSAIDs
- colchicine
- oral corticosteroids,
- IM/IV corticosteroids or other medications

In addition, concomitant pericarditis treatment received during the RW treatment period will also be summarized based on the status of receiving bailout treatment (i.e. concomitant medication received before start of bailout treatment vs after start bailout treatment) for each treatment group in the RW period.

For RI period, use of concomitant pericarditis treatment (i.e., background treatment) will be summarized over time.

5.1.6. Study Drug Administration

The study medication 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 for each of the treatment periods: RI, RW, LTE, and Study Overall.

- Treatment duration in weeks:
  - For RI period, it is defined as [minimum of (date of last study drug +6, date of RI week 12 visit – 1, date of data cutoff) - date of first study drug + 1)/7].
  - For RW period it is defined as [minimum of (date of last study drug +6, date of end of RW visit) - date of first study drug + 1)/7].
  - For LTE and study overall, it is defined as [minimum of (date of last study drug +6, end of study date, date of data cutoff) - date of first study drug + 1)/7.

Number of administrations in each period regardless of full amount or partial amount of syringe injected. The loading dose includes two injections and will be counted as one administration.

Compliance (%) in each period, calculated as (number of administrations) / (protocol planned number of administrations) ×100%. The loading dose includes 2 injections and will be counted as one administration.

Total rilonacept dose administered in each period, defined as the sum of all doses (mg) received in the corresponding period. The actual volume administered will be used to calculate the total dose. For subjects receiving weight-adjusted dose (e.g., 2.2 mg/kg) their weight collected at scheduled visits will be used to calculate the amount of the study drug received.

Percentage of self-administrations by the subject, defined as [Number of self-administrations] / [Total number of administrations received] × 100%. The loading dose will be included in the denominator as one administration. If one of 2 injections in the loading dose is self-administered, it will be counted in the numerator.

5.1.7. Protocol Deviations

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

A blinded review before database lock will be conducted to determine important protocol deviations. Protocol deviations are considered important if based on Sponsor assessment they can impact study integrity or interpretability of study results.

Important protocol deviations will also be evaluated if they have impact on efficacy data. Important protocol deviations with potential impact on efficacy will be used to exclude subjects from PP analysis set.

All protocol deviations will be reviewed and categorized before database lock. All important protocol deviations will be summarized by deviation category (including Inclusion Criteria, Exclusion Criteria, ICF, Concomitant Medication, and other if applicable). The protocol deviation data will also be presented as a by-subject data listing.

5.2. Efficacy Analysis

5.2.1. Primary Efficacy Endpoint

5.2.1.1. Definition

The primary efficacy endpoint is time to pericarditis recurrence, defined as the time from randomization to the date of the first pericarditis recurrence for each subject. Only

CEC-confirmed pericarditis recurrence will be considered as an event for the primary analysis.

Time to pericarditis recurrence is calculated as: Data of Event/Censor – Date of randomization +1.

Pericarditis recurrence is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis. The assessments to be conducted by the investigator is described in protocol Section 6.1.4. At any time during the RW period, subjects who experience a suspected recurrence of pericarditis symptoms will be requested to report to the study site/clinic for a scheduled or unscheduled visit, during which clinical assessments will be performed to gather all the necessary diagnostic data to confirm or rule out the presence of pericarditis recurrence.

Pericarditis recurrence will also be evaluated by the investigators at the following time points:

- Routine assessment (every 4 weeks until week 24 in RW, then every 8 weeks)
- End of RW period
- End of treatment
- Post-treatment safety follow-up
- LTE assessment (every 12 weeks up to 24 months and 18-month visit)

Upon suspected pericarditis recurrence, the event is required to be captured in the electronic data capture (EDC) system within 24 hours of learning of the event, and a pericarditis recurrence event adjudication package must be prepared for adjudication by CEC. Details on endpoint package requirements will be described in the CEC charter. The CEC confirmed pericarditis recurrences will be used for the analysis of primary efficacy endpoint.

The censoring rules in Table 1 will be used in the analysis of the primary efficacy endpoint, in which, the event/censor reason will be provided in a data listing.

Table 1: Censoring Rules for Time to Pericarditis Recurrence in the RW Period

	Scenario*	**Event/ Censor**	**Event/Censor Reason**	**Date of Event/ Censor**
1	Pericarditis recurrence occurred before or without receiving bailout rilonacept, including events after termination of study drug	Event	Recurrence	Date of pericarditis recurrence
2	Pericarditis recurrence occurred after receiving ORT or prednisone	Event	Recurrence after receiving ORT/prednisone	Date of pericarditis recurrence
3	Receiving bailout rilonacept before pericarditis recurrence	Event	Recurrence after receiving bailout	Date of pericarditis recurrence
4	No pericarditis recurrence during RW period with or without receiving ORT/prednisone	Censored	No pericarditis recurrence	Date of last assessment for pericarditis recurrence on or before data

	Scenario*	Event/ Censor	Event/Censor Reason	Date of Event/ Censor
				cutoff.

5.2.1.2. Analysis Methods for the Primary Endpoint

The log rank test will be the primary method for the analysis of time to recurrence based on CEC confirmed events, stratified by the stratification variables for randomization. Analysis based on the ITT analysis set will be used as the primary analysis. Analysis based on the PP analysis set will be considered as a sensitivity analysis.

Time to recurrence will be summarized with the 25th, 50th (median), and 75th percentiles using the Kaplan-Meier (KM) method. The 95% confidence interval (CI) for the percentiles will be calculated using a log-log transformation. The percentage of subjects with pericarditis recurrence and its 95% CI will be calculated at weeks 8, 16, 24, and 36 since randomization, using Greenwood's formula with a log-log transformation.

The hazard ratio for KPL-914 vs. placebo and the corresponding Wald 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate, stratified by randomization strata.

A sensitivity analysis will be performed based on the Investigator's judgement of pericarditis recurrence. A 2×2 table for the concordance/discordance between Investigator's judgement and CEC's adjudication will be generated.

Upon pericarditis recurrence as determined by the investigator, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and have 1 CRP value ≥1 mg/dL (either on the same day or separated by no more than 7 days) will receive bailout rilonacept (2 open-label injections of 160 mg rilonacept [or 4.4 mg/kg for pediatric subjects]) irrespective of randomized treatment assignment and as soon as at least 5 days have passed since the last study drug injection. The subjects transitioning to bailout rilonacept will remain blinded to their randomized treatment assignment.

For subjects who have pericarditis recurrence, the frequency table and listing will be generated for the following treatment prescribed by the Investigator:

- Bailout rilonacept
- Analgesics
- NSAIDS
- Colchicine
- Other.

The following criteria for pericarditis recurrence were provided to CEC to determine pericarditis recurrence:

1. Re-appearance or worsening of typical pericarditis pain (with at least one pain NRS recording ≥4) AND elevated CRP (≥1.0 mg/dL) either on the same day or separated by no more than 7 days

   OR

2. Re-appearance or worsening of typical pericarditis pain (with at least one pain NRS recording ≥4), AND abnormal CRP (>0.5 mg/dL) either on the same day or separated by no more than 7 days AND at least 1 supportive evidence of pericarditis as below

   OR

3. Re-appearance or worsening of typical pericarditis pain (but no NRS scores being ≥4), AND elevated CRP (≥1.0 mg/dL) not attributable to other causes AND at least 1 supportive manifestation of pericarditis as below.

Supportive Evidence (Pericarditis manifestations):

- increased WBC count >upper limit of normal (ULN)
- fever >38°C
- presence of pericardial rub
- ECG changes consistent with pericarditis, i.e., findings of new widespread ST-segment elevation and/ or PR-segment depression
- new or worsened pericardial effusion on echocardiography (ECHO)
- new or worsening pericardial inflammation on MRI or other imaging modality.

The above information will be summarized and listed.

5.2.2. Secondary Efficacy Endpoint in the RW Period

This Section defines secondary efficacy endpoints for the RW period. Endpoints for the RI and LTE periods are defined in Section 5.2.3.

5.2.2.1. Definition of Major Secondary Efficacy Endpoints in the RW Period

This section defines 3 major secondary endpoints. These endpoints will be analyzed with the ITT Week 16 analysis set. Handling of missing data due to end of RW period will be discussed in Section 5.2.2.2.

1. Proportion of subjects who maintained clinical response at Week 16 of the RW period. clinical response is defined as a weekly average of daily pericarditis pain on the 11-point NRS ≤2.0 and CRP level ≤0.5 mg/dL, and on monotherapy of randomized study drug at Week 16.

   Subjects who complete 16-week of double-blinded treatment and meet the clinical response criteria at Week 16 will be considered as responders. Subjects who had recurrence, discontinued double-blinded treatment, lost to follow-up, and used bailout rilonacept or rescue medications (ORT or prednisone) before Week 16 will be considered as non-responders.

   If either weekly average of NRS or CRP is missing at week-16 assessment, the subject will be considered as a non-responder.

2. Percentage of days with pain NRS ≤2 in the first 16 weeks of the RW period. No or minimal pain is defined as non-missing NRS ≤2.

   The denominator will be 168 (=16x7) for every subject. NRS assessments after treatment termination will be included. NRS assessments while on rescue

medications for pericarditis will considered not meeting this criterion. Receiving each administration of bailout rilonacept will disqualify for meeting NRS ≤2 for 7 days. Missing values will be counted as 0 day meeting the criterion.

3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 16 of the RW period.

   Subjects who do not have the assessment due to early termination or other reasons will be considered as not meeting the criterion. Subjects who took rescue medications at the Week 16 assessment or used bailout rilonacept on or before Week 16 will also be considered not meeting the criteria.

5.2.2.2. Analysis Methods for Major Secondary Efficacy Endpoints in the RW Period

These endpoints will be analyzed with the ITT Week 16 analysis set.

1. For the proportion of subjects who maintained Clinical Response at Week 16 of the RW period, the response rate and Clopper–Pearson 95% CI will be obtained for each arm. Difference of response rate (KPL-914 – Placebo) and 95% CI based on normal approximation will be provided. The Cochran–Mantel–Haenszel (CMH) test will be used to test the treatment effect, stratified by the stratification variables for randomization.
2. For the percentage of days with pain NRS ≤2 in the first 16 weeks post randomization, an analysis of covariance will be used for treatment comparison. In addition to treatment arm, the following covariates will be included in this analysis: the stratification variables for randomization, and RI baseline NRS in 2 categories: NRS ≤2 versus NRS >2. LS mean difference and the 95% CI will be provided.
3. For proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 16 of the RW period, the response rate and Clopper–Pearson 95% CI will be obtained for each arm. Difference of response rate (KPL-914 – Placebo) and 95% CI based on normal approximation will be provided. The Cochran–Mantel–Haenszel (CMH) test will be used to test the treatment effect, stratified by the stratification variables for randomization.

5.2.2.3. Other Secondary Efficacy Endpoints in the RW Period and Statistical Method

All time-to-event endpoints start from the day of randomization. The same censoring rules for the primary endpoint will be applied. Missing values will not be imputed unless otherwise specified. Analysis of secondary endpoints will be based on ITT analysis unless otherwise specified.

1. Proportion of subjects who maintained Clinical Response at Week 24 of the RW period based on ITT Week 24 analysis set

   The same rules and method for the first major secondary endpoint will be applied, except that 16 weeks is replaced with 24 weeks.

2. Proportion of subjects who maintained Clinical Response at Week 8 of the RW period based on based on ITT Week 8 analysis set

The same rules and method for the first major secondary endpoint will be applied, except that 16 weeks is replaced with 8 weeks.

3. Percentage of days with minimal or no pain in the first 24 weeks post randomization based on ITT Week 24 analysis set

   The same rules and method for the second major secondary endpoint will be applied, except that 16 weeks is replaced with 24 weeks.

4. Percentage of days with minimal or no pain in the first 8 weeks post randomization based on ITT Week 8 analysis set

   The same rules and method for the second major secondary endpoint will be applied, except that 16 weeks is replaced with 8 weeks.

5. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period based on subjects who were randomized at least 24 weeks before data cutoff

   The same rules and method for the third major secondary endpoint will be applied, except that 16 weeks is replaced with 24 weeks.

6. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 8 of the RW period based on subjects who were randomized at least 8 weeks before data cutoff

   The same rules and method for the third major secondary endpoint will be applied, except that 16 weeks is replaced with 8 weeks.

7. Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period

   The proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period in each arm will be estimated using the KM method, as described in the analysis of the primary endpoint. The same censoring rules will apply. The variance of the difference in proportion between treatment arms will be the sum of the variance in each arm. The p-value and 95% CI will be calculated using a normal approximation.

8. Time to pericarditis pain NRS ≥4

   Use the same method for the primary endpoint.

9. Time to CRP level ≥1 mg/dL. This is for elevation of CRP for which no other cause other than pericarditis was identified.

   Use the same method for the primary endpoint. A manual review for any CRP ≥1 mg/dL will be performed to make sure that the CRP increase was caused by pericarditis.

10. Time to pericardial rub

    Use the same method for the primary endpoint. Subjects with pericardial rub at RW baseline will be excluded from the analysis.

11. Time to widespread ST-segment elevation or PR-segment depression on ECG

    Use the same method for the primary endpoint. Subjects with either condition at RW baseline will be excluded.

12. Time to new or worsening pericardial effusion on ECHO

    Use the same method for the primary endpoint. Proportion of subjects with new or worsening in pericardial effusion on ECHO and its 95% CI in each arm will be estimated using the K-M method.

13. Change in category of ECHO pericardial effusion size at week 24 and end of RW based on central labs

    - The ITT Week 24 analysis set will be used for this endpoint. Effusion size in ECHO has the following categories:
    - None or Trivial/Physiologic
    - Small
    - Moderate
    - Large
    - Very Large
    - NM/ND (Not Measurable/Not Recorded by Site)

    Change in ECHO pericardial effusion size will be summarized by before and including bailout rilonacept in each arm. Shift tables for change from RW baseline to RW weeks 24 and to end of RW visit will be generated. Due to potentially different number of subjects receiving bailout rilonacept between treatment arms, there will be no hypothesis testing for this endpoint.

    Endpoints 14-16 will be summarized for data before receiving bailout rilonacept and for data including bailout rilonacept in each arm. P-values will not be provided due to potentially different number of subjects receiving bailout rilonacept.

14. Change over time in central-lab CRP level

    A mixed model with repeated measures (MMRM) using TYPE=UN option in SAS Proc Mixed will be applied in the analysis of this endpoint. If the model does not converge, an analysis of covariance (ANCOVA) model will be used at each timepoint to calculate least-squares (LS) means. In the model, subjects will have repeated measures for the response variable change from baseline of the endpoint. The explanatory variables will include the baseline value, treatment arm, baseline value by treatment interaction, and the variables for randomization strata. Only observed values will be used in the analysis without imputation.

15. Change over time in the subject's assessments of pericarditis pain (weekly averages)

    The same method for change over time in CRP level will be applied. If bailout rilonacept is used in a week, the week will be considered as after bailout.

16. Number (percentage) of subjects with absent or minimal pericarditis activity over time after RW week 24 based on the PGIPS. The denominator in each arm will be the total number of subjects with the assessment at each visit.

    The CMH test stratified by the randomization strata will be applied.

17. Number (percentage) of subjects with absent or minimal pericarditis activity over time based on the PGA-PA. The denominator in each arm will be the total number of subjects with the assessment at each visit.

    The same analysis method and analysis sets for PGPIS will be applied.

    The endpoints below (18 – 23) from patient reported outcomes will be summarized with descriptive statistics. There will be no hypothesis testing since they are measured at RW baseline and Week 24 only and receiving bailout rilonacept due to recurrence at Week 24 could be a confounding factor.

18. Change from baseline to week 24 in the SF-36 Physical and Mental Component Scores (see below for definition)

19. Change from baseline to week 24 in Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health domains in SF-36.

    The SF-36v2® Health Survey (standard, four-week recall) is a 36-item generic (not indication specific) instrument used to evaluate subject reported health related quality of life (HRQoL) in adult subjects. The questions are organized in eight health domain scales: physical functioning [PF] (10 items), role participation with physical health problems [RP] (four items), bodily pain [BP] (two items), general health status [GH] (one item), vitality [VT] (four items), social functioning [SF] (two items), role participation with emotional health problems [RE] (three items), and mental health (five items). Scores from the eight domains are summarized into a physical component score (PCS) and mental component score (MCS).

    The SF-36v2 utilizes norm-based scoring involving a linear T-score transformation method so that scores for each of the health domain scales and component summary measures have a mean of 50 and a standard deviation of 10, based on the 2009 United States general population. Scores above and below 50 are above and below the average, respectively, in the 2009 United States general population. Also, because the standard deviation is 10, each 1-point difference or change in scores has a direct interpretation; that is, 1 point is one-tenth of a standard deviation, or an effect size of 0.10.

    Subject responses will be scored, including the handling of missing data, consistent with the instructions in the SF-36v2 user manual using the Optum Smart Measurement System Scoring Solution software.

    The possible score for each item is from 1 to 6. Each item response is then assigned a numeric value according to one of 8 scales.

    Items 1, 2, 20, 22, 34, 36: 1=100, 2=75, 3=50, 4=25, 5=0

Items 3, 4, 5, 6, 7, 8, 9, 10, 11, 12: 1=0, 2=50, 3=100
Items 13, 14, 15, 16, 17, 18, 19: 1=0, 2=100
Items 21, 23, 26, 27, 30: 1=100, 2=80, 3=60, 4=40, 5=20, 6=0
Items 24, 25, 28. 29, 31: 1=0, 2=20, 3=40, 4=60, 5=80, 6=100
Items 32, 33, 35: 1=0, 2=25, 3=50, 4=25, 5=0.

Final scores for each scale range from 0 to 100 with higher scores indicating better health. If a subject does not respond to a question, the average score for an item will use the number of non-missing scores for the denominator.

Table 2 displays the items that are categorized. Detailed information can be found in Mark, EM (2011).

Table 2: The 8 Domains in SF-36v2

Scale	Number of items	After recoding, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role-physical (RP)	4	13 14 15 16
Bodily pain	2	21 22
General health	5	1 33 34 35 36
Vitality	4	23 27 29 31
Social functioning	2	20 32
Role-emotional (RE)	3	17 18 19
Mental health	5	24 25 26 28 30

20. Changes in SF-6D, 6 domain scores and the utility index

The SF-6D is calculated based on responses to 11 items on the SF-36, that correspond to 6 domains: physical functioning, role participation (combined role-physical and role-emotional), social functioning, bodily pain, mental health, and vitality.

RP and RE are combined, and general health is not included. The specific SF-36v2 areas or activities contributing to the scoring of this index include:

- ability to engage in both moderate and vigorous activities
- ability to bathe and dress oneself
- limitations in the kind of work or other activities as the result of physical health; accomplishing less due to emotional problems
- bodily pain and its interference with normal work; nervousness, depression, and energy level
- interference with social activities due to physical or emotional problems.

Individual respondents can be classified on any of four to six levels of functioning or limitations for each of six domains, thus allowing a respondent to be classified into any of 18,000 possible unique health states. Using a standard gamble technique, each of these health states were mapped onto the SF-6D index score, which ranges from 0.00 (worst possible health state/death) to 1.00 (best possible health state/perfect health).

The PRO Analytics software calculates and outputs the SF-6D for each subject at each assessment, just as it does for the 8 domain scores and 2 summary scores.

In the 2009 QualityMetric US Normative survey (Maruish 2011), from which the scoring algorithms were derived, the SF-6D calculated for 3,856 participants who completed the standard (4-week recall) form of the SF-36v2 had a mean of 0.74 and a SD of 0.14. Based on a paper from Walters and Brazier (2003), a change of 0.05 in the SF-6D would indicate a minimally important difference.

Table 3: SF-36v2 Health Survey Items Scored for the SF-6D

SF-6D Domains	**SF-36v2™ Health Survey Items**
Physical Functioning	3a, 3b, 3j
Role Participation (RP & PE)	4c, 5b
Social Functioning	10
Bodily Pain	7, 8
Mental Health	9b, 9f
Vitality	9e

21. Change in EQ-5D-5L individual scores and index value

    The EQ-5D-5L is a subject reported health status utility index for adult subjects that is comprised of five questions plus a visual analog scale (VAS). The five questions ask the respondent to assess their health in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The VAS captures the respondent's self-reported level of the health on the day of completion, captured as a numeric input from 0 ('the worst health you can imagine') to 100 ('the best health you can imagine'). Subject responses will be scored, including the handline of missing values, as specified in the EuroQol Research Foundation, EQ-5D-5L User Guide, 2019, available from http://euroqol.org/publications/user-guides.

    Scores from the five questions will be reported individually and converted to a single index value using the value set for US. Health state index scores generally range from less than 0 (where 0 is the value of a health state equivalent to dead; negative values representing values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility.

22. Change in subject's sleep quality assessed with the Insomnia Severity Index (ISI).

    The ISI is a 7-item self-report questionnaire assessing the nature, severity, and impact

of insomnia. The usual recall period is the "last 2 weeks" and the dimensions evaluated are severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (e.g., 0=no problem; 4=very severe problem), yielding a total score ranging from 0 to 28 (Morin et al 2011).

The ISI will be collected in subjects ≥18 years or older as described in the protocol.

23. Change in ISI categories. The ISI total scores are divided to 4 categories:
    - 1) 0–7 = No clinically significant insomnia
    - 2) 8–14 = Subthreshold insomnia
    - 3) 15–21 = Clinical insomnia (moderate severity)
    - 4) 22–28 = Clinical insomnia (severe)

    A shift table will also be used to summarize the changes over time.
24. Cumulative number (percentage) of subjects who received sequential ORT, prednisone, or bailout rilonacept for pericarditis period every 4 weeks cumulatively in the RW period.

    The CMH test stratified by the randomization strata will be applied to this endpoint.
25. Proportion of subjects using ORT (analgesics, NSAIDs, and/or colchicine) for pericarditis in the first 24 weeks. ORT use while waiting for at least 5 days since previous administration of study medication before receiving bailout rilonacept or within 5 days prior to the assessment of pericarditis recurrence visit is excluded. The denominator of the percentages is the number of subjects in the ITT analysis set in each arm. There will be no hypothesis testing for this endpoint.
26. The endpoints below for MRI assessments will be summarized at RW baseline and week 24. P-values will not be calculated.
    - Proportion of subjects with pericardial delayed hyperenhancement
    - Proportion of subjects with myocardial delayed hyperenhancement
    - Proportion of subjects with pericardial effusion, and effusion size

    A subject will have pericardial effusion if the effusion size is rated "Small" or larger.

5.2.3. Secondary Endpoints in RI and LTE Period

These include efficacy endpoints in the RI period and the LTE. Since there is no control arm in these 2 periods, only descriptive statistics will be provided. Summary statistics will be generated following the methodologies stated in Section 3.1 using RIS or LTES analysis sets. All time-to-event endpoints start from the first day of receiving rilonacept in that period. Unless specified otherwise, the denominator of a response rate or percentage will be the total number of subjects treated in that period.

5.2.3.1. Secondary Endpoints in the RI Period

The following efficacy endpoints will be included for the RI period. Unless specified otherwise, change means change from RI baseline to RI week 12, CRP level is from central lab, and the denominator for a proportion is the total number of subjects who were treated in the RI period.

1. Time to pain response, defined as number of days from first dose to the first day a subject's daily pain NRS is ≤ 2 of the 3 days over which, the rolling average daily pain NRS is ≤ 2. Subjects with baseline NRS ≤ 2 will be excluded from the analysis.
2. Time to CRP normalization (≤0.5 mg/dL)

   Time to CRP normalization will be censored at treatment discontinuation, taking prohibited medication, or week 12, whichever occurs first. Subjects with baseline CRP ≤0.5 mg/dL will be excluded from the analysis.
3. Time to rilonacept monotherapy

   Time to rilonacept monotherapy is defined as number of weeks from first dose to the first day of achieving monotherapy. Subjects without background therapies at RI baseline will be excluded from the analysis.
4. Time to treatment response defined as time from first dose to the first day of pain response, and CRP ≤0.5 mg/dL within 7 days before or after pain response. Treatment response day will be the first day that the above criterion is met. If pain response occurs before CRP ≤0.5 mg/dL, each 3-day rolling average of NRS should be ≤2.0 from the day of pain response to the day of CRP ≤0.5 mg/dL. The response day will be the day of pain response. If CRP ≤0.5 mg/dL occurs before pain response, the response day will also be the day of pain response.
5. Proportion of subjects achieving clinical response at RI week 12 based on RIS Week 12 analysis set

   Subjects who stopped background SOC pericarditis therapy on or before week 10, as well as who achieve CRP ≤0.5 mg/dL and weekly average of daily pericarditis pain score ≤2.0 on the 11-point NRS within the 7 days prior to and including the day of randomization on RI Week 12/Randomization are responders.
6. Number (percentage) of subjects with normalization of CRP (≤0.5 mg/dL) at RI Week 12. Subjects with baseline CRP >0.5 mg/dL in the RI week 12 analysis set will be used in the analysis.
7. Change from baseline in pericarditis weekly pain score at RI Week 12 and over time.
8. Change from baseline in CRP level at RI Week 12 and over time.
9. Proportion of subjects with resolution of echocardiographic and ECG abnormalities (yes/no) at RI Week 12.
10. Percentage of days with no or minimal pain (NRS ≤2) while on treatment. The denominator is the number of days on treatment, calculated as [min(date of last dose of study drug in RI period + 6, last date on study, end of RI period) – date of first dose in RI period) +1].

11. Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS over time at baseline, week 6, and week 12.
12. Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA over time at baseline, week 6, and week 12.
13. Change in the SF-36 8 domain scores, as well as the physical and mental scores.
14. Change in the SF-6D 6 domain scores and the utility index.
15. Change in the EQ-5D-5L individual scores and index value.
16. Change in the subject's sleep quality assessed with the ISI (see Section 5.2.2.3).
17. Change in ISI categories.
18. Number (percentage) of subjects who were off background pericarditis medication on or before weeks 4, 8, 10, and 12

    The RI Week 12 Analysis Set will be used for the summary. At each timepoint, the numerator only includes subjects who have reached monotherapy on or before the timepoint and remain on monotherapy until the end of the RI period.

5.2.3.2. Efficacy Endpoints in the LTE Period

The efficacy endpoints below are included in this period. These endpoints will not be included in the primary analysis for the RW period since data will not be available at that time. Each endpoint will be summarized through Week 24 in this period, by subjects who did and did not have an adjudicated pericarditis recurrence in the RW period and by subjects who enter LTE directly from the RI period, respectively, and overall. The baseline for the LTE period will be the last assessment before the first dose in the LTE period.

1. Number (percentage) of subjects with pericarditis recurrences based on investigators' judgement.
2. Proportion of subjects with Clinical Response (rilonacept monotherapy + CRP≤0.5 mg/dL + NRS≤2) at each CRP assessment (weeks 12 and 24). The pain NRS at the visit when CRP was assessed will be used.
3. Change over time in CRP levels.
4. Change over time in pericarditis pain NRS.
5. Proportion of subjects with absent or minimal pericarditis symptoms over time based on PGIPS.
6. Proportion of subjects with absent or minimal pericarditis activity over time based on the PGA-PA.
7. Change from baseline in the SF-36 8 domain scores, as well as the physical and mental scores.
8. Change in the SF-6D 6 domain scores and the utility index.
9. Change from baseline in the EQ-5D-5L individual scores and index value.
10. Change from baseline in the subject's sleep quality assessed with the ISI.
11. Change over time in ISI categories.

12. Number (percentage) of subjects requiring addition of SOC pericarditis therapy every 4 weeks cumulatively.
13. Change from baseline in pericardial signs in ECHO, ECG, and MRI.
14. Prednisone use over time.

    For subjects who are on prednisone at RI baseline, the proportion of subjects using prednisone at LTE will be summarized. The denominator will be the number of subjects using prednisone at RI and entering the LTE. The average daily dose of prednisone (mg/day) will be summarized.
15. In the MRI substudy, resolution in pericardial inflammation among subjects with pericardial inflammation at RI baseline as assessed by cardiac MRI. The endpoints below will be summarized.
    a. Proportion of subjects with pericardial Delayed Hyperenhancement
    b. Proportion of subjects with Myocardial Delayed Hyperenhancement
    c. Proportion of subjects with pericardial effusion, and effusion size
16. Annualized recurrent rate during treatment

    Annualized recurrent rate will be calculated for subjects randomized to KPL-914 utilizing pooled data in RW and LTE periods and there will be no hypothesis testing.

5.3. Safety Analysis

The following safety endpoints will be analyzed:

- Adverse events,
- Clinical laboratory parameters,
- Serology parameters,
- Hematology parameters,
- Non-fasting lipid panel,
- Pregnancy test,
- Vital signs,
- Urinalysis,
- Electrocardiogram, and
- Physical examination.

Descriptive statistics will be used to summarize safety endpoints for all subjects by the following periods:

- RI period (KPL-914)
- RW period
  - KPL-914 vs. Placebo Including Bailout Rilonacept
  - KPL-914 vs. Placebo before Bailout Rilonacept

- LTE period
- Study overall (RI through LTE), KPL-914 or placebo, regardless of receiving bailout Rilonacept.

Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for clinical laboratory analyses, vital signs measurements, ECGs, and physical examination findings.

5.3.1. Adverse Events

Treatment-emergent AEs (TEAEs), defined as AEs that start or increase in severity after the first dose of study drug and before 6 weeks after the last dose of study drug, will be coded to system organ class and preferred term using MedDRA v21.1.

TEAEs will be summarized by each period and study overall. In the RW period, they will also be summarized by including and excluding bailout rilonacept, respectively. The average follow-up duration in weeks for TEAE will be provided in summary tables. The duration of follow-up for each subject is defined as follows.

- For the RI period, it is from first dose in RI period until the day before randomization, last dose day plus 6 weeks, last study day, or data cutoff, whichever occurs first.
- For the RW period including bailout, it is from randomization to data cutoff, last dose day plus 6 weeks, or last study day, whichever occurs first.
- For the RW period before bailout, it is from randomization to the start of using bailout rilonacept, data cutoff, last dose day plus 6 weeks, or last study day, whichever occurs first.
- For the LTE period, it is from first dose day in LTE period to data cutoff, last dose day plus 6 weeks, or last study day, whichever occurs first.
- For study overall, it is from first dose day in RI period to data cutoff, the last dose plus 6 weeks, or last study day, whichever occurs first.

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), relationship to study drug, serious AEs, AEs leading to death, AEs resulting in dose interruption, AEs leading to withdrawal of study treatment, and AEs of injection site reaction.

Any AE of malignancy (excluding basal cell carcinoma of the skin) is of special interest. AE of special interest will also be summarized.

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 by SOC and preferred terms.

Incidence rate per 100 subject-years and its 95% CI will be calculated by the periods defined for follow-up duration above for the following groups of AEs:

- All AEs (include any AE),
- SAE (include any SAE),

- deaths,
- all infections (including serious),
- serious infections (serious only),
- all ISR (injection site reaction, including serious and non-serious),
- only serious ISR,
- all malignancies excluding NMSC (Non-Melanoma Skin Cancer: ie. cutaneous basal cell carcinoma and cutaneous squamous cell carcinoma).

Incidence rate per 100 subject-years = 100 × (number of different AE start days within the treatment period)/(Sum of treatment duration in years from all subjects in the cohort). Multiple events within a subject will be counted as multiple events. Treatment exposure duration and follow-up of AE's in the Study Overall period will be 6 weeks after the last dose. There will be no formal hypothesis testing.

5.3.2. Clinical Laboratory Parameters

Hematology, chemistry, lipid panel, and urinalysis results will be summarized and listed. Pregnancy test will not be summarized but will be listed. Summaries will include descriptive statistics for actual values and change from baseline. Shift tables from baseline condition to the condition at each visit will also be provided. The shift table will include subjects without data so that all subjects in the safety population at the baseline of each period (RI, RW, and LTE) will be included.

A summary of hepatic function abnormalities will be provided for the following criteria:

- >2xULN
- >3xULN
- >5xULN
- The number of percentage of subject's meeting the criteria for Hy's Law defined as elevations in ALT and/or AST of >= 3xULN with accompanying elevations in total bilirubin of >= 2xULN will also be summarized.

The incidence rate per 100 subject-years and its 95% CI for the following lab abnormalities will be calculated:

- Incidence of ALT >5xULN,
- Incidence of AST >5x ULN,
- Incidence of total bilirubin >2xULN
- Incidence of absolute neutrophil count (ANC) <1.0 x 10^3 uL.

Multiple lab abnormalities within a subject will be counted as multiple events within the follow-up period defined in Section 5.3.1 .

Incidence rate per 100 subject years in a cohort = 100 × (# of different lab abnormalities from all subjects within the follow-up period)/(Sum of follow-up duration in years from all subjects in the cohort).

5.3.2.1. Hematology

Hematology tests performed at central study laboratory include WBC count with differential, platelet count, red blood cell count, mean corpuscular volume, hemoglobin, mean corpuscular hemoglobin concentration.

5.3.2.2. Chemistry

Blood chemistry tests performed in the central study laboratory include albumin, total protein, alkaline phosphatase, alanine aminotransferase/serum glutamic pyruvic transminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transminase (AST/SGOT), direct bilirubin, total bilirubin, bicarbonate, chloride, potassium, sodium, creatinine, glucose.

5.3.2.3. Non-fasting Lipid Panel

Subjects treated with rilonacept may experience increases in their lipids, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein HDL, and triglycerides.

Non fasting measurements of total cholesterol, triglycerides, HDL, and direct LDL will be performed by central study laboratory as described in the Schedule of Assessments in Section 13.1.

Investigators should monitor the lipid profiles in study subjects and consider ordering fasting lipid panel and/or lipid lowering therapies as needed based on cardiovascular risk factors and current guidelines.

5.3.2.4. Urinalysis

Urinalysis performed by the central study laboratory includes specific gravity, pH, protein, urobilinogen, ketones, glucose, blood, bilirubin, nitrites, leukocyte esterase will be summarized.

5.3.2.5. Pregnancy Test

For women of child-bearing potential, a urine pregnancy test using a licensed test (dipstick) should be performed prior to receiving the first administration of study drug, and as needed during the study, and also at the SFU visit. When needed, serum pregnancy test should be performed. Pregnancy test results will not be summarized but will be listed.

5.3.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for Temperature, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Rate (PR), Respiratory Rate (RR), temperature, and weight (kg). A data listing of vital signs will also be provided.

5.3.4. Electrocardiogram

Frequency table for the following interpretations will be generated:

- Widespread of ST elevation normal
- PR-segment depression
- ECG Interpretation
  - Normal

- abnormal not clinically significant, and abnormal clinically significant)
- Abnormal not consistent with pericarditis but clinically significant
- Abnormal consistent with pericarditis

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.

5.3.5. Physical Examination

There are full and abbreviated physical examinations. Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal (GI), genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement. Abbreviated physical examination includes at minimum evaluation of vital signs, lung and heart sounds, including evaluation for pericardial rub.

Present or absent in pericardial rub will be recorded. For each assessment of body system, the result will be recorded as normal, abnormal (not clinically significant), or abnormal (clinically significant). The number and percentage of subjects in each result category will be summarized by body system and visit, as well as by arm in the RW period.

All physical examination data will be provided in a listing.

6. PHARMACOKINETIC ANALYSES

For all subjects, serum samples will be collected at time points shown in Section 13.1 in order to quantify concentrations of rilonacept. Only individual listings of serum concentrations will be provided. The analysis plan for PK data will be described in a separate document.

7. PHARMACOGENOMICS SUBSTUDY

Samples for pharmacogenomics in the substudy will be collected according to the Study Schedule of Activities. More details of the analysis will be provided in a separate document.

8. ANTI-RILONACEPT ANTIBODIES

Blood sample for testing anti-rilonacept antibody (ADA) will be collected at RI baseline, RI weeks 2, 6, 12 (= RW baseline), RW week 24, end of RW/LTE baseline, and LTE week 24. ADA status will be categorized as follows.

1. Treatment-emergent ADA, including treatment induced or boosted [increased by one quartile (with all titers collected) from the previous assessment]
2. Prior existing ADA (without treatment boosted)
3. ADA negative at every assessment.

For subjects with treatment-emergent ADA, the maximum post-baseline titer level (low, medium, high) will be summarized. The 3 levels (low, medium, high) will be divided based on 25^{th} and 75^{th} percentiles from all ADA titers pooled.

The following endpoints will be summarized for each category of ADA status above:

- Number and percentage of subjects with injection site reactions within 24 hours of administration
- Subjects with Neutralizing antibody in the first 2 categories above.

A summary table will be provided for number and percent of subjects with positive or negative anti-rilonacept antibody by visit. Individual's ADA status and titer level (if positive) at each visit will be provided.

The number and percent of subjects with anti-rilonacept-antibody positive at any visit vs. those with negative at every visit will also be provided. The summary statistics of CRP and NRS level will be provided for these 2 subsets of subjects at each visit by study period, and by treatment arm in the RW period (before vs. after receiving bailout rilonacept and overall).

The following 3 categories will be used in the subgroup analysis for the primary endpoint, Summary of NRS scores and CRP levels over time, summary of TEAEs (overall and drug related), and blood concentration over time:

1. Subjects with ADA Positive at Any Assessment
2. Subjects with ADA Positive and Neutralizing Antibody at Any Assessment
3. Subjects with ADA Negative at Every Assessment

9. BIOMARKER

Serum and plasma will be collected according to the Study Schedule of Activities for biomarker analysis. More details of the biomarker analysis will be provided in a separate document.

10. INTERIM ANALYSIS

No interim analysis for claiming efficacy is planned. Interim safety review will be conducted by a Data Monitoring Committee (DMC). The analysis will be performed by a designated CRO. Details are in DMC charter and DMC SAP.

11. CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

Analysis in the SAP	**Analysis planed in the protocol**	**Reason**
Section 5.2.3.1 Time to pain response, defined as number of days from fist dose to the first day a subject's daily pain NRS is ≤ 2 of the 3 days over which, the rolling average daily pain NRS is ≤ 2.	Section 7.3.1 Time to pain response defined as a rolling average of NRS score of 2 or less on three consecutive days.	A score of 3 or higher on the first day of the rolling average should not qualify pain response.

Analysis in the SAP	**Analysis planed in the protocol**	**Reason**
Section 5.2.3.1 Time to treatment response defined as time from first dose to the first day of pain response, and CRP ≤0.5 within 7 days before or after pain response. Treatment response day will be the first day that the above criterion is met. If pain response occurs before CRP ≤0.5, each 3-day rolling average of NRS should be ≤2.0 from the day of pain response to the day of CRP ≤0.5. The response day will be the day of pain response. If CRP ≤0.5 occurs before pain response, the response day will also be the day of pain response.	Section 7.3.1 Time to clinical response (monotherapy + NRS ≤2 + CRP ≤0.5 mg/dL)	Subjects were enrolled with a qualifying episode and on background therapy. The endpoint of interest is to evaluate how soon subjects will reach response in both pain and CRP after initiating rilonacept while on background therapy.

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13. APPENDICES

13.1. Schedule of Assessments

Table 4: Study Schedule of Activities – Screening and Run-In Period

Trial Period	**SCREENING[a]**	**RUN-IN (12 weeks)[m]**								
		ENROLLMENT								**RANDOMIZATION [-q]**
Visit Name	**Screening Visit**	**RI Baseline**	**RI Day 2**	**RI Day 4**	**RI Week 1**	**RI Week 2**	**RI Week 4**	**RI Week 6**	**RI Week 10**	**RI Week 12/ RW Baseline**
Visit Window[b] (days)	**(-28)**	**NA**	**NA**	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 3**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**TC/RN**	**TC/RN**	**TC/RN**	**TC/RN**	**Clinic**	**TC**	**Clinic**
Informed Consent Form	X									
Inclusion and Exclusion criteria	X	X								
Demographics	X									
Medical/Surgical History	X									
Pericarditis Diagnosis & History	X	X								
Concomitant medications	X	X		X	X	X	X	X	X	X
Pericarditis Concomitant medications	X	X		X	X	X	X	X	X	X
Pericarditis Concomitant medication tapering					X	X	X	X	X	
Full Physical Examination[c]	X									
Abbreviated Physical Examination[d]		X								X
Body weight and height		X								X
12-Lead ECG		X								X
Echo[e]		X[e]								X[e]
MRI (substudy only)		X								
Pericardial pain (11-point NRS)	X[f]	DAILY[g]								X[g]

Trial Period	**SCREENING[a]**	**RUN-IN (12 weeks)[m]**								
		ENROLLMENT								**RANDOMIZATION [-q]**
Visit Name	**Screening Visit**	**RI Baseline**	**RI Day 2**	**RI Day 4**	**RI Week 1**	**RI Week 2**	**RI Week 4**	**RI Week 6**	**RI Week 10**	**RI Week 12/ RW Baseline**
Visit Window[b] (days)	**(-28)**	**NA**	**NA**	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 3**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**TC/RN**	**TC/RN**	**TC/RN**	**TC/RN**	**Clinic**	**TC**	**Clinic**
EQ-5D		X								X
SF-36		X								X
ISI		X								X
PGIPS		X						X		X
PGA-PA		X						X		X
Hematology, Chemistry Labs (Central)		X						X		X
Lipid Panel (Central)[h]		X								X
CRP (Local)	X[f]									X
CRP (Central)	(X)	X		X	X	X	X	X		X
Hematology, Chemistry, IGRA[r], hepatitis serology, HIV (Local)	X									
Chest X-Ray	X									
Urine Pregnancy (Local or Central)[j]	X	X								
Urinalysis (Central)		X								
PK (Central)[s]			X[i]		X	X	X			
ADA (Central)[s]		X				X		X		
Biomarkers (Central)		X			X		X			
Pharmacogenomics Informed Consent[k]		X								
Pharmacogenomics Sampling (Central)[k]							X			
IWRS Subject Status Update	X	X								X
IWRS Weight Input (pediatric only)		X								X

Trial Period	**SCREENING[a]**	**RUN-IN (12 weeks)[m]**								
		ENROLLMENT								**RANDOMIZATION [-q]**
Visit Name	**Screening Visit**	**RI Baseline**	**RI Day 2**	**RI Day 4**	**RI Week 1**	**RI Week 2**	**RI Week 4**	**RI Week 6**	**RI Week 10**	**RI Week 12/ RW Baseline**
Visit Window[b] (days)	**(-28)**	**NA**	**NA**	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 3**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**TC/RN**	**TC/RN**	**TC/RN**	**TC/RN**	**Clinic**	**TC**	**Clinic**
IWRS Drug Dispensing		X		X				X		X
In Clinic Study Drug Administration[o]		X[n]						X		X
Outpatient Study Drug Administration[o]					WEEKLY					
Study Drug Compliance Review		X			X	X	X	X	X	X
Clinical Response Evaluation										X[p]
Adverse Event Reporting[l]	X	X		X	X	X	X	X	X	X

a The screening and enrollment visit can be combined.
b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.
c Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement.
d Abbreviated physical examination includes at minimum evaluation of vital signs, lung and heart sounds, including evaluation for pericardial rub.
e ECHO is required to be obtained according to the central core lab parameters and then read locally and submitted to the central core lab for separate review and analysis.
f Both a documented CRP $\geq$ 1.0 mg/dL AND a pericarditis pain level of $\geq$ 4 is required 7 days prior to and including the Run-In Baseline visit. These are not required to occur on the same day.
g Subjects missing $\geq$ 4 daily pain measurements during the 7 days prior to and including the Randomization Withdrawal baseline visit will be unable to proceed to randomization due to lack of data required for treatment response evaluation.
h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
i Applicable to 24-hour post dose PK sub-study participants only.
j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.
k Pharmacogenomics informed consent and subsequent sampling can be performed at any time in the study however, it is preferable to have this completed at the beginning of the study.
l Adverse event reporting begins following the subject providing informed consent.
m All procedures are to be completed prior to study drug administration.

n The first dose of study drug is a loading dose. Adult subjects receive 2 SC doses 160 mg (total 320 mg); pediatric subjects (subjects ≥12 and <18 years of age) receive 2 SC doses of 2 x 2.2 mg/kg.
o Study drug administration is once weekly with a minimum of 5 days required between doses.
p Randomization and subsequent study drug dispensing to occur after confirmation of Clinical Response (see definition of Clinical Response in Section 6.2.2).
q The Randomization visit serves as both the RI Week 12 visit and the RW baseline visit.
s PK and ADA samples will be collected prior to study drug administration. PK at enrollment/baseline will be taken from ADA

Table 5: Study Schedule of Activities – Randomized Withdrawal

Trial Period	**RANDOMIZED WITHDRAWAL (event-driven)[m]**								
									END OF RANDOMIZED WITHDRAWAL (EORW)[t]
Visit Name	**RW Week 4**	**RW Week 8**	**RW Week 12**	**RW Week 16**	**RW Week 20**	**RW Week 24**	**RW Every 8 Weeks**	**RW Every 8 Weeks**	**Per Announced End Date[u]/ LTE-Baseline**
Visit Window[b] (days)	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 7**
Visit Type	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**Clinic**
Informed Consent Form									X
Concomitant medications	X	X	X	X	X	X	X	X	X
Pericarditis Concomitant medications	X	X	X	X	X	X	X	X	X
Full Physical Examination[c]						X			X
Abbreviated Physical Examination[d]									
Body weight and height		X		X		X		X	X
12-Lead ECG						X			X
Echo[e]						X[e]			X[e]
MRI (substudy only)						X			
Pericardial pain (11-point NRS)	DAILY								
EQ-5D						X			X
SF-36						X			X
ISI						X			X
PGIPS		X		X		X		X	X
PGA-PA		X		X		X		X	X
Hematology, Chemistry Labs (Central)		X				X		X	X
Lipid Panel (Central)[h]						X			X
CRP (Local)									

Trial Period	**RANDOMIZED WITHDRAWAL (event-driven)[m]**								
									END OF RANDOMIZED WITHDRAWAL (EORW)[t]
Visit Name	**RW Week 4**	**RW Week 8**	**RW Week 12**	**RW Week 16**	**RW Week 20**	**RW Week 24**	**RW Every 8 Weeks**	**RW Every 8 Weeks**	**Per Announced End Date[u]/ LTE-Baseline**
Visit Window[b] (days)	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 7**
Visit Type	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**Clinic**
CRP(Central	X	X	X	X	X	X	X	X	X
PK (Central)		X				X			X
ADA (Central)						X			X
Biomarkers (Central)		X				X			
Urine Pregnancy[j] (Local or Central)									X
Urinalysis									X
IWRS Subject Status Update									X
IWRS Weight Input (pediatric only)		X		X		X		X	X
IWRS Drug Dispensing		X		X		X		X	X[v]
In Clinic Study Drug Administration[o]		X		X		X		X	X[v]
Outpatient Study Drug Administration[o]	X	WEEKLY							
Study Drug Compliance Review	X	X	X	X	X	X	X	X	X
Assessment of Pericarditis Recurrence	X	X	X	X	X	X	X	X	X
Adverse Event Reporting[l]	X	X	X	X	X	X	X	X	X

b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.

c Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement.

d Abbreviated physical examination includes at minimum evaluation of vital signs, lung and heart sounds, including evaluation for pericardial rub.
e ECHO is required to be obtained according to the central core lab parameters and then read locally and submitted to the central core lab for separate review and analysis.
h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.
l Adverse event reporting begins following the subject providing informed consent.
m All procedures are to be completed prior to study drug administration.
o Study drug administration is once weekly with a minimum of 5 days required between doses.
s PK and ADA samples will be collected prior to study drug administration. PK at enrollment/baseline will be taken from ADA. As required, ADA samples will be collected at EOS, ET, and Unscheduled visits.
t The EORW visit serves as both the last visit of the RW period and the baseline visit of the LTE period.
u For all subjects, the final clinic visit of the end of RW period is to be scheduled once the End of the Randomization Withdrawal end date is announced by Sponsor. This includes subjects that are taking blinded study drug, open-label rilonacept, or who have prematurely discontinued study drug.
v Study drug administration to occur only after subject provides informed consent for the open-label extension period.

Table 6: Study Schedule of Activities – Long Term Extension

Trial Period	**LONG TERM EXTENSION (up to 24 months)**			
	Long Term Extension Treatment (up to 24 Months)[m]			
Visit Name	**LTE Week 12**	**LTE Week 24**	**LTE Every 12 Weeks**	**LTE 18-month Assessment**
Visit Window[b] (days)	**+/- 2**	**+/- 2**	**+/- 2**	**18 months from most recent recurrence**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Concomitant medications	X	X	X	X
Pericarditis Concomitant medications	X	X	X	X
Full Physical Examination[c]		X		X
12-Lead ECG		X		X
Echo[e]		X		X
MRI		X[z]		X[z]
EQ-5D		X		
SF-36		X		
ISI		X		
PGIPS	X	X	X	
PGA-PA	X	X	X	
Hematology, Chemistry Labs (Central)	X	X	X	
Lipid Panel (Central)[h]		X		
CRP (Central)	X	X	X	X
PK (Central)		X		X
ADA (Central)		X		
Biomarkers (Central)		X		
Urine Pregnancy[j] (Local or Central)		X		X
Urinalysis		X		
IWRS Subject Status Update		X		X
IWRS Weight Input (pediatric only)	X		X	X
IWRS Drug Dispensing	X	X	X	X
In Clinic Study Drug Administration[o]	X	X	X	
Outpatient Study Drug Administration[o]	WEEKLY			
Study Drug Compliance Review	X	X	X	X
Assessment of Pericarditis Recurrence	X	X	X	X
Adverse Event Reporting[l]	X	X	X	X

a The screening and enrollment visit can be combined.

b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.
c Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement.
e ECHO is required to be obtained according to the central core lab parameters and then read locally and submitted to the central core lab for separate review and analysis.
h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.
l Adverse event reporting begins following the subject providing informed consent.
m All procedures are to be completed prior to study drug administration.
o Study drug administration is once weekly with a minimum of 5 days required between doses.
z The MRI to occur only if the previous MRI was done longer than 6 months ago.

Table 7: Study Schedule of Activities – Supplemental Visits

Visit Name	**PERICARDITIS RECURRENCE ASSESSMENT**	**END of TREATMENT (EOT)[x]**	**SAFETY FOLLOW UP (SFU)[y] (6 weeks post last dose)**
Visit Window[b] (days)	**N/A**	**N/A**	**+/- 2**
Visit Type	**Clinic**	**Clinic**	**Clinic or TC/RN**
Concomitant medications	X	X	X
Pericarditis Concomitant medications	X	X	X
Full Physical Examination[c]		X	
Abbreviated Physical Examination[d]	X		
Body weight and height	X		
12-Lead ECG	X	X	
Echo[e]	X[e]	X	
MRI (substudy only)		X[z]	
Pericardial pain (11-point NRS)	X	X	
EQ-5D	X	X	
SF-36	X	X	
ISI	X	X	
PGIPS	X	X	
PGA-PA	X	X	
Hematology, Chemistry Labs (Central)		X	
Lipid Panel (Central)[h]		X	
CRP (Local)	X		
CRP(Central	X	X	
PK (Central)	X	X	X
ADA (Central)	X	X	X
Biomarkers (Central)	X	X	
Urine Pregnancy[j] (Local or Central)			X
Urinalysis		X	
IWRS Subject Status Update	X[s]	X	
IWRS Weight Input (pediatric only)	X		
IWRS Drug Dispensing	X		

Visit Name	**PERICARDITIS RECURRENCE ASSESSMENT**	**END of TREATMENT (EOT)[x]**	**SAFETY FOLLOW UP (SFU)[y] (6 weeks post last dose)**
Visit Window[b] (days)	**N/A**	**N/A**	**+/- 2**
Visit Type	**Clinic**	**Clinic**	**Clinic or TC/RN**
Study Drug Compliance Review	X	X	
Assessment of Pericarditis Recurrence	X	X	X
Adverse Event Reporting[l]	X	X	X

b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.

h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.

j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.

l Adverse event reporting begins following the subject providing informed consent.

s PK at enrollment/baseline will be taken from ADA.

x An EOT visit is to be conducted throughout the course of the study when a subject permanently discontinues study drug.

y An SFU is required to be conducted within 6 weeks of the last dose of rilonacept at any time throughout the course of the study including the RI period, the RW period, and the LTE period.

z The MRI to occur only if the previous MRI was done longer than 6 months ago.

13.2. Missing Data Imputation Rules

Partial missing dates will be imputed for start/stop dates of AE and prior/concomitant medications, as well as start date of each pericarditis episode according to the rules below.

Table 8: Imputation Rules for Partial Missing Dates

Category	Scenario	Rule for missing dates
General rule	All	If year is missing, do not impute, unless otherwise specified
AE and prior/concomitant medication start date	Day is missing and (month, year) same as the first dose date	The day will be imputed as the same day of the first dose day or stop date, whichever is earlier.
	Day is missing and (month, year) not the same as the first dose date	The day will be imputed as the first day of the month or stop date, whichever is earlier.
	Month and day missing, year the same as the first dose date	Date will be imputed with the first dose date or stop date, whichever is earlier.
	Month and day missing, year different from the first dose date	Impute with the first day of the year.
AE and prior/concomitant medication end date	Day is missing	Impute with min(last day of the month, data cutoff, end of study date)
	Day and month are missing	Impute with min(last day of the year, data cutoff, end of study date)
	Entirely missing	Impute with min(data cutoff, end of study date)
First pericarditis episode start date	Day missing	Use first day of the month
	Month missing	Use January 01
Second or later pericarditis episode start date	Day missing	Use max(first day of the month, stop day of previous episode +1)
	Month missing	January 01
Other	Non-specific	For missing data handling rules not covered in this table, they will be defined in the ADaM Define file.

13.3. EQ-5D-5L Scoring

The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score.

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents. The EQ VAS asks respondents to simply 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below'.

The EQ-5D-5L Crosswalk Index Value Calculator can be found using the following link: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

13.4. Calculation of 95% CI for Incidence Rate per 100 Subject-Years of Exposure/Observation

We first construct a formula to calculate the exact 100(1-α)% 2-sided CI for the number of events in a time interval. When this formula is applied to the number of events in a time interval of 100 subject-years in a study, we obtain the desired result to construct Fisher's exact 2-sided 100(1-α)% confidence interval for an incidence rate of interest per 100 subject-years. When $\alpha = 0.05$, it provides a 95% CI.

The number of events of interest in a time interval can be modelled using a Poisson distribution with parameter λ, where λ is the average number of events in this time interval. The probability of observing k events in this time interval is:

$P(k \text{ events in interval}) = e^{-\lambda}\frac{\lambda^k}{k!}$

If k events were observed in the interval, the lower bound l and upper bound u of the 100(1-α)% CI must satisfy the following conditions for Fisher's exact CI:

$$\text{Lower bound: } \sum_{x=0}^{k} \frac{e^{-l_l} x}{x!} = 1 - \alpha/2$$

Upper bound: $\sum_{x=0}^{k} \frac{e^{-u}u^{x}}{x!} = 1 - \alpha/2$

The parameter λ can be estimated with *k.* Using the relationship between the cumulative distribution functions of the Poisson and chi-squared distributions, the above lower and upper bounds can be expressed as follows:

$$\frac{1}{2}x^2(\frac{\alpha}{2}; 2k) \leq \lambda \leq \frac{1}{2}x^2(1 - \frac{\alpha}{2}; 2k + 2), \qquad (1)$$

where $x^2(a; v)$ is the chi-square quantile for lower tail probability with *v* degrees of freedom.

The inequalities in (1) are used in the SAS macro below to construct the confidence interval for the number of events. The lower bound, number of events, and upper bound are divided by the total treatment exposure expressed as subject-year to construct the incidence rate and its CI. Each number is then multiplied by 100 to obtain the incidence rate per 100 subject-years.

SAS Macro for the 95% CI of incidence rate per 100 subject-years

```
%macro nppy(x=5, n=100, alpha=0.05);
 ***     x=5 --# of events;
 ***  n = # of subject-years.;
 ***  alpha=2-sided type-I error rate, alpha=0.05 for 95% CI.;


data temp;
 x=&x;
 n=&n;
 alpha=&alpha;
 length CI_coverage $12.;
 CI_coverage=compress(round(100*(1-&alpha), 0.1))||'%';
 r=round((x/n)*100, 0.001);
if x=0 then Lower  bound=0;
 else Lower_bound = round((quantile('CHISQ',&alpha/2,2*&x)/2/n)*100, 0.001);
  Upper_bound = round((quantile('CHISQ',1-&alpha/2,2*(x+1))/2/n)*100, 0.001);
          label x='# of events'
                                    n='# subject years'
                                    r='# of events per 100 subject-years'
                                    alpha='2-sided alpha';
call symput('ci', compress(ci_coverage));
proc print data=temp label noobs;
  title1 "&CI confidence interval for # of events per 100 subject-years";
          title2 '--Exact method using the relationship between Poisson and Chi Square
distributions';
run;
%mend;

*%nppy(x=14, n=400, alpha=0.05);
```

Signature Page for RIM-CLIN-000261 v1.0

Approval	[redacted] 01-Apr-2020 21:06:50 GMT+0000

Approval	[redacted] 01-Apr-2020 21:07:38 GMT+0000

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STATISTICAL ANALYSIS PLAN

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPENLABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – Rilonacept inHibition of interleukin-1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes stuDY (RHAPSODY)

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Study Drug:	Rilonacept (KPL-914)
Protocol Number:	KPL-914-C002
Date of Issue:	16 JUN 2020
Version:	2.0

History of Changes

This document is prepared based on the following protocol version:

Version Number	Version Date	Description
3.0	10 MAR 2020	Protocol Amendment #2 (Version 3.0)

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	02 APR 2020	Original draft SAP submitted to FDA
2.0	16 JUN 2020	SAP Signed off version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
CEC	Clinical Endpoint Committee
CMH	Cochran–Mantel–Haenszel
CRO	Contract Research Organization
CRP	C-reactive protein
CS	corticosteroids
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiography; echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EORW	End of Randomized Withdrawal (visit)

Abbreviation	Definition
EOT	End of Treatment (visit)
EQ-5D-5L	5-level EuroQoL-5D
ESR	erythrocyte sedimentation rate
FDA	US Food and Drug Administration
GI	gastrointestinal
HDL	High density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ISI	Insomnia Severity Index
ISR	injection site reaction
ITT	intent to treat
IV	intravenous(ly)
IWRS	interactive web response system
KM	Kaplan-Meier
KPL-914	rilonacept
LDL	Low density lipoprotein
LTE	Long Term Extension Treatment Period
MedDRA	Medical Dictionary for Regulatory Activities
cMRI	cardiac magnetic resonance imaging
MRI	magnetic resonance imaging
NMSC	Non Melanoma Skin Cancer
NSAID	nonsteroidal anti-inflammatory drug
NRS	Numerical Rating Scale
ORT	Oral Rescue Therapy
PGA-PA	Physician Global Assessment of Pericarditis Activity

Abbreviation	Definition
PGIPS	Patient Global Impression of Pericarditis Severity
PK	pharmacokinetic(s)
POC	point of care
RE	Role participation with emotional health problems in SF-6D
RI	Run-In (period)
RP	Role participation with physical health problems in SF-6D
RW	Randomized Withdrawal (period)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	subcutaneous(ly)
SF-36	36-Item Short Form Health Survey
SFU	safety follow up
SOC	standard of care
TEAE	Treatment emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

1. STUDY OBJECTIVES

1.1. Study Objectives

1.1.1. Primary Objective

The primary objective of this study is to assess the efficacy of rilonacept treatment in subjects with recurrent pericarditis.

1.1.2. Secondary Objectives

The secondary objective of this study is to assess the safety of rilonacept treatment in subjects with recurrent pericarditis.

2. STUDY DESIGN

2.1. Design Overview

This study has the following periods:

- **Screening period**, during which assessment of disease characteristics, baseline therapy, and the pretreatment workup is completed (up to 4 weeks).
- **Single-blind Run-In (RI) period** (12 weeks), during which blinded rilonacept is administered subcutaneously (SC) once weekly in all subjects after the loading dose of double injections. The RI period includes the following:
  - 1-week Stabilization period, during which blinded rilonacept is administered in addition to standard of care (SOC) pericarditis therapy and the ongoing pericarditis episode is treated.
  - 9-week Weaning period, during which subjects are weaned off background SOC pericarditis therapy, as applicable, while treatment with blinded rilonacept continues.
  - 2-week Monotherapy period during which subjects who have successfully weaned off background SOC pericarditis therapy will continue to receive blinded rilonacept.

In the single blind RI period (subjects are blinded regarding the time of transition from the single- blind to the double- blind- period), adult subjects ≥18 years old will receive rilonacept as an initial loading dose of 320 mg (2 SC injections of 160 mg each) at the RI baseline visit (2 × 2 mL), followed by a 160 mg (2 ml) SC dose once weekly throughout the RI period. Pediatric subjects ((≥12 and <18 years old) will receive an initial loading dose of rilonacept 4.4 mg/kg (2 SC injections of 2.2 mg/kg each) at the RI baseline visit (maximum 2 × 2 mL), and then 2.2 mg/kg (maximum 2 mL) SC once weekly throughout RI period.

Subjects who achieve clinical response at RI Week 12 defined as stopping background pericarditis therapy no later than Week 10 and weekly average of daily pericarditis pain score ≤2.0 on the 11-point Numerical Rating Scale (NRS) within the 7 days prior to and including the day of randomization on RI Week 12/Randomization Withdrawal (RW) baseline and a C-reactive protein (CRP) level ≤0.5 mg/dL at the RI Week 12/RW baseline visit, will proceed into the double-blind placebo-controlled RW period.

Subjects who do not achieve clinical response at RI Week 12/RW baseline on rilonacept monotherapy will be discontinued from study drug, transitioned to SOC pericarditis therapy at the Investigator's discretion and followed through the end of the RW period.

Additionally, after the randomized withdrawal period has been closed when at least 22 confirmed recurrent pericarditis events have been accrued, subjects who have not yet completed the full 12 weeks of RI period at that time will be allowed to continue tapering of concomitant meds in the RI period; those subjects who achieved clinical response by Week 12 will be given the option to receive open-label rilonacept in the Long-term Extension Treatment period (LTE) without having to proceed through the RW period.

- **Double-blind placebo-controlled RW period** (pericarditis recurrence event-driven duration), during which subjects who were able to stop background SOC pericarditis therapy and who achieve clinical response at RI Week 12/RW baseline are randomized in a double-blind manner at a 1:1 ratio to the following:
  - Rilonacept 160 mg (2.2 mg/kg in pediatric subjects) SC injections once weekly
  - Matching placebo SC injections once weekly

Pericarditis Recurrence in the RW Period

Pericarditis recurrence is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis. Upon pericarditis recurrence, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11point NRS and have 1 CRP value ≥1 mg/dL (either on the same day or separated by no more than 7 days) will receive bailout rilonacept (2 open-label injections of 160 mg rilonacept [or 4.4 mg/kg for pediatric subjects] followed by once weekly open-label rilonacept SC injections of 160 mg [or 2.2 mg/kg for pediatric subjects]) irrespective of randomized treatment assignment and as soon as at least 5 days have passed since the last study drug injection. Sequential oral rescue therapy (ORT), i.e., analgesics first, then NSAIDs, and then colchicine, can be added if needed at the discretion of the Investigator, as outlined in the protocol and Pharmacy Manual.

Subjects with pericarditis recurrence and who do not meet the protocol criteria for bailout rilonacept will continue blinded study drug until the protocol criteria for bailout rilonacept are met or through the end of the RW period. For those subjects, sequential ORT can be added to blinded study drug at the discretion of the Investigator, as outlined in the protocol and Pharmacy Manual.

All suspected pericarditis recurrence events in the RW period will be formally adjudicated by the Clinical Endpoint Committee (CEC), and only events that are confirmed by the CEC as pericarditis recurrences will be used in the Primary Endpoint analysis.

- **Long-term Extension Treatment period (LTE)** (variable, up to 24 months), during which all subjects in the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) and subjects who are in the Run-In period after closure of the RW period, will have an option to receive up to 24 months of open-label rilonacept 160 mg (or 2.2 mg/kg for pediatric subjects) SC injections once weekly based on their clinical status and at the discretion of the Investigator, after signing LTE informed consent.

  Subjects will be reviewed at 18 months after their most recent recurrence, (i.e., the qualifying episode for their original study enrollment prior to enrolling in the RI

period or a recurrence in RW which was treated with bailout rilonacept, whichever is the later). During this month's visit, the Investigator and subject will decide whether to continue treatment with open-label rilonacept, to continue in the study off-treatment for observation and rilonacept bailout upon subsequent recurrence, or discontinuation from the LTE. This review may be supplemented by:

- cMRI and/or echocardiogram and/or additional diagnostic testing as determined by the Investigator.
- subjects may be unblinded at that time (if available) at the request of the Investigator per procedures outlined in the Unblinding Plan to assist in clinical decision-making.

Safety data will be reviewed throughout the LTE by the Data Monitoring Committee.

2.2. Schedule of Assessments

The schedule of assessments is in Section 13.1.

2.3. Sample Size Calculation and Randomization

2.3.1. Sample Size Calculation

Sample size calculation is based on the primary endpoint, time to pericarditis recurrence defined as the time from randomization to the date of the first pericarditis recurrence for each subject. Time to pericarditis recurrence is assumed to follow an exponential distribution. An event of interest is defined as a subject's first adjudicated recurrence of pericarditis. The following assumptions are used in the sample size calculation using EAST 6.4.1:

- 1-sided significance level: 2.5%
- Power: 90%
- Median time to event (in weeks) in placebo: 8
- Hazard ratio (rilonacept/placebo): 0.244
- Percentage of subjects in the RI period that will not reach RW: 10%.

Given these assumptions, a total of 22 adjudicated pericarditis recurrence events is required to achieve the power. About 25 subjects per arm (a total of 50 subjects) or more will be randomized. Considering 10% of subjects in the RI period that will not reach the RW period, approximately 56 subjects will be enrolled in this study.

Subject enrollment and the pericarditis recurrence event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion during the RW period. If the number of subjects randomized is less than 50 and/or the time anticipated for the number of events required for the analysis of primary efficacy endpoint significantly exceeds the projected timeline, additional subjects may be enrolled and/or randomized at Kiniksa Pharmaceutical's discretion. However, at this time it is anticipated that no more than 100 subjects will be enrolled into this study.

2.3.2. Randomization

Subjects who achieve clinical response at RI Week 12 (Section 2.1) will proceed into the double-blind placebo controlled RW period. An interactive web response system (IWRS) will be used to administer the randomization schedule. CRO Biostatistics will generate the

randomization schedule using SAS® software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for the IWRS, which will link sequential subject randomization numbers to treatment codes. The randomization schedule will be stratified by 2 factors:

- Oral CS use at baseline (RI baseline, i.e., beginning of RI period): yes or no
- Diagnosis of recurrent idiopathic pericarditis (RI baseline): yes or no

2.4. Timing of Analysis

The data cutoff for the primary analysis will be the end of RW period. When at least 22 adjudicated pericarditis recurrence events have occurred, end of RW period will be announced. The sites will have their subjects return to the site for the end-of-RW assessment (EORW). Data cutoff will occur after all subjects have completed this assessment. All data for this cutoff will be used in the primary analysis for efficacy and safety.

After the RW period, there will be a Long-term Extension Treatment period. An analysis will also be conducted after the end of the study. Since the data cutoff for the primary analysis will be done by the end of RW period, summary for LTE period will not be included in the primary analysis.

No interim analysis for claiming efficacy is planned. Interim safety review will be conducted by a Data Monitoring Committee (DMC). The analysis will be performed by a designated CRO. Details are in DMC charter and DMC Statistical Analysis Plan (SAP).

2.5. Responsibilities

The statistical analysis for the study will be performed by Kiniksa Biostatistics or its designated CROs.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. General Methods

Statistical analysis will be performed using SAS® software Version 9.4 or later. Continuous variables will be summarized using the mean, the standard deviation, median, minimum value, and maximum value. Time-to-event variables will be summarized using percent censored, event rate, and 25^{th}, 50^{th}, and 75^{th} percentiles with 95% CI, if estimable. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

At RI, RW, and LTE periods, baseline will be the last value before the first dose of study drug within each individual period unless otherwise specified. For change-over-time endpoints in the RW period, by-visit analysis will be performed at each scheduled visit for at least 24 weeks.

When weekly average of NRS is used, it will be calculated based on every 7 days starting on the day after the first injection in each period. If there are missing values during the 7- day period, the average will be calculated based on the non-missing values. If 50% or more values (≥4 days) are missing, the average value will be set to missing.

By-visit analyses will be based on nominal visits and observed data, with unscheduled visits excluded.

3.2. Stratified Analysis

There are two stratification variables for randomization: oral CS use at baseline (yes or no), and diagnosis of recurrent idiopathic pericarditis at RI baseline (yes or no). When an analysis is to be stratified by these variables and a stratum has ≤5 events of interest in a log-rank test or the same response in all subjects in a CMH test, the strata for diagnosis of recurrent idiopathic pericarditis will be pooled. If the same situation still exists, the analysis will be done without stratification.

3.3. Testing Hypotheses and Multiplicity Adjustment

All statistical tests for the treatment comparison of efficacy endpoints in the RW period will be based on a 1-sided α=0.025. For each endpoint, the null hypothesis is that the effects of rilonacept and placebo are the same. The alternative hypothesis is that rilonacept is better than the placebo.

In order to control the overall 1-sided type I error rate at the 0.025 level, a gatekeeping procedure in combination with Hochberg's procedure will be applied to testing the primary and major secondary endpoints. If the 1-sided p-value for testing the primary endpoint is ≤0.025, a significant treatment effect on the primary endpoint will be claimed.

Section 5.2.2.1 provides the order of major secondary endpoints. If the primary endpoint is significant, the first major secondary endpoint, i.e., proportion of subjects who maintained clinical response at Week 16 of RW period will be tested at 1-sided α=0.025. A significant treatment effect on this major secondary endpoint will be claimed if the 1-sided p-value is ≤0.025. If the treatment effect is not significant on the primary endpoint, significance on this major secondary endpoint cannot be claimed regardless of the result.

If both primary and first major secondary endpoints are significant following the above procedure, the second and third major secondary endpoints defined in Section 5.2.2.1 will be tested with Hochberg's procedure at overall 1-sided α=0.025. If both 1-sided unadjusted p-values are ≤0.025, claim significance of rilonacept for both endpoints. If the larger 1-sided p-value is >0.025, compare the smaller 1-sided p-value with 0.0125. If the smaller 1-sided p-value is ≤0.0125, claim significance of rilonacept on this endpoint.

3.4. Subgroups to be Analyzed

Subgroup analyses for the primary efficacy endpoint will be performed by the following variables for the RW period:

- Oral CS use at baseline (RI baseline, i.e., beginning of RI period): yes or no
- Diagnosis of recurrent idiopathic pericarditis (RI baseline): yes or no
- Age group: 12 - <18, 18 - <65, and 65 – (maximum age in ITT analysis set) [Analysis for the pediatric group (12- <18) may not be performed if the sample size is too small.]
- Gender: males vs. females
- Race: Caucasian vs. non-Caucasian
- Region: USA vs. non-USA
- Number of pericarditis episodes at enrollment (including index and qualifying episodes): <5 vs. ≥5

- ADA status: ADA positive at any assessment, ADA positive with neutralizing antibody at any assessment, and ADA negative at every assessment.

P-values and summary statistics will be generated following Section 5.2, with the understanding that the sample size is likely too small to have an adequate power. The forest plot with 95% CI will be provided for the primary efficacy endpoint.

3.5. Handling of Missing Data

To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study. Unless otherwise specified, missing data will not be imputed and only the observed data will be used in the analyses.

Additional rules for missing data imputation are provided in Section 13.2.

4. ANALYSIS SETS

4.1. Intent-to-Treat (ITT) Analysis Set

All subjects who are randomized in the RW period will be included in the Intent-to-Treat (ITT) analysis set. The primary analysis for efficacy endpoints in the RW period will be based on the ITT analysis set unless otherwise specified. Treatment comparisons for all analyses will be based on each subject's treatment assignment from randomization.

The following analysis sets are defined for the analysis of secondary endpoints:

- ITT Week 24 analysis set: All subjects randomized at least 24 weeks before data cutoff will be included. This analysis set will be used for secondary efficacy endpoints measured at week 24 in the RW period.
- ITT Week 16 analysis set: All subjects randomized at least 16 weeks before data cutoff will be included. This analysis set will be used for secondary efficacy endpoints measured at week 16 in the RW period.
- ITT Week 8 analysis set: All subjects randomized at least 8 weeks before data cutoff will be included. This analysis set will be used for secondary efficacy endpoints measured at week 8 in the RW period.

4.2. Safety Analysis Set (SS)

All subjects who take at least 1 dose of study drug in the RI period will be included in the Safety Analysis set (SS). Safety analyses will be based on the actual treatment a subject received.

4.3. Run-in Analysis Set (RIS)

All subjects who received at least 1 dose of study drug in the RI period will be included in the RI analysis set (RIS).

4.4. Long Term Extension Analysis Set (LTES)

All subjects who received at least 1 dose of study drug in the LTE will be included in the Long-term Extension Analysis set (LTES).

4.5. Per Protocol (PP) Analysis Set

The Per Protocol Analysis set (PP) is a subset of the ITT analysis set with the exclusion of subjects with important protocol violations or violations that may potentially bias statistical analyses or the ethical conduct of the study. The criteria of these violations will be determined prior to unblinding. This analysis set may be used for sensitivity analyses for efficacy endpoints in the RW period.

4.6. Pharmacokinetics Analysis Set

The Pharmacokinetic (PK) Analysis set includes subjects who receive at least 1 dose of study drug and have at least 1 post-baseline PK sample. The PK analysis set will be used for all PK analyses.

4.7. Verification of Analysis Sets

A blinded review to verify all defined analysis sets excluding LTES will be conducted before database lock of primary analysis. The results will be documented. The document will list subjects excluded from each analysis set with reason(s).

5. STATISTICAL METHODOLOGY

5.1. Population Characteristics

5.1.1. Study Subjects Disposition

Subject disposition will be summarized as follows.

- RI period
  - Screened Subjects (Signed Informed Consent)
    - Enrolled
    - Subjects treated in RI period
    - Subjects completed RI treatment
    - Subjects with early treatment discontinuation and reasons for treatment termination
    - Subjects with treatment ongoing at end of RI period
- RW Period
  - Number of subjects randomized, by arm
    - Subjects treated in RW period
    - Subjects who completed RW period
    - Subjects who discontinued study drug before end of RW period with reason of discontinuation
    - Subjects with treatment ongoing at end of RW period
- Number of subjects who consented to the LTE period
- LTE
  - Subjects who completed the Treatment Period

  - Subjects who discontinued study drug with reasons for treatment discontinuation
- Study disposition
  - Subjects who completed
  - Subjects who terminated early and reasons for early termination
  - Subjects with study ongoing at data cutoff

5.1.2. Baseline Demographic

Frequency counts (n) and percentages (%) will be presented for sex, race, ethnicity, and age group (i.e., 12-17 years, 18-64 years, and 65 years to the maximum age in the ITT analysis set). Descriptive statistics such as number of subjects (n), mean, standard deviation, median, minimum and maximum will be presented for age (years), weight (kg), Height (cm), and body mass index (BMI) kg/m^2.

5.1.3. Baseline Disease Characteristics

Baseline disease characteristics include the following:

- Oral corticosteroid use at RI Baseline (yes/no)
- Diagnosis of recurrent idiopathic pericarditis at RI (yes/no)
- Type of recurrent Pericarditis
  - Idiopathic
  - Pericardiotomy syndrome
  - Dressler's syndrome
  - Still's disease
  - Other
- Duration of disease from first episode to the date of inform consent
- Total number of pericarditis episodes, total number of episodes in the past year until first injection in the RI period, and annualized number of episodes per year,
- Time since beginning of qualifying episode in days
- Baseline central CRP value and weekly pain NRS score
- Baseline pericardial rub, effusion, tamponade, electrocardiogram (ECG) findings (widespread ST-elevation and PR-Depression), ECG interpretation
- Pericarditis treatment at baseline
  - Analgesics
    - Non-opioid analgesics
    - Opioid analgesics
  - Nonsteroidal anti-inflammatory drug (NSAIDs)
    - Aspirin

  - Other NSAIDs
- Colchicine
- Corticosteroids
  - Oral corticosteroids
  - IM/IV corticosteroids
- Other

Disease characteristics for the qualifying episode, including the following:

- Number and proportion of subjects with presence of pericarditis pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, new or worsening in pericardial effusion, and pericardial inflammation on magnetic resonance imaging (MRI).
- Values of pain level, CRP (mg/dL), fever (Celsius), white blood cell (WBC; 10^3/uL), and erythrocyte sedimentation rate (ESR) (mm/hr).
- Treatment for the qualifying episode
  - Analgesics
    - Non-opioid analgesics
    - Opioid analgesics
  - Nonsteroidal anti-inflammatory drug (NSAIDs)
    - Aspirin
    - Other NSAIDs
  - Colchicine
  - Corticosteroids
    - Oral corticosteroids
    - IM/IV corticosteroids
  - Other

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using n, mean, median, standard deviation, and range (minimum, maximum). Summaries will be presented for the RI, RW, and LTE periods.

Baseline disease characteristics will also be summarized for subjects who are on corticosteroid at RI baseline. In addition to those specified above, the following baseline data will be summarized:

- Duration (in weeks) of using oral corticosteroid prior to enrollment
- Average dose (mg/day) of oral corticosteroid prior to enrollment
- Cumulative dose (mg) of oral corticosteroid prior to enrollment

5.1.4. Medical/Surgical History

Medical/Surgical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA; v21.1) 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 electronic case report form (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.

5.1.5. 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 treatment period which is from the date of first dose to the date of last dose plus 6 weeks.

Additionally, the medications will be considered concomitant if the start date of the medication is missing.

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 coded using World Health Organization (WHO) Drug (version March 2018). Medications will be summarized by ATC level 2 code and preferred term. Summary will be done by periods (i.e., RI, RW, and LTE) and by treatment (KPL-914 vs placebo) for RW period. One subject will be counted once within one preferred term and one ATC class. The medication information will be presented in a by-subject listing with ATC class (level 2) and WHO Drug Dictionary preferred term, start and stop date, dosage, route, frequency and indication.

Concomitant pericarditis treatment will be summarized by period and by treatment for RW period using the following categories:

- Analgesics
  - Non-opioid analgesics
  - Opioid analgesics
- Nonsteroidal anti-inflammatory drug (NSAIDs)
  - Aspirin
  - Other NSAIDs
- Colchicine
- Corticosteroids
  - Oral corticosteroids
  - IM/IV corticosteroids
- Other

In addition, concomitant pericarditis treatment received during the RW treatment period will also be summarized based on the status of receiving bailout treatment (i.e. concomitant

medication received before start of bailout treatment vs after start bailout treatment) for each treatment group in the RW period.

For RI period, use of concomitant pericarditis treatment (i.e., background treatment) will be summarized over time.

5.1.6. Study Drug Administration

The study medication 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 for each of the treatment periods: RI, RW, LTE, and Study Overall.

- Treatment duration in weeks:
  - For RI period, it is defined as [minimum of (date of last study drug +6, date of RI week 12 visit – 1, date of data cutoff) - date of first study drug + 1)/7].
  - For RW period it is defined as [minimum of (date of last study drug +6, date of end of RW visit) - date of first study drug + 1)/7].
  - For LTE and study overall, it is defined as [minimum of (date of last study drug +6, end of study date, date of data cutoff) - date of first study drug + 1)/7.

Number of administrations in each period regardless of full amount or partial amount of syringe injected. The loading dose includes two injections and will be counted as one administration.

Compliance (%) in each period, calculated as (number of administrations) / (protocol planned number of administrations) ×100%. The loading dose includes 2 injections and will be counted as one administration.

Total rilonacept dose administered in each period, defined as the sum of all doses (mg) received in the corresponding period. The actual volume administered will be used to calculate the total dose. For subjects receiving weight-adjusted dose (e.g., 2.2 mg/kg) their weight collected at scheduled visits will be used to calculate the amount of the study drug received.

Percentage of self-administrations by the subject, defined as [Number of self-administrations] / [Total number of administrations received] × 100%. The loading dose will be included in the denominator as one administration. If one of 2 injections in the loading dose is self-administered, it will be counted in the numerator.

5.1.7. Protocol Deviations

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

A blinded review before database lock will be conducted to determine important protocol deviations. Protocol deviations are considered important if based on Sponsor assessment they can impact study integrity or interpretability of study results.

Important protocol deviations will also be evaluated if they have impact on efficacy data. Important protocol deviations with potential impact on efficacy will be used to exclude subjects from PP analysis set.

All protocol deviations will be reviewed and categorized before database lock. All important protocol deviations will be summarized by deviation category (including Inclusion Criteria,

Exclusion Criteria, ICF, Concomitant Medication, and other if applicable). The protocol deviation data will also be presented as a by-subject data listing.

5.2. Efficacy Analysis

5.2.1. Primary Efficacy Endpoint

5.2.1.1. Definition

The primary efficacy endpoint is time to pericarditis recurrence, defined as the time from randomization to the date of the first pericarditis recurrence for each subject. Only CEC-confirmed pericarditis recurrence will be considered as an event for the primary analysis.

Time to pericarditis recurrence is calculated as: Data of Event/Censor – Date of randomization +1.

Pericarditis recurrence is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis. The assessments to be conducted by the investigator is described in protocol Section 6.1.4. At any time during the RW period, subjects who experience a suspected recurrence of pericarditis symptoms will be requested to report to the study site/clinic for a scheduled or unscheduled visit, during which clinical assessments will be performed to gather all the necessary diagnostic data to confirm or rule out the presence of pericarditis recurrence.

Pericarditis recurrence will also be evaluated by the investigators at the following time points:

- Routine assessment (every 4 weeks until week 24 in RW, then every 8 weeks)
- End of RW period
- End of treatment
- Post-treatment safety follow-up
- LTE assessment (every 12 weeks up to 24 months and 18-month visit)

Upon suspected pericarditis recurrence, the event is required to be captured in the electronic data capture (EDC) system within 24 hours of learning of the event, and a pericarditis recurrence event adjudication package must be prepared for adjudication by CEC. Details on endpoint package requirements will be described in the CEC charter. The CEC confirmed pericarditis recurrences will be used for the analysis of primary efficacy endpoint.

The censoring rules in Table 1 will be used in the analysis of the primary efficacy endpoint, in which, the event/censor reason will be provided in a data listing.

Table 1: Censoring Rules for Time to Pericarditis Recurrence in the RW Period

	Scenario*	Event/ Censor	Event/Censor Reason	Date of Event/ Censor
1	Pericarditis recurrence occurred before or without receiving bailout rilonacept, including events after termination of study drug	Event	Recurrence	Date of pericarditis recurrence
2	Pericarditis recurrence occurred after receiving ORT* or corticosteroid	Event	Recurrence after receiving ORT/corticosteroid	Date of pericarditis recurrence
3	Receiving bailout rilonacept before pericarditis recurrence	Event	Recurrence after receiving bailout	Date of pericarditis recurrence
4	No pericarditis recurrence during RW period with or without receiving ORT/corticosteroid	Censored	No pericarditis recurrence	Date of last assessment for pericarditis recurrence on or before data cutoff.

*Excluding subjects receiving ORT/corticosteroid while waiting for at least 5 days since previous administration of study medication before receiving bailout rilonacept or within 5 days prior to recurrence visit.

5.2.1.2. Analysis Methods for the Primary Endpoint

The log rank test will be the primary method for the analysis of time to recurrence based on CEC confirmed events, stratified by the stratification variables for randomization. Analysis based on the ITT analysis set will be used as the primary analysis. Analysis based on the PP analysis set will be considered as a sensitivity analysis.

Time to recurrence will be summarized with the 25^{th}, 50^{th} (median), and 75^{th} percentiles using the Kaplan-Meier (KM) method. The 95% confidence interval (CI) for the percentiles will be calculated using a log-log transformation. The percentage of subjects with pericarditis recurrence and its 95% CI will be calculated at weeks 8, 16, 24, and 36 since randomization, using Greenwood's formula with a log-log transformation.

The hazard ratio for KPL-914 vs. placebo and the corresponding Wald 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate, stratified by randomization strata.

A sensitivity analysis will be performed based on the Investigator's judgement of pericarditis recurrence. A 2×2 table for the concordance/discordance between Investigator's judgement and CEC's adjudication will be generated.

Upon pericarditis recurrence as determined by the investigator, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and have 1 CRP value ≥1 mg/dL (either on the same day or separated by no more than 7 days) will receive bailout rilonacept (2 open-label injections of 160 mg rilonacept [or 4.4 mg/kg for pediatric subjects]) irrespective of randomized treatment assignment and as soon as at least 5 days have passed since the last study drug injection. The subjects transitioning to bailout rilonacept will remain blinded to their randomized treatment assignment.

For subjects who have pericarditis recurrence, the frequency table and listing will be generated for the following treatment prescribed by the Investigator:

- Bailout rilonacept
- Analgesics
- NSAIDS
- Colchicine
- Other.

The following criteria for pericarditis recurrence were provided to CEC to determine pericarditis recurrence:

1. Re-appearance or worsening of typical pericarditis pain (with at least one pain NRS recording ≥4) AND elevated CRP (≥1.0 mg/dL) either on the same day or separated by no more than 7 days

   OR

2. Re-appearance or worsening of typical pericarditis pain (with at least one pain NRS recording ≥4), AND abnormal CRP (>0.5 mg/dL) either on the same day or separated by no more than 7 days AND at least 1 supportive evidence of pericarditis as below

   OR

3. Re-appearance or worsening of typical pericarditis pain (but no NRS scores being ≥4), AND elevated CRP (≥1.0 mg/dL) not attributable to other causes AND at least 1 supportive manifestation of pericarditis as below.

Supportive Evidence (Pericarditis manifestations):

- increased WBC count >upper limit of normal (ULN)
- fever >38°C
- presence of pericardial rub
- ECG changes consistent with pericarditis, i.e., findings of new widespread ST-segment elevation and/ or PR-segment depression
- new or worsened pericardial effusion on echocardiography (ECHO)
- new or worsening pericardial inflammation on MRI or other imaging modality.

The above information will be summarized and/or listed.

5.2.2. Secondary Efficacy Endpoint in the RW Period

This Section defines secondary efficacy endpoints for the RW period. Endpoints for the RI and LTE periods are defined in Section 5.2.3.

5.2.2.1. Definition of Major Secondary Efficacy Endpoints in the RW Period

This section defines 3 major secondary endpoints. These endpoints will be analyzed with the ITT Week 16 analysis set. Handling of missing data due to end of RW period will be discussed in Section 5.2.2.2.

1. Proportion of subjects who maintained clinical response at Week 16 of the RW period. clinical response is defined as a weekly average of daily pericarditis pain on the 11-point NRS ≤2.0 and CRP level ≤0.5 mg/dL, and on monotherapy of randomized study drug at Week 16.

   Subjects who complete 16-week of double-blinded treatment and meet the clinical response criteria at Week 16 will be considered as responders. Subjects who had recurrence, discontinued double-blinded treatment, lost to follow-up, and used bailout rilonacept or rescue medications (ORT or corticosteroid) before Week 16 will be considered as non-responders.

   If either weekly average of NRS or CRP is missing at week-16 assessment, the subject will be considered as a non-responder.

2. Percentage of days with pain NRS ≤2 in the first 16 weeks of the RW period. No or minimal pain is defined as non-missing NRS ≤2.

   The denominator will be 112 (=16x7) for every subject. NRS assessments after treatment termination will be included. NRS assessments while on rescue medications for pericarditis will considered not meeting this criterion. Receiving each administration of bailout rilonacept will disqualify for meeting NRS ≤2 for 7 days. Missing values will be counted as 0 day meeting the criterion.

3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 16 of the RW period.

   Subjects who do not have the assessment due to early termination or other reasons will be considered as not meeting the criterion. Subjects who took rescue medications at the Week 16 assessment or used bailout rilonacept on or before Week 16 will also be considered not meeting the criteria.

5.2.2.2. Analysis Methods for Major Secondary Efficacy Endpoints in the RW Period

These endpoints will be analyzed with the ITT Week 16 analysis set.

1. For the proportion of subjects who maintained Clinical Response at Week 16 of the RW period, the response rate and Clopper–Pearson 95% CI will be obtained for each arm. Difference of response rate (KPL-914 – Placebo) and 95% CI based on normal approximation will be provided. The Cochran–Mantel–Haenszel (CMH) test will be used to test the treatment effect, stratified by the stratification variables for randomization.
2. For the percentage of days with pain NRS ≤2 in the first 16 weeks post randomization, an analysis of covariance will be used for treatment comparison. In addition to treatment arm, the following covariates will be included in this analysis: the stratification variables for randomization, and RI baseline NRS in 2 categories: NRS ≤2 versus NRS >2. LS mean difference and the 95% CI will be provided.
3. For proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 16 of the RW period, the response rate and Clopper–Pearson 95% CI will be obtained for each arm. Difference of response rate (KPL-914 – Placebo) and 95% CI based on normal approximation will be provided. The Cochran–

Mantel–Haenszel (CMH) test will be used to test the treatment effect, stratified by the stratification variables for randomization.

5.2.2.3. Other Secondary Efficacy Endpoints in the RW Period and Statistical Method

All time-to-event endpoints start from the day of randomization. The same censoring rules for the primary endpoint will be applied. Missing values will not be imputed unless otherwise specified. Analysis of secondary endpoints will be based on ITT analysis unless otherwise specified.

1. Proportion of subjects who maintained Clinical Response at Week 24 of the RW period based on ITT Week 24 analysis set

   The same rules and method for the first major secondary endpoint will be applied, except that 16 weeks is replaced with 24 weeks.

2. Proportion of subjects who maintained Clinical Response at Week 8 of the RW period based on based on ITT Week 8 analysis set

   The same rules and method for the first major secondary endpoint will be applied, except that 16 weeks is replaced with 8 weeks.

3. Percentage of days with minimal or no pain in the first 24 weeks post randomization based on ITT Week 24 analysis set

   The same rules and method for the second major secondary endpoint will be applied, except that 16 weeks is replaced with 24 weeks.

4. Percentage of days with minimal or no pain in the first 8 weeks post randomization based on ITT Week 8 analysis set

   The same rules and method for the second major secondary endpoint will be applied, except that 16 weeks is replaced with 8 weeks.

5. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period based on subjects who were randomized at least 24 weeks before data cutoff

   The same rules and method for the third major secondary endpoint will be applied, except that 16 weeks is replaced with 24 weeks.

6. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 8 of the RW period based on subjects who were randomized at least 8 weeks before data cutoff

   The same rules and method for the third major secondary endpoint will be applied, except that 16 weeks is replaced with 8 weeks.

7. Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period

   The proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period in each arm will be estimated using the KM method, as described in the

analysis of the primary endpoint. The same censoring rules will apply. The variance of the difference in proportion between treatment arms will be the sum of the variance in each arm. The p-value and 95% CI will be calculated using a normal approximation.

8. Time to pericarditis pain NRS ≥4

   Use the same method for the primary endpoint.

9. Time to CRP level ≥1 mg/dL. This is for elevation of CRP for causes.

   Use the same method for the primary endpoint. A manual review for any CRP ≥1 mg/dL will be performed to make sure that the CRP increase was caused by pericarditis.

10. Time to pericardial rub

    Use the same method for the primary endpoint. Subjects with pericardial rub at RW baseline will be excluded from the analysis.

11. Time to widespread ST-segment elevation or PR-segment depression on ECG

    Use the same method for the primary endpoint. Subjects with either condition at RW baseline will be excluded.

12. Time to new or worsening pericardial effusion on ECHO

    Use the same method for the primary endpoint. Proportion of subjects with new or worsening in pericardial effusion on ECHO and its 95% CI in each arm will be estimated using the K-M method.

13. Change in category of ECHO pericardial effusion size at week 24 and end of RW based on central labs

    - The ITT Week 24 analysis set will be used for this endpoint. Effusion size in ECHO has the following categories:
    - None or Trivial/Physiologic
    - Small
    - Moderate
    - Large
    - Very Large
    - NM/ND (Not Measurable/Not Recorded by Site)

    Shift tables for change from RW baseline to RW weeks 24 and to end of RW visit will be generated. Due to potentially different number of subjects receiving bailout rilonacept between treatment arms, there will be no hypothesis testing for this endpoint.

    Endpoints 14-16 will be summarized for data before receiving bailout rilonacept and

for data including bailout rilonacept in each arm. P-values will not be provided due to potentially different number of subjects receiving bailout rilonacept.

14. Change over time in central-lab CRP level

    A mixed model with repeated measures (MMRM) using TYPE=UN option in SAS Proc Mixed will be applied in the analysis of this endpoint. If the model does not converge, an analysis of covariance (ANCOVA) model will be used at each timepoint to calculate least-squares (LS) means. In the model, subjects will have repeated measures for the response variable change from baseline of the endpoint. The explanatory variables will include the baseline value, treatment arm, baseline value by treatment interaction, and the variables for randomization strata. Only observed values will be used in the analysis without imputation.

15. Change over time in the subject's assessments of pericarditis pain (weekly averages)

    The same method for change over time in CRP level will be applied. If bailout rilonacept is used in a week, the week will be considered as after bailout.

16. Number (percentage) of subjects with absent or minimal pericarditis activity over time after RW week 24 based on the PGIPS. The denominator in each arm will be the total number of subjects with the assessment at each visit.

17. Number (percentage) of subjects with absent or minimal pericarditis activity over time based on the PGA-PA. The denominator in each arm will be the total number of subjects with the assessment at each visit.

    The same analysis method and analysis sets for PGPIS will be applied.

    The endpoints below (18 – 23) from patient reported outcomes will be summarized with descriptive statistics. There will be no hypothesis testing since they are measured at RW baseline and Week 24 only and receiving bailout rilonacept due to recurrence at Week 24 could be a confounding factor.

18. Change from baseline to week 24 in the SF-36 Physical and Mental Component Scores (see below for definition)

19. Change from baseline to week 24 in Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health domains in SF-36.

    The SF-36v2® Health Survey (standard, four-week recall) is a 36-item generic (not indication specific) instrument used to evaluate subject reported health related quality of life (HRQoL) in adult subjects. The questions are organized in eight health domain scales: physical functioning [PF] (10 items), role participation with physical health problems [RP] (four items), bodily pain [BP] (two items), general health status [GH] (one item), vitality [VT] (four items), social functioning [SF] (two items), role participation with emotional health problems [RE] (three items), and mental health (five items). Scores from the eight domains are summarized into a physical component score (PCS) and mental component score (MCS).

    The SF-36v2 utilizes norm-based scoring involving a linear T-score transformation

method so that scores for each of the health domain scales and component summary measures have a mean of 50 and a standard deviation of 10, based on the 2009 United States general population. Scores above and below 50 are above and below the average, respectively, in the 2009 United States general population. Also, because the standard deviation is 10, each 1-point difference or change in scores has a direct interpretation; that is, 1 point is one-tenth of a standard deviation, or an effect size of 0.10.

Subject responses will be scored, including the handling of missing data, consistent with the instructions in the SF-36v2 user manual using the Optum Smart Measurement System Scoring Solution software.

The possible score for each item is from 1 to 6. Each item response is then assigned a numeric value according to one of 8 scales.

Items 1, 2, 20, 22, 34, 36: 1=100, 2=75, 3=50, 4=25, 5=0
Items 3, 4, 5, 6, 7, 8, 9, 10, 11, 12: 1=0, 2=50, 3=100
Items 13, 14, 15, 16, 17, 18, 19: 1=0, 2=100
Items 21, 23, 26, 27, 30: 1=100, 2=80, 3=60, 4=40, 5=20, 6=0
Items 24, 25, 28. 29, 31: 1=0, 2=20, 3=40, 4=60, 5=80, 6=100
Items 32, 33, 35: 1=0, 2=25, 3=50, 4=25, 5=0.

Final scores for each scale range from 0 to 100 with higher scores indicating better health. If a subject does not respond to a question, the average score for an item will use the number of non-missing scores for the denominator.

Table 2 displays the items that are categorized. Detailed information can be found in Mark, EM (2011).

Table 2: The 8 Domains in SF-36v2

Scale	Number of items	After recoding, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role-physical (RP)	4	13 14 15 16
Bodily pain	2	21 22
General health	5	1 33 34 35 36
Vitality	4	23 27 29 31
Social functioning	2	20 32
Role-emotional (RE)	3	17 18 19
Mental health	5	24 25 26 28 30

20. Changes in SF-6D utility index score

The SF-6D is calculated based on responses to 11 items on the SF-36, that correspond

to 6 domains: physical functioning, role participation (combined role-physical and role-emotional), social functioning, bodily pain, mental health, and vitality.

RP and RE are combined, and general health is not included. The specific SF-36v2 areas or activities contributing to the scoring of this index include:

- ability to engage in both moderate and vigorous activities
- ability to bathe and dress oneself
- limitations in the kind of work or other activities as the result of physical health; accomplishing less due to emotional problems
- bodily pain and its interference with normal work; nervousness, depression, and energy level
- interference with social activities due to physical or emotional problems.

Individual respondents can be classified on any of four to six levels of functioning or limitations for each of six domains, thus allowing a respondent to be classified into any of 18,000 possible unique health states. Using a standard gamble technique, each of these health states were mapped onto the SF-6D index score, which ranges from 0.00 (worst possible health state/death) to 1.00 (best possible health state/perfect health).

The PRO Analytics software calculates and outputs the SF-6D for each subject at each assessment, just as it does for the 8 domain scores and 2 summary scores.

In the 2009 QualityMetric US Normative survey (Maruish 2011), from which the scoring algorithms were derived, the SF-6D calculated for 3,856 participants who completed the standard (4-week recall) form of the SF-36v2 had a mean of 0.74 and a SD of 0.14. Based on a paper from Walters and Brazier (2003), a change of 0.05 in the SF-6D would indicate a minimally important difference.

Table 3: SF-36v2 Health Survey Items Scored for the SF-6D

SF-6D Domains	SF-36v2™ Health Survey Items
Physical Functioning	3a, 3b, 3j
Role Participation (RP & PE)	4c, 5b
Social Functioning	10
Bodily Pain	7, 8
Mental Health	9b, 9f
Vitality	9e

21. Change in EQ-5D-5L individual scores and index value

The EQ-5D-5L is a subject reported health status utility index for adult subjects that is comprised of five questions plus a visual analog scale (VAS). The five questions ask the respondent to assess their health in terms of mobility, self-care, usual activities,

pain/discomfort, and anxiety/depression. The VAS captures the respondent's self-reported level of the health on the day of completion, captured as a numeric input from 0 ('the worst health you can imagine') to 100 ('the best health you can imagine'). Subject responses will be scored, including the handline of missing values, as specified in the EuroQol Research Foundation, EQ-5D-5L User Guide, 2019, available from http://euroqol.org/publications/user-guides.

Scores from the five questions will be reported individually and converted to a single index value using the value set for US. Health state index scores generally range from less than 0 (where 0 is the value of a health state equivalent to dead; negative values representing values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility.

22. Change in subject's sleep quality assessed with the Insomnia Severity Index (ISI).

    The ISI is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The usual recall period is the "last 2 weeks" and the dimensions evaluated are severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (e.g., 0=no problem; 4=very severe problem), yielding a total score ranging from 0 to 28 (Morin et al 2011).

    The ISI will be collected in subjects ≥18 years or older as described in the protocol.

23. Change in ISI categories. The ISI total scores are divided to 4 categories:
    - 1) 0–7 = No clinically significant insomnia
    - 2) 8–14 = Subthreshold insomnia
    - 3) 15–21 = Clinical insomnia (moderate severity)
    - 4) 22–28 = Clinical insomnia (severe)

    A shift table will also be used to summarize the changes over time.

24. Cumulative number (percentage) of subjects who received sequential ORT, corticosteroid, or bailout rilonacept for pericarditis period every 4 weeks cumulatively in the RW period.

    The CMH test stratified by the randomization strata will be applied to this endpoint.

25. Proportion of subjects using ORT (analgesics, NSAIDs, and/or colchicine) for pericarditis in the first 24 weeks. ORT use while waiting for at least 5 days since previous administration of study medication before receiving bailout rilonacept or within 5 days prior to the assessment of pericarditis recurrence visit is excluded. The denominator of the percentages is the number of subjects in the ITT analysis set in each arm. There will be no hypothesis testing for this endpoint.

26. The endpoints below for MRI assessments will be summarized at RW baseline and week 24. P-values will not be calculated.
    - Proportion of subjects with pericardial delayed hyperenhancement

- Proportion of subjects with myocardial delayed hyperenhancement
- Proportion of subjects with pericardial effusion, and effusion size

A subject will have pericardial effusion if the effusion size is rated "Small" or larger.

5.2.3. Secondary Endpoints in RI and LTE Period

These include efficacy endpoints in the RI period and the LTE. Since there is no control arm in these 2 periods, only descriptive statistics will be provided. Summary statistics will be generated following the methodologies stated in Section 3.1 using RIS or LTES analysis sets. All time-to-event endpoints start from the first day of receiving rilonacept in that period. Unless specified otherwise, the denominator of a response rate or percentage will be the total number of subjects treated in that period.

5.2.3.1. Secondary Endpoints in the RI Period

The following efficacy endpoints will be included for the RI period. Unless specified otherwise, change means change from RI baseline to RI week 12, and the denominator for a proportion is the total number of subjects who were treated in the RI period.

1. Time to pain response, defined as number of days from first dose to the first day a subject's daily pain NRS is ≤ 2 of the 3 days over which, the rolling average daily pain NRS is ≤ 2. Subjects with baseline NRS ≤ 2 will be excluded from the analysis. If one or more daily NRS score is missing, rolling average will be considered not meeting the response criteria.
2. Time to CRP normalization (≤0.5 mg/dL)

   Time to CRP normalization will be censored at treatment discontinuation, taking prohibited medication, or week 12, whichever occurs first. Subjects with baseline CRP ≤0.5 mg/dL will be excluded from the analysis.
3. Time to rilonacept monotherapy

   Time to rilonacept monotherapy is defined as number of weeks from first dose to the first day of achieving monotherapy. Subjects without background therapies at RI baseline will be excluded from the analysis.
4. Time to treatment response defined as time from first dose to the first day of pain response (defined in endpoint 1 above), and CRP ≤0.5 mg/dL within 7 days before or after pain response. Treatment response day will be the day of pain response, whether pain response occurs before or after CRP ≤0.5 mg/dL.
5. Proportion of subjects achieving clinical response at RI week 12 based on RIS analysis set

   Subjects who stopped background SOC pericarditis therapy on or before week 10, as well as who achieve CRP ≤0.5 mg/dL and weekly average of daily pericarditis pain score ≤2.0 on the 11-point NRS within the 7 days prior to and including the day of randomization on RI Week 12/Randomization are responders.

   Additional analysis will be done base done the completers who finished the 12-weeks of RI treatment.

6. Number (percentage) of subjects with normalization of CRP (≤0.5 mg/dL) at RI Week 12. Subjects with baseline CRP >0.5 mg/dL in the RI analysis set will be used in the analysis.
7. Change from baseline in pericarditis weekly pain score at RI Week 12 and over time.
8. Change from baseline in CRP level at RI Week 12 and over time.
9. Proportion of subjects with resolution of echocardiographic and ECG abnormalities (yes/no) at RI Week 12.
10. Percentage of days with no or minimal pain (NRS ≤2) while on treatment. The denominator is the number of days on treatment, calculated as [min(date of last dose of study drug in RI period + 6, last date on study, end of RI period) – date of first dose in RI period) +1].
11. Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS over time at baseline, week 6, and week 12.
12. Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA over time at baseline, week 6, and week 12.
13. Change in the SF-36 8 domain scores, as well as the physical and mental scores.
14. Change in the SF-6D 6 domain scores and the utility index.
15. Change in the EQ-5D-5L individual scores and index value.
16. Change in the subject's sleep quality assessed with the ISI (see Section 5.2.2.3).
17. Change in ISI categories.
18. Number (percentage) of subjects who were off background pericarditis medication on or before weeks 4, 8, 10, and 12

    The RI Analysis Set will be used for the summary. At each timepoint, the numerator only includes subjects who have reached monotherapy on or before the timepoint and remain on monotherapy until the end of the RI period.

5.2.3.2. Efficacy Endpoints in the LTE Period

The efficacy endpoints below are included in this period. These endpoints will not be included in the primary analysis for the RW period since data will not be available at that time. Each endpoint will be summarized through Week 24 in this period, by subjects who did and did not have an adjudicated pericarditis recurrence in the RW period and by subjects who enter LTE directly from the RI period, respectively, and overall. The baseline for the LTE period will be the last assessment before the first dose in the LTE period.

1. Number (percentage) of subjects with pericarditis recurrences based on investigators' judgement.
2. Proportion of subjects with Clinical Response (rilonacept monotherapy + CRP≤0.5 mg/dL + NRS≤2) at each CRP assessment (weeks 12 and 24). The pain NRS at the visit when CRP was assessed will be used.
3. Change over time in CRP levels.
4. Change over time in pericarditis pain NRS.

5. Proportion of subjects with absent or minimal pericarditis symptoms over time based on PGIPS.
6. Proportion of subjects with absent or minimal pericarditis activity over time based on the PGA-PA.
7. Change from baseline in the SF-36 8 domain scores, as well as the physical and mental scores.
8. Change in the SF-6D 6 domain scores and the utility index.
9. Change from baseline in the EQ-5D-5L individual scores and index value.
10. Change from baseline in the subject's sleep quality assessed with the ISI.
11. Change over time in ISI categories.
12. Number (percentage) of subjects requiring addition of SOC pericarditis therapy every 4 weeks cumulatively.
13. Change from baseline in pericardial signs in ECHO, ECG, and MRI.
14. Corticosteroid use over time.

    For subjects who are on corticosteroid at RI baseline, the proportion of subjects using corticosteroid at LTE will be summarized. The denominator will be the number of subjects using corticosteroid at RI and entering the LTE. The average daily dose of corticosteroid (mg/day) will be summarized.
15. In the MRI substudy, resolution in pericardial inflammation among subjects with pericardial inflammation at RI baseline as assessed by cardiac MRI. The endpoints below will be summarized.
    a. Proportion of subjects with pericardial Delayed Hyperenhancement
    b. Proportion of subjects with Myocardial Delayed Hyperenhancement
    c. Proportion of subjects with pericardial effusion, and effusion size
16. Annualized recurrent rate during treatment

    Annualized recurrent rate will be calculated for subjects randomized to KPL-914 utilizing pooled data in RW and LTE periods and there will be no hypothesis testing.

5.3. Safety Analysis

The following safety endpoints will be analyzed:

- Adverse events,
- Clinical laboratory parameters,
- Serology parameters,
- Hematology parameters,
- Non-fasting lipid panel,
- Pregnancy test,
- Vital signs,

- Urinalysis,
- Electrocardiogram, and
- Physical examination.

Descriptive statistics will be used to summarize safety endpoints for all subjects by the following periods:

- RI period (KPL-914)
- RW period
  - KPL-914 vs. Placebo Including Bailout Rilonacept
  - KPL-914 vs. Placebo before Bailout Rilonacept
- LTE period
- Study overall (RI through LTE), KPL-914 or placebo, regardless of receiving bailout Rilonacept.

Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for clinical laboratory analyses, vital signs measurements, ECGs, and physical examination findings.

5.3.1. Adverse Events

Treatment-emergent AEs (TEAEs), defined as AEs that start or increase in severity after the first dose of study drug and before 6 weeks after the last dose of study drug, will be coded to system organ class and preferred term using MedDRA v21.1.

TEAEs will be summarized by each period and study overall. In the RW period, they will also be summarized by including and excluding bailout rilonacept, respectively. The average follow-up duration in weeks for TEAE will be provided in summary tables. The duration of follow-up for each subject is defined as follows.

- For the RI period, it is from first dose in RI period until the day before randomization, last dose day plus 6 weeks, last study day, or data cutoff, whichever occurs first.
- For the RW period including bailout, it is from randomization to data cutoff, last dose day plus 6 weeks, or last study day, whichever occurs first.
- For the RW period before bailout, it is from randomization to the start of using bailout rilonacept, data cutoff, last dose day plus 6 weeks, or last study day, whichever occurs first.
- For the LTE period, it is from first dose day in LTE period to data cutoff, last dose day plus 6 weeks, or last study day, whichever occurs first.
- For study overall, it is from first dose day in RI period to data cutoff, the last dose plus 6 weeks, or last study day, whichever occurs first.

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), relationship to study drug, serious AEs, AEs leading to death, AEs resulting in dose interruption, AEs leading to withdrawal of study treatment, and AEs of injection site reaction.

Any AE of malignancy (excluding basal cell carcinoma of the skin) is of special interest. AE of special interest will also be summarized.

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 by SOC and preferred terms.

Incidence rate per 100 subject-years and its 95% CI will be calculated by the periods defined for follow-up duration above for the following groups of AEs:

- All AEs (include any AE),
- SAE (include any SAE),
- deaths,
- all infections (including serious),
- serious infections (serious only),
- all ISR (injection site reaction, including serious and non-serious),
- only serious ISR,
- all malignancies excluding NMSC (Non-Melanoma Skin Cancer: ie. cutaneous basal cell carcinoma and cutaneous squamous cell carcinoma).

Incidence rate per 100 subject-years = 100 × (number of different AE start days within the treatment period)/(Sum of treatment duration in years from all subjects in the cohort). Multiple events within a subject will be counted as multiple events. Treatment exposure duration and follow-up of AE's in the Study Overall period will be 6 weeks after the last dose. There will be no formal hypothesis testing.

5.3.2. Clinical Laboratory Parameters

Hematology, chemistry, lipid panel, and urinalysis results will be summarized and listed. Pregnancy test will not be summarized but will be listed. Summaries will include descriptive statistics for actual values and change from baseline. Shift tables from baseline condition to the condition at each visit will also be provided. The shift table will include subjects without data so that all subjects in the safety population at the baseline of each period (RI, RW, and LTE) will be included.

A summary of hepatic function abnormalities will be provided for the following criteria:

- >2xULN
- >3xULN
- >5xULN
- The number of percentage of subject's meeting the criteria for Hy's Law defined as elevations in ALT and/or AST of >= 3xULN with accompanying elevations in total bilirubin of >= 2xULN will also be summarized.

The incidence rate per 100 subject-years and its 95% CI for the following lab abnormalities will be calculated:

- Incidence of ALT >5xULN,

- Incidence of AST >5x ULN,
- Incidence of total bilirubin >2xULN
- Incidence of absolute neutrophil count (ANC) <1.0 x 10^3 uL.

Multiple lab abnormalities within a subject will be counted as multiple events within the follow-up period defined in Section 5.3.1 .

Incidence rate per 100 subject years in a cohort = 100 × (# of different lab abnormalities from all subjects within the follow-up period)/(Sum of follow-up duration in years from all subjects in the cohort).

5.3.2.1. Hematology

Hematology tests performed at central study laboratory include WBC count with differential, platelet count, red blood cell count, mean corpuscular volume, hemoglobin, mean corpuscular hemoglobin concentration.

5.3.2.2. Chemistry

Blood chemistry tests performed in the central study laboratory include albumin, total protein, alkaline phosphatase, alanine aminotransferase/serum glutamic pyruvic transminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transminase (AST/SGOT), direct bilirubin, total bilirubin, bicarbonate, chloride, potassium, sodium, creatinine, glucose.

5.3.2.3. Non-fasting Lipid Panel

Subjects treated with rilonacept may experience increases in their lipids, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein HDL, and triglycerides.

Non fasting measurements of total cholesterol, triglycerides, HDL, and direct LDL will be performed by central study laboratory as described in the Schedule of Assessments in Section 13.1.

Investigators should monitor the lipid profiles in study subjects and consider ordering fasting lipid panel and/or lipid lowering therapies as needed based on cardiovascular risk factors and current guidelines.

5.3.2.4. Urinalysis

Urinalysis performed by the central study laboratory includes specific gravity, pH, protein, urobilinogen, ketones, glucose, blood, bilirubin, nitrites, leukocyte esterase will be summarized.

5.3.2.5. Pregnancy Test

For women of child-bearing potential, a urine pregnancy test using a licensed test (dipstick) should be performed prior to receiving the first administration of study drug, and as needed during the study, and also at the SFU visit. When needed, serum pregnancy test should be performed. Pregnancy test results will not be summarized but will be listed.

5.3.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for Temperature, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Rate

(PR), Respiratory Rate (RR), temperature, and weight (kg). A data listing of vital signs will also be provided.

5.3.4. Electrocardiogram

Frequency table for the following interpretations will be generated:

- Widespread of ST elevation normal
- PR-segment depression
- ECG Interpretation
  - Normal
  - abnormal not clinically significant, and abnormal clinically significant)
  - Abnormal not consistent with pericarditis but clinically significant
  - Abnormal consistent with pericarditis

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.

5.3.5. Physical Examination

There are full and abbreviated physical examinations. Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal (GI), genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement. Abbreviated physical examination includes at minimum evaluation of vital signs, lung and heart sounds, including evaluation for pericardial rub.

Present or absent in pericardial rub will be recorded. For each assessment of body system, the result will be recorded as normal, abnormal (not clinically significant), or abnormal (clinically significant). The number and percentage of subjects in each result category will be summarized by body system and visit, as well as by arm in the RW period.

All physical examination data will be provided in a listing.

6. PHARMACOKINETIC ANALYSES

For all subjects, serum samples will be collected at time points shown in Section 13.1 in order to quantify concentrations of rilonacept. Only individual listings of serum concentrations will be provided. The analysis plan for PK data will be described in a separate document.

7. PHARMACOGENOMICS SUBSTUDY

Samples for pharmacogenomics in the substudy will be collected according to the Study Schedule of Activities. More details of the analysis will be provided in a separate document.

8. ANTI-RILONACEPT ANTIBODIES

Blood sample for testing anti-rilonacept antibody (ADA) will be collected at RI baseline, RI weeks 2, 6, 12 (= RW baseline), RW week 24, end of RW/LTE baseline, and LTE week 24. ADA status will be categorized as follows.

1. Treatment-emergent ADA, including treatment induced or boosted [increased by one quartile (with all titers collected) from the previous assessment]
2. Prior existing ADA (without treatment boosted)
3. ADA negative at every assessment.

For subjects with treatment-emergent ADA, the maximum post-baseline titer level (low, medium, high) will be summarized. The 3 levels (low, medium, high) will be divided based on 25th and 75th percentiles from all ADA titers pooled.

The following endpoints will be summarized for each category of ADA status above:

- Number and percentage of subjects with injection site reactions within 24 hours of administration
- Subjects with Neutralizing antibody in the first 2 categories above.

A summary table will be provided for number and percent of subjects with positive or negative anti-rilonacept antibody by visit. Individual's ADA status and titer level (if positive) at each visit will be provided.

The number and percent of subjects with anti-rilonacept-antibody positive at any visit vs. those with negative at every visit will also be provided. The summary statistics of CRP and NRS level will be provided for these 2 subsets of subjects at each visit by study period, and by treatment arm in the RW period (before vs. after receiving bailout rilonacept and overall).

The following 3 categories will be used in the subgroup analysis for the primary endpoint, Summary of NRS scores and CRP levels over time, summary of TEAEs (overall and drug related), and blood concentration over time:

1. Subjects with ADA Positive at Any Assessment
2. Subjects with ADA Positive and Neutralizing Antibody at Any Assessment
3. Subjects with ADA Negative at Every Assessment

9. BIOMARKER

Serum and plasma will be collected according to the Study Schedule of Activities for biomarker analysis. More details of the biomarker analysis will be provided in a separate document.

10. INTERIM ANALYSIS

No interim analysis for claiming efficacy is planned. Interim safety review will be conducted by a Data Monitoring Committee (DMC). The analysis will be performed by a designated CRO. Details are in DMC charter and DMC SAP.

11. CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

11.1. Changes from Protocol

Analysis in the SAP	Analysis planed in the protocol	Reason
Section 5.2.2.3 Changes in SF-6D utility index score.	Section 7.2.2 Change in the SF-6D 6 domain scores and the utility index.	The 6 domains were not generated for analysis by the Optum software. They were used to calculate the utility index score only.
Section 5.2.3.1 Time to pain response, defined as number of days from fist dose to the first day a subject's daily pain NRS is ≤ 2 of the 3 days over which, the rolling average daily pain NRS is ≤ 2.	Section 7.3.1 Time to pain response defined as a rolling average of NRS score of 2 or less on three consecutive days.	A score of 3 or higher on the first day of the rolling average should not qualify pain response.
Section 5.2.3.1 Time to treatment response defined as time from first dose to the first day of pain response, and CRP ≤0.5 within 7 days before or after pain response. Treatment response day will be the first day that the above criterion is met. If pain response occurs before CRP ≤0.5, each 3-day rolling average of NRS should be ≤2.0 from the day of pain response to the day of CRP ≤0.5. The response day will be the day of pain response. If CRP ≤0.5 occurs before pain response, the response day will also be the day of pain response.	Section 7.3.1 Time to clinical response (monotherapy + NRS ≤2 + CRP ≤0.5 mg/dL)	Subjects were enrolled with a qualifying episode and on background therapy. The endpoint of interest is to evaluate how soon subjects will reach response in both pain and CRP after initiating rilonacept while on background therapy.

11.2. Impact of COVID-19 Pandemic

The KPL-914-C002 study was nearing the end of Randomized Withdrawal (RW) phase of the study when COVID-19 pandemic started. The impact of the pandemic to the study conduct is limited. A separate document will be prepared to summarize any protocol deviations which occurred as a result of the pandemic.

There are no special data handling rules and analyses implemented for COVID-19 related protocol deviations.

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13. APPENDICES

13.1. Schedule of Assessments

Table 4: Study Schedule of Activities – Screening and Run-In Period

Trial Period	**SCREENING[a]**	**RUN-IN (12 weeks)[m]**								
		ENROLLMENT								**RANDOMIZATION [-q]**
Visit Name	**Screening Visit**	**RI Baseline**	**RI Day 2**	**RI Day 4**	**RI Week 1**	**RI Week 2**	**RI Week 4**	**RI Week 6**	**RI Week 10**	**RI Week 12/ RW Baseline**
Visit Window[b] (days)	**(-28)**	**NA**	**NA**	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 3**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**TC/RN**	**TC/RN**	**TC/RN**	**TC/RN**	**Clinic**	**TC**	**Clinic**
Informed Consent Form	X									
Inclusion and Exclusion criteria	X	X								
Demographics	X									
Medical/Surgical History	X									
Pericarditis Diagnosis & History	X	X								
Concomitant medications	X	X		X	X	X	X	X	X	X
Pericarditis Concomitant medications	X	X		X	X	X	X	X	X	X
Pericarditis Concomitant medication tapering					X	X	X	X	X	
Full Physical Examination[c]	X									
Abbreviated Physical Examination[d]		X								X
Body weight and height		X								X
12-Lead ECG		X								X
Echo[e]		X[e]								X[e]
MRI (substudy only)		X								
Pericardial pain (11-point NRS)	X[f]	DAILY[g]								X[g]

Trial Period	**SCREENING[a]**	**RUN-IN (12 weeks)[m]**								
		ENROLLMENT								**RANDOMIZATION [-q]**
Visit Name	**Screening Visit**	**RI Baseline**	**RI Day 2**	**RI Day 4**	**RI Week 1**	**RI Week 2**	**RI Week 4**	**RI Week 6**	**RI Week 10**	**RI Week 12/ RW Baseline**
Visit Window[b] (days)	**(-28)**	**NA**	**NA**	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 3**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**TC/RN**	**TC/RN**	**TC/RN**	**TC/RN**	**Clinic**	**TC**	**Clinic**
EQ-5D		X								X
SF-36		X								X
ISI		X								X
PGIPS		X						X		X
PGA-PA		X						X		X
Hematology, Chemistry Labs (Central)		X						X		X
Lipid Panel (Central)[h]		X								X
CRP (Local)	X[f]									X
CRP (Central)	(X)	X		X	X	X	X	X		X
Hematology, Chemistry, IGRA[r], hepatitis serology, HIV (Local)	X									
Chest X-Ray	X									
Urine Pregnancy (Local or Central)[j]	X	X								
Urinalysis (Central)		X								
PK (Central)[s]			X[i]		X	X	X			
ADA (Central)[s]		X				X		X		
Biomarkers (Central)		X			X		X			
Pharmacogenomics Informed Consent[k]		X								
Pharmacogenomics Sampling (Central)[k]							X			
IWRS Subject Status Update	X	X								X
IWRS Weight Input (pediatric only)		X								X

Trial Period	**SCREENING[a]**	**RUN-IN (12 weeks)[m]**								
		ENROLLMENT								**RANDOMIZATION [-q]**
Visit Name	**Screening Visit**	**RI Baseline**	**RI Day 2**	**RI Day 4**	**RI Week 1**	**RI Week 2**	**RI Week 4**	**RI Week 6**	**RI Week 10**	**RI Week 12/ RW Baseline**
Visit Window[b] (days)	**(-28)**	**NA**	**NA**	**+/- 1**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 3**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**TC/RN**	**TC/RN**	**TC/RN**	**TC/RN**	**Clinic**	**TC**	**Clinic**
IWRS Drug Dispensing		X		X				X		X
In Clinic Study Drug Administration[o]		X[n]						X		X
Outpatient Study Drug Administration[o]					WEEKLY					
Study Drug Compliance Review		X			X	X	X	X	X	X
Clinical Response Evaluation										X[p]
Adverse Event Reporting[l]	X	X		X	X	X	X	X	X	X

a The screening and enrollment visit can be combined.
b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.
c Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement.
d Abbreviated physical examination includes at minimum evaluation of vital signs, lung and heart sounds, including evaluation for pericardial rub.
e ECHO is required to be obtained according to the central core lab parameters and then read locally and submitted to the central core lab for separate review and analysis.
f Both a documented CRP $\geq$ 1.0 mg/dL AND a pericarditis pain level of $\geq$ 4 is required 7 days prior to and including the Run-In Baseline visit. These are not required to occur on the same day.
g Subjects missing $\geq$ 4 daily pain measurements during the 7 days prior to and including the Randomization Withdrawal baseline visit will be unable to proceed to randomization due to lack of data required for treatment response evaluation.
h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
i Applicable to 24-hour post dose PK sub-study participants only.
j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.
k Pharmacogenomics informed consent and subsequent sampling can be performed at any time in the study however, it is preferable to have this completed at the beginning of the study.
l Adverse event reporting begins following the subject providing informed consent.
m All procedures are to be completed prior to study drug administration.

n The first dose of study drug is a loading dose. Adult subjects receive 2 SC doses 160 mg (total 320 mg); pediatric subjects (subjects ≥12 and <18 years of age) receive 2 SC doses of 2 x 2.2 mg/kg.
o Study drug administration is once weekly with a minimum of 5 days required between doses.
p Randomization and subsequent study drug dispensing to occur after confirmation of Clinical Response (see definition of Clinical Response in Section 6.2.2).
q The Randomization visit serves as both the RI Week 12 visit and the RW baseline visit.
s PK and ADA samples will be collected prior to study drug administration. PK at enrollment/baseline will be taken from ADA

Table 5: Study Schedule of Activities – Randomized Withdrawal

Trial Period	**RANDOMIZED WITHDRAWAL (event-driven)[m]**								
									END OF RANDOMIZED WITHDRAWAL (EORW)[t]
Visit Name	**RW Week 4**	**RW Week 8**	**RW Week 12**	**RW Week 16**	**RW Week 20**	**RW Week 24**	**RW Every 8 Weeks**	**RW Every 8 Weeks**	**Per Announced End Date[u]/ LTE-Baseline**
Visit Window[b] (days)	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 7**
Visit Type	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**Clinic**
Informed Consent Form									X
Concomitant medications	X	X	X	X	X	X	X	X	X
Pericarditis Concomitant medications	X	X	X	X	X	X	X	X	X
Full Physical Examination[c]						X			X
Abbreviated Physical Examination[d]									
Body weight and height		X		X		X		X	X
12-Lead ECG						X			X
Echo[e]						X[e]			X[e]
MRI (substudy only)						X			
Pericardial pain (11-point NRS)	DAILY								
EQ-5D						X			X
SF-36						X			X
ISI						X			X
PGIPS		X		X		X		X	X
PGA-PA		X		X		X		X	X
Hematology, Chemistry Labs (Central)		X				X		X	X
Lipid Panel (Central)[h]						X			X
CRP (Local)									

Trial Period	**RANDOMIZED WITHDRAWAL (event-driven)[m]**								
									END OF RANDOMIZED WITHDRAWAL (EORW)[t]
Visit Name	**RW Week 4**	**RW Week 8**	**RW Week 12**	**RW Week 16**	**RW Week 20**	**RW Week 24**	**RW Every 8 Weeks**	**RW Every 8 Weeks**	**Per Announced End Date[u]/ LTE-Baseline**
Visit Window[b] (days)	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 7**
Visit Type	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**TC/RN**	**Clinic**	**Clinic**
CRP(Central	X	X	X	X	X	X	X	X	X
PK (Central)		X				X			X
ADA (Central)						X			X
Biomarkers (Central)		X				X			
Urine Pregnancy[j] (Local or Central)									X
Urinalysis									X
IWRS Subject Status Update									X
IWRS Weight Input (pediatric only)		X		X		X		X	X
IWRS Drug Dispensing		X		X		X		X	X[v]
In Clinic Study Drug Administration[o]		X		X		X		X	X[v]
Outpatient Study Drug Administration[o]	X	WEEKLY							
Study Drug Compliance Review	X	X	X	X	X	X	X	X	X
Assessment of Pericarditis Recurrence	X	X	X	X	X	X	X	X	X
Adverse Event Reporting[l]	X	X	X	X	X	X	X	X	X

b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.

c Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement.

d Abbreviated physical examination includes at minimum evaluation of vital signs, lung and heart sounds, including evaluation for pericardial rub.
e ECHO is required to be obtained according to the central core lab parameters and then read locally and submitted to the central core lab for separate review and analysis.
h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.
l Adverse event reporting begins following the subject providing informed consent.
m All procedures are to be completed prior to study drug administration.
o Study drug administration is once weekly with a minimum of 5 days required between doses.
s PK and ADA samples will be collected prior to study drug administration. PK at enrollment/baseline will be taken from ADA. As required, ADA samples will be collected at EOS, ET, and Unscheduled visits.
t The EORW visit serves as both the last visit of the RW period and the baseline visit of the LTE period.
u For all subjects, the final clinic visit of the end of RW period is to be scheduled once the End of the Randomization Withdrawal end date is announced by Sponsor. This includes subjects that are taking blinded study drug, open-label rilonacept, or who have prematurely discontinued study drug.
v Study drug administration to occur only after subject provides informed consent for the open-label extension period.

Table 6: Study Schedule of Activities – Long Term Extension

Trial Period	**LONG TERM EXTENSION (up to 24 months)**			
	Long Term Extension Treatment (up to 24 Months)[m]			
Visit Name	**LTE Week 12**	**LTE Week 24**	**LTE Every 12 Weeks**	**LTE 18-month Assessment**
Visit Window[b] (days)	**+/- 2**	**+/- 2**	**+/- 2**	**18 months from most recent recurrence**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Concomitant medications	X	X	X	X
Pericarditis Concomitant medications	X	X	X	X
Full Physical Examination[c]		X		X
12-Lead ECG		X		X
Echo[e]		X		X
MRI		X[z]		X[z]
EQ-5D		X		
SF-36		X		
ISI		X		
PGIPS	X	X	X	
PGA-PA	X	X	X	
Hematology, Chemistry Labs (Central)	X	X	X	
Lipid Panel (Central)[h]		X		
CRP (Central)	X	X	X	X
PK (Central)		X		X
ADA (Central)		X		
Biomarkers (Central)		X		
Urine Pregnancy[j] (Local or Central)		X		X
Urinalysis		X		
IWRS Subject Status Update		X		X
IWRS Weight Input (pediatric only)	X		X	X
IWRS Drug Dispensing	X	X	X	X
In Clinic Study Drug Administration[o]	X	X	X	
Outpatient Study Drug Administration[o]	WEEKLY			
Study Drug Compliance Review	X	X	X	X
Assessment of Pericarditis Recurrence	X	X	X	X
Adverse Event Reporting[l]	X	X	X	X

a The screening and enrollment visit can be combined.

b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.
c Full physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. The decision to perform examination of genitourinary system should be guided by clinical judgement.
e ECHO is required to be obtained according to the central core lab parameters and then read locally and submitted to the central core lab for separate review and analysis.
h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.
l Adverse event reporting begins following the subject providing informed consent.
m All procedures are to be completed prior to study drug administration.
o Study drug administration is once weekly with a minimum of 5 days required between doses.
z The MRI to occur only if the previous MRI was done longer than 6 months ago.

Table 7: Study Schedule of Activities – Supplemental Visits

Visit Name	**PERICARDITIS RECURRENCE ASSESSMENT**	**END of TREATMENT (EOT)[x]**	**SAFETY FOLLOW UP (SFU)[y] (6 weeks post last dose)**
Visit Window[b] (days)	**N/A**	**N/A**	**+/- 2**
Visit Type	**Clinic**	**Clinic**	**Clinic or TC/RN**
Concomitant medications	X	X	X
Pericarditis Concomitant medications	X	X	X
Full Physical Examination[c]		X	
Abbreviated Physical Examination[d]	X		
Body weight and height	X		
12-Lead ECG	X	X	
Echo[e]	X[e]	X	
MRI (substudy only)		X[z]	
Pericardial pain (11-point NRS)	X	X	
EQ-5D	X	X	
SF-36	X	X	
ISI	X	X	
PGIPS	X	X	
PGA-PA	X	X	
Hematology, Chemistry Labs (Central)		X	
Lipid Panel (Central)[h]		X	
CRP (Local)	X		
CRP(Central	X	X	
PK (Central)	X	X	X
ADA (Central)	X	X	X
Biomarkers (Central)	X	X	
Urine Pregnancy[j] (Local or Central)			X
Urinalysis		X	
IWRS Subject Status Update	X[s]	X	
IWRS Weight Input (pediatric only)	X		
IWRS Drug Dispensing	X		

Visit Name	**PERICARDITIS RECURRENCE ASSESSMENT**	**END of TREATMENT (EOT)[x]**	**SAFETY FOLLOW UP (SFU)[y] (6 weeks post last dose)**
Visit Window[b] (days)	**N/A**	**N/A**	**+/- 2**
Visit Type	**Clinic**	**Clinic**	**Clinic or TC/RN**
Study Drug Compliance Review	X	X	
Assessment of Pericarditis Recurrence	X	X	X
Adverse Event Reporting[l]	X	X	X

b Scheduling of visits within visit windows requires cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.

h Lipid panels are non-fasting and are to be drawn at a minimum of every 6months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.

j For women of child bearing potential - urine pregnancy testing can be repeated as needed throughout the course of the study and serum pregnancy can be drawn as needed; urine pregnancy is required to be performed at enrollment and 6 weeks after the last dose of study drug.

l Adverse event reporting begins following the subject providing informed consent.

s PK at enrollment/baseline will be taken from ADA.

x An EOT visit is to be conducted throughout the course of the study when a subject permanently discontinues study drug.

y An SFU is required to be conducted within 6 weeks of the last dose of rilonacept at any time throughout the course of the study including the RI period, the RW period, and the LTE period.

z The MRI to occur only if the previous MRI was done longer than 6 months ago.

13.2. Missing Data Imputation Rules

Partial missing dates will be imputed for start/stop dates of AE and prior/concomitant medications, as well as start date of each pericarditis episode according to the rules below.

Table 8: Imputation Rules for Partial Missing Dates

Category	Scenario	Rule for missing dates
General rule	All	If year is missing, do not impute, unless otherwise specified
AE and prior/concomitant medication start date	Day is missing and (month, year) same as the first dose date	The day will be imputed as the same day of the first dose day or stop date, whichever is earlier.
	Day is missing and (month, year) not the same as the first dose date	The day will be imputed as the first day of the month or stop date, whichever is earlier.
	Month and day missing, year the same as the first dose date	Date will be imputed with the first dose date or stop date, whichever is earlier.
	Month and day missing, year different from the first dose date	Impute with the first day of the year.
AE and prior/concomitant medication end date	Day is missing	Impute with min(last day of the month, data cutoff, end of study date)
	Day and month are missing	Impute with min(last day of the year, data cutoff, end of study date)
	Entirely missing	Impute with min(data cutoff, end of study date)
First pericarditis episode start date	Day missing	Use first day of the month
	Month missing	Use January 01
Second or later pericarditis episode start date	Day missing	Use max(first day of the month, stop day of previous episode +1)
	Month missing	January 01
Other	Non-specific	For missing data handling rules not covered in this table, they will be defined in the ADaM Define file.

13.3. EQ-5D-5L Scoring

The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score.

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents. The EQ VAS asks respondents to simply 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below'.

The EQ-5D-5L Crosswalk Index Value Calculator can be found using the following link: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

13.4. Calculation of 95% CI for Incidence Rate per 100 Subject-Years of Exposure/Observation

We first construct a formula to calculate the exact 100(1-α)% 2-sided CI for the number of events in a time interval. When this formula is applied to the number of events in a time interval of 100 subject-years in a study, we obtain the desired result to construct Fisher's exact 2-sided 100(1-α)% confidence interval for an incidence rate of interest per 100 subject-years. When $\alpha = 0.05$, it provides a 95% CI.

The number of events of interest in a time interval can be modelled using a Poisson distribution with parameter λ, where λ is the average number of events in this time interval. The probability of observing k events in this time interval is:

$P(k \text{ events in interval}) = e^{-\lambda}\frac{\lambda^k}{k!}$

If k events were observed in the interval, the lower bound l and upper bound u of the 100(1-α)% CI must satisfy the following conditions for Fisher's exact CI:

$$\text{Lower bound: } \sum_{x=0}^{k} \frac{e^{-l_l}x}{x!} = 1 - \alpha/2$$

Upper bound: $\sum_{x=0}^{k} \frac{e^{-u}u^{x}}{x!} = 1 - \alpha/2$

The parameter λ can be estimated with *k*. Using the relationship between the cumulative distribution functions of the Poisson and chi-squared distributions, the above lower and upper bounds can be expressed as follows:

$$\frac{1}{2}x^2(\frac{\alpha}{2}; 2k) \leq \lambda \leq \frac{1}{2}x^2(1 - \frac{\alpha}{2}; 2k + 2), \qquad (1)$$

where $x^2(a; v)$ is the chi-square quantile for lower tail probability with *v* degrees of freedom.

The inequalities in (1) are used in the SAS macro below to construct the confidence interval for the number of events. The lower bound, number of events, and upper bound are divided by the total treatment exposure expressed as subject-year to construct the incidence rate and its CI. Each number is then multiplied by 100 to obtain the incidence rate per 100 subject-years.

SAS Macro for the 95% CI of incidence rate per 100 subject-years

```
%macro nppy(x=5, n=100, alpha=0.05);
 ***     x=5 --# of events;
 ***  n = # of subject-years.;
 ***  alpha=2-sided type-I error rate, alpha=0.05 for 95% CI.;


data temp;
 x=&x;
 n=&n;
 alpha=&alpha;
 length CI_coverage $12.;
 CI_coverage=compress(round(100*(1-&alpha), 0.1))||'%';
 r=round((x/n)*100, 0.001);
if x=0 then Lower_bound=0;
 else Lower_bound = round((quantile('CHISQ',&alpha/2,2*&x)/2/n)*100, 0.001);
  Upper_bound = round((quantile('CHISQ',1-&alpha/2,2*(x+1))/2/n)*100, 0.001);
          label x='# of events'
                                    n='# subject years'
                                    r='# of events per 100 subject-years'
                                    alpha='2-sided alpha';
call symput('ci', compress(ci_coverage));
proc print data=temp label noobs;
  title1 "&CI confidence interval for # of events per 100 subject-years";
          title2 '--Exact method using the relationship between Poisson and Chi Square
distributions';
run;
%mend;

*%nppy(x=14, n=400, alpha=0.05);
```

Signature Page for RIM-CLIN-000261 v2.0

Approval	[redacted] 16-Jun-2020 20:27:24 GMT+0000

Approval	[redacted] 16-Jun-2020 21:20:20 GMT+0000

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CHANGES TO STATISTICAL ANALYSIS PLAN

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPENLABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – Rilonacept inHibition of interleukin-1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes stuDY (RHAPSODY)

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Study Drug:	Rilonacept (KPL-914)
Protocol Number:	KPL-914-C002
Date of Issue:	June 16, 2020

Draft Statistical Analysis Plan (Version 1.0) for KPL-914-C002 was submitted to FDA on 03APR2020. Final SAP version 2.0 was signed off on 16JUN2020. This document summarized the changes made to the draft version submitted to FDA.

Analysis in the draft SAP submitted to FDA on 03APR2020	**Analysis in the final singed off version 1.0**	**Reason**
Section 3.4: Subgroups to be Analyze Type of pericarditis: idiopathic, post pericardiotomy syndrome, Dressler's syndrome, and Still's disease	Deleted	Categories are almost identical to categories for diagnosis of recurrent idiopathic pericarditis (RI baseline): yes or no
Section 4: included Run-in Week 12 Analysis Set	Removed Run-in Week 12 Analysis Set	All subjects enrolled 12 weeks before the cutoff.
Section 5.1.3 and 5.1.5: Baseline and concomitant pericarditis medication categories: – Non-opioid analgesics – Opioid analgesics – Aspirin – NSAIDs – Colchicine – Oral corticosteroids – IM/IV corticosteroids – Other	Baseline and concomitant pericarditis medication categories: – Analgesics – Non-opioid analgesics – Opioid analgesics – NSAIDs – Aspirin – Other NSAIDs – Colchicine – Corticosteroids – Oral corticosteroids – IM/IV corticosteroids – Other	To reorganize categories
Throughout the SAP: rescue medications (ORT or prednisone)	rescue medications (ORT or corticosteroid)	To change the wording from "prednisone" to "corticosteroid" to include all types of corticosteroid
Section 5.2.1.1: Table 1 has no footnote	Added footnote below to Table 1 "*Excluding subjects receiving ORT/corticosteroid while waiting for at least 5 days since previous administration of study medication before receiving bailout rilonacept or within 5 days prior to recurrence visit."	To clarify the definition of using ORT/Corticosteroid.

Analysis in the draft SAP submitted to FDA on 03APR2020	Analysis in the final singed off version 1.0	Reason
Section 5.2.2.3 endpoint #9 time to CRP	Removed condition of CRP increase caused of pericarditis recurrence from the definition.	CRP increase is not specific to pericarditis recurrence. However, it is challenging to determine whether a CRP increase is caused by pericarditis recurrence or not. So, we decided to remove this condition.
Section 5.2.2.3 endpoint #13: Change in ECHO pericardial effusion size will be summarized by before and including bailout rilonacept in each arm.	Deleted	Central ECHO data collected change from previous visit which is not change from baseline. Shift tables for effusion size were produced to summarize the change from baseline.
Section 5.2.2.3 endpoint #16: The CMH test stratified by the randomization strata will be applied.	Deleted	SAP specified that for Endpoints 14-16, p-values will not be provided. This sentence was left in the SAP inadvertently.
Section 5.2.3.1 endpoint #1 time to pain response	Add “If one or more daily NRS score is missing, rolling average will be considered not meeting the response criteria.”	To clarify pain response criteria.

Analysis in the draft SAP submitted to FDA on 03APR2020	**Analysis in the final singed off version 1.0**	**Reason**
Section 5.2.3.1 endpoint #4 Time to treatment response defined as time from first dose to the first day of pain response, and CRP ≤0.5 within 7 days before or after pain response. Treatment response day will be the first day that the above criterion is met. If pain response occurs before CRP ≤0.5, each 3-day rolling average of NRS should be ≤2.0 from the day of pain response to the day of CRP ≤0.5. The response day will be the day of pain response. If CRP ≤0.5 occurs before pain response, the response day will also be the day of pain response.	Time to treatment response defined as time from first dose to the first day of pain response (defined in endpoint 1 above), and CRP ≤0.5 mg/dL within 7 days before or after pain response. Treatment response day will be the day of pain response, whether pain response occurs before or after CRP ≤0.5 mg/dL.	Simplify definition and not requiring all 3-day rolling averages ≤2 before CRP≤0.5
	Add the following analysis to Section 5.2.3.1 endpoint #5 proportion of subjects achieving clinical response at RI week 12: Additional analysis will be done base done the completers who finished the 12-weeks of RI treatment	Add analysis for different analysis population
	Add a new Section 11.2 for impact of COVID-19 pandemic	To evaluate the COVID-19 pandemic impact on study