KPL-914-C002 Protocol

Kiniksa Pharmaceuticals, Ltd.

CLINICAL STUDY PROTOCOL

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPEN-LABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – **R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY** **(RHAPSODY)**

VERSION 1.0, 26 September 2018

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KPL-914-C002

Sponsor: 

Sponsor Study Contact: 

Sponsor Medical Contact 

Medical Monitor: 

Version of Protocol: Version 1.0

Date of Protocol: 26 September 2018

Protocol Approval - Sponsor Signatory

Study Title	Phase 3, double-blind, placebo-controlled, randomized \Vithdrmval study ,vith open-label extension. to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis **(RHAPSODY)**
Protocol Number	KPL-914-C002
Protocol Date	26 September 2018

Protocol accepted and approved by·

Chief Medical Officer

[redacted]

Protocol Approval - Lead Statistician

Study Title	Phase 3, double-blind, placebo-controlled, randomized withdrm'val study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects v,·ith recurrent pericarditis **(RHAPSODY)**
Protocol Number	KPL-914-C002
Protocol Date	26 September 2018

Protocol accepted and approved by·

Lead Statistician

[redacted]

[redacted]

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis (RHAPSODY)" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1, dated 26 September 2018, the International Council for Harmonisation tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Kiniksa Pharmaceuticals or implement protocol changes without Institutional Review Board Independent Ethics Committee approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Kiniksa Pharmaceuticals.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

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PROTOCOL SYNOPSIS

Protocol Number:	KPL-914-C002
Title:	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis
Study Acronym:	**R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY** **RHAPSODY**
Sponsor:	[redacted]
Study Phase:	3
Study Sites:	Multicenter, global
Indication:	Recurrent pericarditis
Study Rationale:	Recurrent pericarditis is a rare autoinflammatory condition with no approved therapies. Current treatments, utilizing nonspecific inhibitors of inflammation (nonsteroidal anti-inflammatory drugs [NSAIDs], colchicine, corticosteroids [CS]), result in significant morbidity with chronic use. Some patients develop CS dependency or require surgical pericardiectomy to treat the symptoms of their disease. The interleukin-1 (IL-1) pathway plays a major role in the pathophysiology of recurrent pericarditis. Rilonacept (KPL-914) is a recombinant fusion protein that blocks IL-1 signaling. It is currently approved for treatment of another autoinflammatory condition, Cryopyrin-Associated Periodic Syndrome (CAPS). Based on its IL-1–antagonistic properties and pharmacokinetics (PK), which allow for once-weekly subcutaneous (SC) injections, it is reasonable to evaluate the efficacy and safety of rilonacept in subjects with recurrent pericarditis to address the unmet need in treatment of this disease.
Study Objectives:	
Primary:	To assess the efficacy of rilonacept treatment in subjects with recurrent pericarditis.
Secondary:	To assess the safety of rilonacept treatment in subjects with recurrent pericarditis.

Study Population:

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 prior pericarditis episodes (including the first episode and 1 recurrence). Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present at screening with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale (NRS) and C-reactive protein (CRP) value ≥1 mg/dL (either on the same day or separated by no more than 7 days) within 7 days prior to first study drug administration.

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to first administration of study drug, and that changes in medications made within this time period (for instance, 1-time use of NSAIDs) are not anticipated by the investigator to significantly alter assessments of baseline disease activity.

Study Design:

This study has 5 periods:

(1) Screening period, during which assessment of disease characteristics, baseline therapy, and the pre-treatment workup is completed (up to 4 weeks)

(2) Single-blind Run-In (RI) period (12 weeks), during which blinded rilonacept is administered SC once weekly in all subjects. 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 stopped background SOC pericarditis therapy and who achieve Clinical Response at RI Week 12, defined as the 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 Withdrawal (RW) baseline and a 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

Study Design Continued

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.

(3) Double-blind placebo-controlled RW period (pericarditis recurrence event-driven duration, with a minimum of 24 weeks), 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 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] 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.

(4) Long Term Extension Treatment Period (LTE-TP) (24 weeks), during which all subjects completing the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) will have an option to receive up to 24 weeks 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. Any subject who, in the opinion of investigator, should not continue open-label rilonacept will be offered participation in the LTE off study drug and after signing LTE informed consent.

(5) Long Term Extension Follow-Up Period (LTE-FUP) (24 weeks), during which all subjects in the LTE-TP will be followed in the LTE-FUP for safety and potential pericarditis recurrences.

Estimated Study Duration:

Subjects completing LTE-TP are projected to be dosed with rilonacept for a minimum of approximately 1.2 years and up to 3 years based on enrollment assumptions and pericarditis recurrence events accrual time.

Study Efficacy Assessments:

- Daily pericarditis pain on the 11-point NRS in the subject's electronic diary
- CRP level
- Electrocardiogram (ECG)
- Echocardiography (ECHO)
- Patient Global Impression of Pericarditis Severity (PGIPS)
- Physician Global Assessment of Pericarditis Activity (PGA-PA)
- 36-Item Short Form Health Survey (SF-36)
- 5-Level EuroQoL-5D (EQ-5D-5L)
- Insomnia Severity Index (ISI)
- Cardiac magnetic resonance imaging (in a substudy in approximately 10 subjects)

Study Pharmacokinetic or Pharmacodynamic Assessments:

Pharmacokinetic or pharmacodynamic assessments will include:

- PK analysis
- Anti-rilonacept antibodies
- Biomarkers
- Peripheral blood mononuclear cell isolation (for subjects who sign the separate informed consent for pharmacogenomics assessments)

Study Safety Assessments:

Safety assessments during the study will include:

- Physical examination
- Vital signs measurements
- Adverse event (AE) monitoring
- Chest x-ray
- Tuberculosis screening
- Laboratory tests

Investigational Medicinal Product, Dosage, and Route of Administration:

Rilonacept (KPL-914) is a recombinant fusion protein consisting of the extracellular domains of human IL-1 cytokine receptor and the Fc portion of human immunoglobulin G1 (IgG1). It acts as a soluble decoy receptor binding IL-1α/IL-1β and prevents their interaction with the IL-1 cell-surface receptor.

Study drug (rilonacept or placebo) is supplied in a single use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml of placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

The first injection of rilonacept loading dose at the RI baseline visit will be administered at the study site by study site staff. The second injection of rilonacept loading dose at the RI baseline visit will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration.

Sample Size:

Approximately 56 subjects (not to exceed 75 subjects) with recurrent pericarditis will be enrolled, which will allow approximately 50 subjects to be randomly assigned to blinded treatment.

Statistical Methods:

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 efficacy analysis. A sensitivity analysis will be done based on the investigator's assessment of the pericarditis recurrence.

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 efficacy endpoints.

Major secondary efficacy endpoints for the RW period include:

- Proportion of subjects who maintained Clinical Response at Week 24 of the RW period
- Percentage of days with no or minimal pain (pain ≤1 on the 11-point NRS) in the first 24 weeks of the RW period
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point rating scale of PGIPS) at Week 24 of the RW period

Other secondary efficacy endpoints for the RW period include:

- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to pericarditis pain NRS ≥4

Statistical Methods Continued:

- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO
- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain (weekly average)
- Proportion of subjects with absent or minimal pericarditis activity based on Physician Global Assessment of Pericarditis Activity (PGA-PA)
- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who receive sequential ORT therapy for pericarditis recurrence (analgesics, NSAIDs, and/or colchicine) in the RW period

Efficacy endpoints for the RI period include:

- Proportion of subjects who achieved Clinical Response at the RI Week 12 visit
- Time to CRP normalization
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12
- Change from baseline in CRP level at RI Week 12
- Resolution of echocardiographic and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on the PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who were off background SOC pericarditis therapy at RI Week 12

Efficacy endpoints for the LTE-TP include:

- Number (percentage) of subjects with pericarditis recurrences
- Proportion of subjects with Clinical Response
- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on PGA-PA

Statistical Methods Continued:

- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects requiring addition of SOC pericarditis therapy

Primary analysis of this study will be done after the 22nd CEC-confirmed pericarditis recurrence and after all subjects in the RW period have been treated for 24 weeks. Subjects who have not had an adjudicated pericarditis recurrence will be censored on the day of the last available assessment before data cutoff.

Details of the analyses will be specified in the Statistical Analysis Plan.

Protocol Version and Date:	Version 1.0 26 Sep 2018

STUDY SCHEDULE OF ACTIVITIES

Table 1–1 Study Schedule of Activities – Screening and Run-In Period (Part 1 of 2)

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]
EQ-5D		X								X
SF-36		X								X
ISI		X								X
PGIPS		X						X		X
PGA-PA		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

[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.

[m] All procedures are to be completed prior to study drug administration.

[q] The Randomization visit serves as both the RI Week 12 visit and the RW baseline visit.

Table 1–1 Study Schedule of Activities – Screening and Run-In Period (Part 2 of 2)

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
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, hepatitis serology, HIV (Local)	X									
Chest X-Ray	X									
Urine Pregnancy (Local or Central)[j]	X	X								
Urinalysis (Central)		X								
PK (Central)			X[i]		X	X	X			X
ADA (Central)		X				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
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.

[f] Both a documented CRP ≥ 1.0 mg/dL AND a pericarditis pain level of ≥ 4 is required 7 days prior to and including the Run-In Baseline visit. These are not required to occur on the same day.

[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.

Table 1–2 Study Schedule of Activities – Randomized Withdrawal (Part 1 of 2)

Trial Period	RANDOMIZATION WITHDRAWAL (minimum 24 weeks)[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

[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

[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.

[m] All procedures are to be completed prior to study drug administration.

[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.

Table 1–2 Study Schedule of Activities – Randomized Withdrawal (Part 2 of 2)

Trial Period	RANDOMIZATION WITHDRAWAL (minimum 24 weeks)[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
Hematology, Chemistry Labs (Central)		X		X		X		X	X
Lipid Panel (Central)[h]						X			X
CRP (Local)									
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)									
Urinalysis (Central)									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]
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.

[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.

[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 1–3 Study Schedule of Activities – Long Term Extension (Part 1 of 2)

Trial Period	LONG TERM EXTENSION (48 WEEKS)				
	Long Term Extension Treatment (24 Weeks)[m]			Long Term Extension Follow Up (24 Weeks)	
Visit Name	LTE Week 8	LTE Week 16	LTE Week 24	LTE Week 30	EOS/ LTE Week 48
Visit Window[b] (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2
Visit Type	Clinic	Clinic	Clinic	Clinic	TC
Concomitant medications	X	X	X	X	X
Pericarditis Concomitant medications	X	X	X	X	X
Full Physical Examination[c]			X		
12-Lead ECG			X		
Echo[e]			X		
MRI (substudy only)			X		
Pericardial pain (11-point NRS)	DAILY				
EQ-5D			X		
SF-36			X		
ISI			X		
PGIPS	X	X	X		
PGA-PA	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

[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.

[m] All procedures are to be completed prior to study drug administration.

Table 1–3 Study Schedule of Activities – Long Term Extension (Part 2 of 2)

Trial Period	LONG TERM EXTENSION (48 WEEKS)				
	Long Term Extension Treatment (24 Weeks)[m]			Long Term Extension Follow Up (24 Weeks)	
Visit Name	LTE Week 8	LTE Week 16	LTE Week 24	LTE Week 30	EOS/ LTE Week 48
Visit Window[b] (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2
Visit Type	Clinic	Clinic	Clinic	Clinic	TC
Hematology, Chemistry Labs (Central)	X	X	X		
Lipid Panel (Central)[h]			X		
CRP (Central)	X	X	X		
PK (Central)			X	X	
ADA (Central)			X	X	
Biomarkers (Central)			X		
Urine Pregnancy[j] (Local or Central)				X	
Urinalysis			X		
IWRS Subject Status Update			X		
IWRS Weight Input (pediatric only)	X	X			
IWRS Drug Dispensing	X	X			
In Clinic Study Drug Administration[o]	X	X	X		
Outpatient Study Drug Administration[o]	WEEKLY				
Study Drug Compliance Review	X	X	X		
Assessment of Pericarditis Recurrence	X	X	X	X	X
Adverse Event Reporting[l]	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.

[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.

Table 1–4 Study Schedule of Activities – Supplemental Visits (Part 1 of 2)

Trial Period	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	

[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

[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.

[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.

Table 1–4 Study Schedule of Activities – Supplemental Visits (Part 2 of 2)

Trial Period	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**
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
Biomarkers (Central)	X		
Urine Pregnancy[j] (Local or Central)			X
Urinalysis (Central)		X	
IWRS Subject Status Update	X[s]	X	
IWRS Weight Input (pediatric only)	X		
IWRS Drug Dispensing	X		
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] Upon investigator confirmation of pericarditis recurrence, the IWRS is to be updated.

[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.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAPS	Cryopyrin Associated Periodic Syndrome
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CMH	Cochran–Mantel–Haenszel
CRP	C-reactive protein
CS	corticosteroids
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiography; echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EORW	End of Randomized-Withdrawal(visit)
EOS	End of Study
EOT	End of Treatment (visit)
EQ-5D-5L	5-level EuroQoL-5D
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG1	human immunoglobulin G1
IGRA	Interferon Gamma Release Assay
IL-1	interleukin-1
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ISR	injection site reaction
ITT	intent to treat
IV	intravenous(ly)
IWRS	interactive web response system
KPL-914	rilonacept

LDL	low-density lipoprotein
LTE-FUP	Long Term Extension Follow-Up Period
LTE-TP	Long Term Extension Treatment Period
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MWS	Muckle-Wells Syndrome
NSAID	nonsteroidal anti-inflammatory drug
NRS	Numerical Rating Scale
ORT	Oral Rescue Therapy
PHV	Pharmacovigilance
PGA-PA	Physician Global Assessment of Pericarditis Activity
PGIPS	Patient Global Impression of Pericarditis Severity
PK	pharmacokinetic(s)
POC	point of care
PRO	patient-reported outcome
RI	Run-In (period)
RN	visiting registered nurse
RW	Randomized-Withdrawal (period)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SF-36	36-Item Short Form Health Survey
SFU	safety follow-up
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TC	site telephone visit (telephone contact)
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell
WFI	Water for Injection

1 Introduction

Pericarditis is inflammation of the pericardium, the double-walled sac surrounding the heart. Etiologies of pericarditis include infectious causes (viral, bacterial, fungal, and parasitic) and non-infectious causes (idiopathic, autoimmune, neoplastic, metabolic, traumatic, post-surgical, and drug-related) (Adler et al 2015). In 80% of cases in developed countries, the cause of pericarditis is either post-viral or "idiopathic" in that it cannot be attributed to a specific condition (Imazio et al 2010; Zayas et al 1995).

The underlying pathogenesis of recurrent pericarditis remains unclear, although a growing body of evidence suggests that abnormal immune responses play a role in the pathogenic processes. While the adaptive immune system plays a role in autoimmune disorders that manifest with pericarditis as one of the many organ systems involved (such as in systemic lupus erythematosus or rheumatoid arthritis), the innate immune system, including interleukin 1 (IL-1) signaling, is often the major effector in autoinflammatory disorders, such as isolated pericarditis (Baskar et al 2016; Brucato et al 2016; Imazio et al 2016, Dinarello et al 2012).

Diagnosis of pericarditis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic changes, pericardial effusion, or elevated levels of inflammation markers (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Adler et al 2015). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define an acute pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rubs, new widespread ST-segment elevation or PR-segment depression based on electrocardiogram (ECG) findings, and pericardial effusion (new or worsening). Elevations of certain markers of inflammation (i.e., CRP, ESR, and WBC) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]) are used as supportive findings (Adler et al 2015).

Recurrent pericarditis is characterized by the recurrence of pericarditis signs and symptoms after a symptom-free period of at least 4 to 6 weeks (Adler et al 2015). Recurrent pericarditis affects 20% to 30% of patients with acute pericarditis (Imazio 2014) and can be debilitating for patients due to pain and limitations in physical function during pericarditis episodes. Pericarditis recurrences result in increased emergency room admissions and hospitalizations. In the United States, 5% of patients presenting to the emergency room with non-ischemic chest pain are diagnosed with pericarditis (Agarwal et al 2015).

The estimated prevalence of recurrent pericarditis in the US and Europe is 70,000 to 160,000 patients including approximately 8,000 to 21,000 patients who are refractory or intolerant to current therapies or who require long-term administration of corticosteroids (CS) to control their disease (Brucato et al 2016; Lazaros et al 2016; Imazio et al 2010; Khandaker et al 2010; Imazio et al 2008).

1.1 Current Therapeutic Management of Pericarditis

There are no approved therapies for the treatment of recurrent pericarditis. Current treatments include nonspecific inhibitors of inflammation, i.e., aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and CS (Lilly et al 2013).

Aspirin and other NSAIDs are the first-line approach. Because high doses of aspirin and NSAIDs are often required, consideration must be given to gastric protection therapy, as potential risks of therapy include stomach ulcers and gastrointestinal (GI) bleeding, as well as renal and cardiovascular toxicity. Colchicine is another mainstay therapy for pericarditis and is commonly used with NSAIDs to hasten the response to NSAIDs and reduce the risk of subsequent recurrences. However, its use may be associated with the risk of fatal overdosing, significant drug interactions, and neuromuscular toxicity. In addition, approximately 10% to 15% of patients experience significant GI side effects with colchicine, including GI intolerance or severe diarrhea, requiring treatment discontinuation (Imazio et al 2016).

Available ESC guidelines stipulate that CS should be prescribed for the management of pericarditis episodes only in cases of incomplete response, intolerance, or contraindications to NSAIDs and colchicine because of their unfavorable long-term benefit-risk profile. Corticosteroid use is associated with side effects, including weight gain, diabetes, osteoporosis, avascular bone necrosis, and increased risk for infections (Imazio et al 2008). For the management of pericarditis, CS are usually administered at low to moderate doses and can provide rapid control of symptoms. However, they often require many months of tapering after the normalization of CRP levels. In addition, there is a high rate of pericarditis relapse when CS use is tapered or stopped (Lotrionte et al 2010; Imazio et al 2005; Maisch et al 2004), particularly in the absence of concurrent colchicine treatment.

Patients with recurrent pericarditis who are refractory or intolerant to current therapeutic management options or who require long-term administration of CS to control their disease can be particularly challenging to manage. As a last resort, some refractory patients are being referred to the surgical procedure of pericardiectomy, with variable outcomes. Multiple immunosuppressive medications have been used without consistent benefit (Baskar et al 2016). [redacted]

1.2 Pathogenesis of Recurrent Pericarditis: Role of IL-1

Interleukin-1 is a key cytokine that drives the pathophysiology of many inflammatory processes, and it is implicated as a causative factor in various inflammatory diseases in humans.

The two distinct IL-1 genes, *IL1A* and *IL1B*, encode IL-1α and IL-1β, respectively. IL-1α and IL-1β bind to the universally-expressed cell surface receptor, IL-1 receptor type-1, triggering a cascade of inflammatory mediators. The precursor form of IL-1α is expressed in keratinocytes, mucous membrane epithelial cells, and organs such as the liver and vascular endothelium in healthy individuals. During pathological states, IL-1α moves to the cell surface or is released after cell death to activate IL-1 receptors in adjacent cells, thus beginning the cascade of sterile inflammation. IL-1β,

however, is not expressed in healthy individuals until a stimulus, such as microbial products or other chemokines, triggers its transcription in monocytes, tissue macrophages, and dendritic cells via the inflammasome. IL-1 drives the inflammatory cascade in classic autoinflammatory conditions, such as tumor necrosis factor (TNF)-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) and plays a significant role in systemic onset of juvenile idiopathic arthritis and in autoimmune diseases such as rheumatoid arthritis (Baskar et al 2016).

IL-1–blocking therapies are effective at controlling end-organ disease and damage in patients with various autoinflammatory disorders, and different strategies to block IL-1 have been used in clinical trials and demonstrated substantial success in controlling episodes of fever and elevations in acute-phase reactants (Cantarini et al 2015).

This mechanistic plausibility of IL-1 antagonism in addressing pathophysiology related to the inflammasome extends to other conditions characterized by sterile acute inflammation, such as recurrent pericarditis.

[redacted]

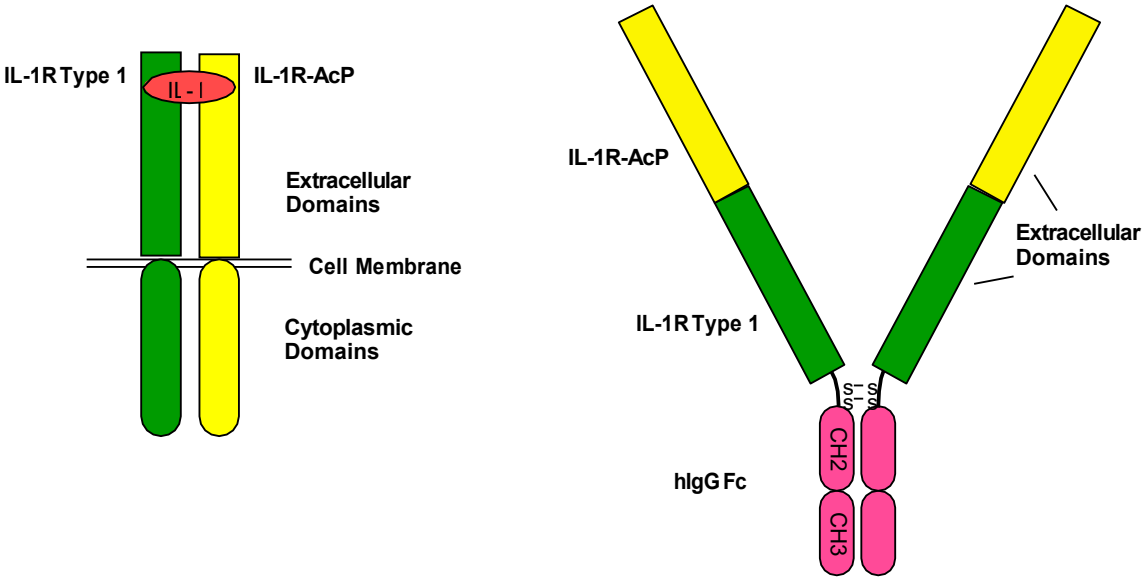
1.3 Rilonacept (KPL-914)

Rilonacept (designated in Kiniksa Pharmaceutical's development program as KPL-914) was developed by Regeneron Pharmaceuticals, Inc. (Regeneron) of Tarrytown, NY, and is approved with the trade name ARCALYST® in the US for the treatment of CAPS, including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children age 12 and older. Rilonacept is currently manufactured and marketed as ARCALYST® by Regeneron. Rilonacept received marketing authorization in the European Union for the treatment of CAPS with severe symptoms, including FCAS and MWS in adults and children aged 12 years and older, but based on a request from Regeneron, the marketing authorization was withdrawn. The withdrawal was a business decision and was not related to any concern with the safety or efficacy of rilonacept.

Rilonacept is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human IgG1. Rilonacept is a dimeric glycoprotein with a total molecular weight of approximately 250 kDa. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1 type I receptor (IL-1R1) and the IL-1 receptor accessory protein (IL-1R-AcP) (Figure 1).

Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells. Rilonacept blocks IL-1 by acting as a soluble decoy receptor that binds IL-1 and prevents its interaction with cell surface receptors.

Figure 1: Schematic of Rilonacept (KPL-914)



1.3.1 Safety of Rilonacept

For a detailed review of the available rilonacept safety data, please refer to the current Investigator Brochure and the ARCALYST® package insert (Section 13.1: ARCALYST® Prescribing Information). The available rilonacept safety data is summarized below.

Rilonacept has been evaluated in 23 studies, including 22 complete and 1 ongoing. In the completed studies, 2243 subjects (2152 patients and 91 healthy volunteers) were exposed to rilonacept. Thirty of these patients were pediatric (<18 years of age).

Doses up to 320 mg subcutaneously (SC) once weekly and 2000 mg intravenously (IV) monthly have been studied for different indications, including CAPS, gout, and other inflammatory disorders.

Injection Site Reactions

In clinical studies with rilonacept, the most common and consistently reported AE associated with rilonacept was injection site reaction (ISR). The ISRs included erythema, swelling, pruritus, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth, and hemorrhage. Most ISRs were mild to moderate. In the gout clinical studies, approximately 1% of subjects treated with rilonacept discontinued due to ISRs. Similar results have been seen in other patient populations.

Infections

Interleukin-1 blockade may interfere with immune response to infections. Serious life-threatening infections have been reported in clinical trials in subjects treated with rilonacept.

Changes in Laboratory Parameters

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Subjects treated with rilonacept in clinical trials experienced increases in their mean total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Antibodies directed against the receptor domains of rilonacept were detected using an enzyme-linked immunosorbent assay (ELISA). In clinical trials with rilonacept, approximately 30% to 35% of subjects tested positive for treatment-emergent antibodies to rilonacept on at least 1 occasion.

Systemic Hypersensitivity Reactions

Hypersensitivity reactions are a potential risk with protein therapeutics in general. In clinical studies with rilonacept, systemic hypersensitivity reactions have been rare.

Malignancies

The impact of treatment with rilonacept on the development of malignancies is not known. However, treatment with immunosuppressants, including rilonacept, may result in an increase in the risk for malignancies.

Fetal Defects

There are no adequate and well-controlled studies of rilonacept in pregnant women. Based on animal data, rilonacept may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15, or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human dose of 160 mg based on body surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100, or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

Nonteratogenic effects: A peri- and postnatal reproductive toxicology study was performed in which mice were administered a murine analog of rilonacept at doses of 20, 100, and 200 mg/kg SC 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F1 offspring during maturation at all doses tested.

1.3.2 KPL-914-C001 Study with Rilonacept (KPL-914) in Recurrent Pericarditis

KPL-914-C001 is an open-label, single active-arm Phase 2 proof-of-concept study in subjects age ≥6 to 75 years old with recurrent idiopathic or post-pericardiotomy syndrome (PPS) pericarditis. The study includes a 6-week Treatment Period in which all the subjects receive once-weekly rilonacept 160 mg SC (2.2 mg/kg for subjects ≥6 and <18 years old) following a loading dose of 320 mg SC in subjects ≥18 years old (4.4 mg/kg in subjects ≥6 and <18 years old) in addition to background pericarditis therapies (NSAIDS, colchicine, CS). After completing the 6-week Treatment Period and based on response status, the subjects have the option to enter the 18-week Extension Period during which they continue to receive rilonacept at the same dose, but during which investigators are encouraged to wean and stop background pericarditis medications.

The primary objectives of the study are to explore clinical and biochemical endpoints of recurrent pericarditis symptomatology, as well as to assess feasibility to wean from concomitant pericarditis medication in the Extension Period while continuing treatment with rilonacept. The study population includes the following 5 subject categories (Parts):

- Part 1 enrolls symptomatic subjects with recurrent idiopathic pericarditis with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 2 enrolls symptomatic subjects with recurrent idiopathic pericarditis with CRP level ≤1 mg/dL that, in the opinion of the investigator, can be attributed to concomitant medications (e.g., CS) and with pericardial inflammation present on cardiac MRI confirmed by the imaging core lab.
- Part 3 enrolls subjects with CS-dependent recurrent idiopathic pericarditis not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.
- Part 4 enrolls symptomatic subjects with recurrent PPS with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 5 enrolls subjects with CS-dependent recurrent PPS not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.

Preliminary data in this ongoing study suggest that subjects enrolled in Part 1 experience improvements in pain, CRP levels, and other pericarditis parameters compared to baseline.

Adverse events observed in the study are consistent with the overall rilonacept safety profile.

2 Study Objectives and Endpoints

2.1 Primary Objective

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

2.2 Secondary Objective

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

3 Investigational Plan

3.1 Study Design

This is a Phase 3, multi-center, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis. This study has 5 periods (Figure 2).

3.1.1 Screening Period (up to 4 weeks)

During the screening period, assessment of disease characteristics, baseline therapy, and thepre-treatment workup will be completed during a period of up to 4 weeks.

3.1.2 Single-blind Run-In (RI) Period (12 weeks)

During the single-blind RI period, treatment with blinded rilonacept is administered and subjects are weaned off background standard of care (SOC) therapy for their pericarditis disease. Subjects will be blinded regarding the time of transition from the single-blind to the double-blind period; i.e., they will not be aware of the duration of the RI period.

In the single-blind RI period, subjects ≥18 years old will receive blinded 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 blinded 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 the RI period.

The RI period includes:

- 1-week Stabilization period, during which blinded rilonacept is administered in addition to 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. The dosages of CS, NSAIDs, and colchicine will be tapered according to the weaning protocol in the Pharmacy Manual (for the purpose of the protocol, aspirin is considered an NSAID). In general, CS doses will be tapered off starting at RI Week 1 and will be withdrawn by RI Week 10 (over a total of 9 weeks). NSAID and colchicine doses will be tapered off starting at RI Week 4 and will be withdrawn by RI Week 10 (over a total of 6 weeks).
- 2-week Monotherapy period: Subjects who have been successfully weaned off background SOC pericarditis therapy will continue to receive blinded rilonacept.

Subjects who stopped background pericarditis medications and achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will proceed into the double-blind placebo-controlled Randomized-Withdrawal (RW) period of the study. For definition of Clinical Response, refer to Section 6.2.2.

Subjects who are unable to achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline are to be discontinued from study drug, transitioned to SOC pericarditis therapy at the investigator's discretion, and followed through the end of the RW period.

3.1.3 Double-blind Placebo-controlled RW Period (pericarditis recurrence event-driven duration with a minimum of 24 weeks)

During the RW period, subjects who were able to stop background pericarditis medications and who achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will be randomized 1:1 to double-blinded administration of study drug:

- Rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects ≥12 and <18 years old) SC injections once weekly OR
- Matching placebo SC injections once weekly

Pericarditis Recurrence in the RW Period

For the definition of pericarditis recurrence, refer to Section 6.2.3.

Upon pericarditis recurrence, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale [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 prior RW period treatment assignment. 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 Section 5.8.3 and detailed in the Pharmacy Manual.

Subjects with pericarditis recurrence who do not meet the protocol criteria for bailout rilonacept will continue blinded study drug until they meet the protocol criteria for bailout rilonacept 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 Section 5.8.3 and detailed in the 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.

The RW period will continue until the prespecified number of primary endpoint (CEC-confirmed pericarditis recurrence) events have occurred and approximately 50 randomized subjects have

achieved a minimum of 24 weeks of treatment in the RW period. Based on projected event accrual and subject randomization, Kiniksa Pharmaceutical will determine the end of the RW period and announce to sites so that subject End of Randomized Withdrawal (EORW) visits can occur. All subjects, including those who have transitioned to open-label rilonacept or who prematurely discontinued study drug, should complete an EORW visit.

3.1.4 Long Term Extension Treatment Period (LTE-TP) (24 weeks)

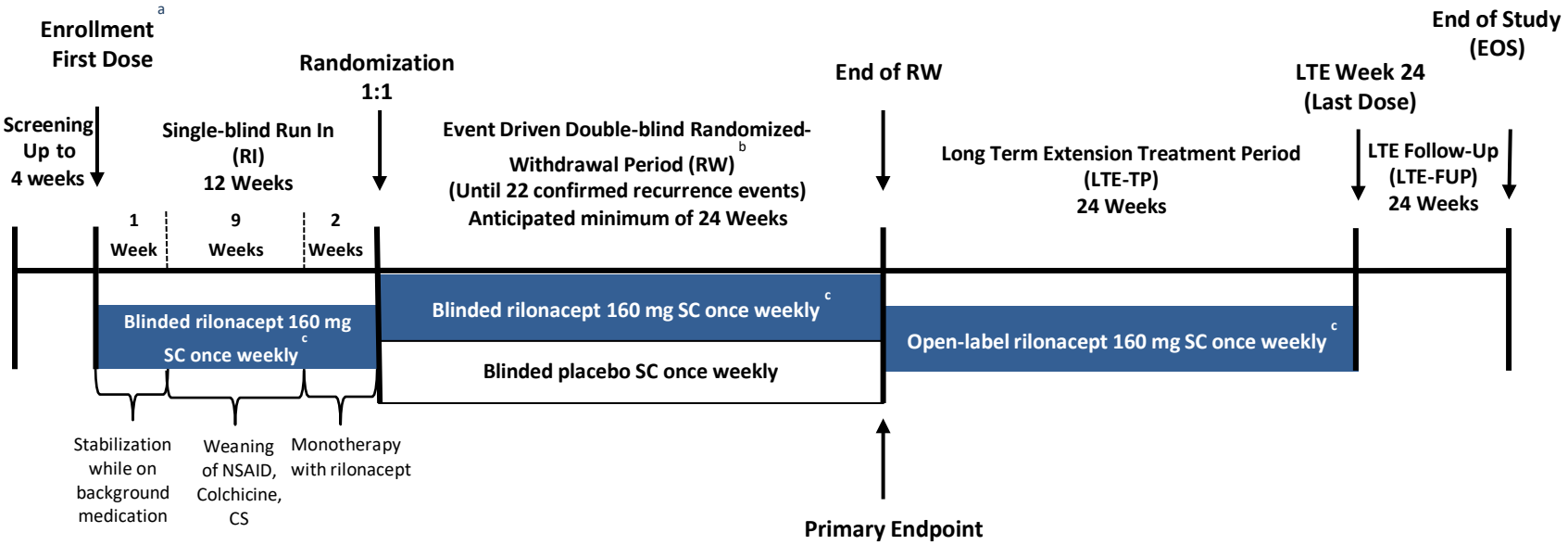
Upon completion of the RW period and the EORW visit (site and subject unblinding), all subjects completing the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) will have an option to receive up to 24 weeks of open-label rilonacept 160 mg (or 2.2 mg/kg for pediatric subjects) SC injections once weekly based on their clinical status and at the discretion of the investigator, after signing LTE informed consent. Any subject who, in the opinion of investigator, should not continue open-label rilonacept will be offered participation in the LTE off study drug after signing LTE informed consent.

3.1.5 Long Term Extension Follow-Up Period (LTE-FUP) (24 weeks)

All subjects in the LTE-TP will be followed in the LTE-FUP for an additional 24 weeks for safety and for potential pericarditis recurrence assessments.

The total duration of the study will be determined by the rate of enrollment, the rate of first recurrence of pericarditis events during the RW period, and the minimum duration of follow-up in the RW of 24 weeks. It is anticipated that study completers (including LTE-TP) will be dosed with rilonacept for approximately 1.2 years and up to 3 years based on enrollment assumptions and pericarditis recurrence events accrual time.

Figure 2: Overview of KPL-914-C002 Trial Design



Abbreviations: CS=corticosteroid; EOS=end of study, LTE=Long Term Extension; NSAID=nonsteroidal anti-inflammatory drug; RI=run in, RW=randomized withdrawal, SC=subcutaneously, TP=treatment period

a. The first dose given is a loading dose of rilonacept. In adult subjects ≥18 years old, 320 mg is given as 2 SC doses of 160 mg. In pediatric subjects ≥12 and <18 years old, 4.4 mg/kg is given as 2 SC doses of 2.2 mg/kg. After the loading dose, rilonacept will be administered as a 160 mg (adults) or 2.2 mg/kg (pediatric subjects) SC dose once weekly.

b. Subject's treatment duration will depend on when the subject is enrolled relative to the end of RW.

c. The adult dose is 160 mg SC once weekly. The pediatric dose is 2.2 mg/kg SC once weekly.

Note: This picture is not drawn to scale.

3.1.6 Rationale of Study Design

Subjects eligible for this KPL-914-C002 study will be subjects with recurrent pericarditis presenting with an acute pericarditis episode at screening.

The KPL-914-C002 study design ensures that during the RI period all subjects will receive rilonacept, a drug with evidence supporting clinical activity based on the preliminary clinical data with rilonacept from Part 1 of the ongoing Phase 2 proof-of-concept study (KPL-914-C001) obtained to date. During the RI period, pericarditis will be stabilized with symptoms controlled and background pericarditis medications (NSAIDs, colchicine, CS) will be tapered and withdrawn, while rilonacept treatment continues.

The design then allows half of the subjects to continue receiving active treatment after having achieved Clinical Response on that treatment, which maximizes subject exposure to a potentially beneficial therapy. The temporary withdrawal of rilonacept (by switching to placebo) in the half of the subjects who were randomly assigned to placebo is expected to result in an accelerated time to pericarditis recurrence and a higher recurrence rate compared to those who continue on active treatment, a finding that demonstrates that the underlying pericarditis etiology is still ongoing and will provide further support for the anticipated observation of the clinical effect of rilonacept during the RI period of the study. The period of exposure to an ineffective treatment is minimized in this design, as subjects will be removed from blinded treatment when the condition returns to a specified severity (i.e., for having met the criteria of pericarditis pain ≥4 on the 11-point NRS and CRP level ≥1 mg/dL) without unblinding them to prior treatment assignment, thus protecting the primary efficacy endpoint of the study. All subjects who meet the pain and CRP criteria described above will be treated with open-label bailout rilonacept using a loading dose, followed by once-weekly SC injections. In addition, sequential ORT such as NSAIDs and/or colchicine will be allowed upon recurrence at the investigator's discretion based on the subject's clinical status, as outlined in Section 5.8.3 and as stipulated in the Pharmacy Manual. Subjects with pericarditis recurrence not meeting criteria for bailout rilonacept, can be treated with sequential ORT based on investigator judgement and as described in protocol Section 5.8.3 and the Pharmacy Manual. If the subject requires the addition of CS treatment to control the pericarditis recurrence, the subject will be discontinued from study drug. All subjects will be followed for the duration of RW period.

In summary, the proposed RW trial with rilonacept allows all enrolled subjects an opportunity to receive the active drug during the acute episode of pericarditis yet provides pivotal-quality data on the efficacy of rilonacept in this enriched cohort by subsequently randomly assigning subjects to placebo versus active treatment after they achieve a predefined clinical response. Subjects with pericarditis recurrences after randomization will receive bailout rilonacept treatment and/or sequential ORT according to the protocol. This approach minimizes the exposure to placebo, which is important for a study that requires active disease upon enrollment and includes a pediatric population. The available regulatory guidance supports the use of an RW study design in the setting of recurrent pericarditis as

a means of establishing the long-term effectiveness of rilonacept, an approved product for the treatment of another rare autoinflammatory condition (CAPS).

3.1.7 Justification for Rilonacept Dose Selection

The rilonacept dosing regimen utilized in the current study [redacted] i.e., 320 mg SC loading dose (4.4 mg/kg in subjects ≥12 and <18 years old), followed by once-weekly SC doses at 160 mg (2.2 mg/kg in subjects ≥12 and <18 years old).

In the rilonacept development program in CAPS, gout, rheumatoid arthritis, and other inflammatory conditions, over 2000 subjects were exposed to rilonacept, including 1650 subjects receiving a rilonacept dose of 160 mg or higher. A total of 103 and 169 subjects were exposed to any rilonacept dose for at least 1 year or 6 months, respectively. Most of the real-life experience with rilonacept comes from the CAPS population treated at this marketed dose. As of March 2018, approximately 365 CAPS patients have been exposed to rilonacept in the post-marketing setting since 2008. The safety data accumulated so far support the benefit/risk ratio for the rilonacept dose intended to be evaluated in subjects with recurrent pericarditis.

Based on the preliminary clinical data with rilonacept from Part 1 of the Phase 2 proof of concept study (KPL-914-C001) obtained to date, it is expected that rilonacept doses [redacted] (320 mg followed by 160 mg SC once weekly and corresponding pediatric doses), and evaluated in the KPL-914-C001 study, will consistently provide adequate suppression of clinical inflammatory response, including CRP levels, in patients with recurrent pericarditis.

Bailout Rilonacept Dose

Subjects who meet the protocol criteria for bailout rilonacept upon pericarditis recurrence in the RW period of the study (Sections 3.1 and 6.2.3), irrespective of treatment assignment at randomization, will receive open-label rilonacept (loading dose of 320 mg SC followed by once-weekly SC injections of 160 mg, or the corresponding pediatric doses). [redacted]

The rationale for bailout rilonacept treatment upon pericarditis recurrence for subjects who were randomly assigned to placebo is that rilonacept had controlled their disease activity during the RI period; therefore, re-initiation of rilonacept is justified to regain control of pericarditis signs and symptoms upon recurrence. Subjects who were randomly assigned to rilonacept and qualify for bailout rilonacept upon pericarditis recurrence in the RW period were initial responders to rilonacept treatment during the RI period; thus it could be assumed that the loss of response during the RW

period could be due to development of resistance to rilonacept due to different mechanisms, e.g., higher IL-1 levels or a change in rilonacept pharmacokinetics (PK)/ pharmacodynamics. Therefore, re-administration of a loading dose of rilonacept may help to restore Clinical Response.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 56 subjects will be enrolled (and not more than 75 subjects), which will allow at least 50 subjects to be randomized at approximately 50 sites globally. Subjects will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 pericarditis episodes (including the first episode and 1 recurrence) prior to screening. Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and CRP level ≥1 mg/dL within 7 days prior to the first study drug administration.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent form (ICF) or assent form (for pediatric subjects ≥12 and <18 years old), has provided signed and witnessed written informed consent or assent (as applicable), and agrees to comply with protocol requirements.
2. Is male or female 12 years of age or older with body weight of at least 23.6 kg (52 Lbs).
3. Has a diagnosis of recurrent pericarditis.
4. At least 1 of the pericarditis episodes experienced prior to screening has met at least 2 of the following 4 criteria, in the opinion of the investigator and based on the documented available data, according to the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al 2015):
    a. Pericarditic chest pain
    b. Pericardial rub
    c. New widespread ST-segment elevation or PR-segment depression according to ECG findings
    d. Pericardial effusion (new or worsening)
5. Presents with at least the third episode of pericarditis during screening (i.e., at least the second pericarditis recurrence following the first pericarditis episode), and within 7 days* prior to and including RI baseline (first administration of study drug) has:
    a. At least 1 day with pericarditis pain ≥4 on the 11-point NRS, **AND**
    b. CRP level ≥1.0 mg/dL (for details of CRP collection see Section 6.1.1)

    *Pericarditis pain ≥4 and CRP ≥1 mg/dL are not required to be present on the same day.
6. Has received NSAIDs and/or colchicine and/or CS (in any combination), if used, at stable dose levels (or at least not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs) are not anticipated, in the opinion of the investigator, to significantly alter assessments of baseline disease activity.
7. If using NSAIDs and/or colchicine and/or CS at the time of RI baseline (first administration of study drug), is willing and able, in the opinion of the investigator, to taper and discontinue those medications within the 9-week weaning time in the RI period of the study while continuing rilonacept treatment.

8. Female subjects must be:
    a. Postmenopausal, defined as at least 12 months after the cessation of menses (without an alternative medical cause) OR
    b. Incapable of pregnancy OR
    c. Permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation or having a male partner with vasectomy as affirmed by the subject OR
    d. If of childbearing potential, must agree to use a highly effective method of contraception during the study and for 3 months after the last study drug administration (i.e., hormonal contraceptives associated with inhibition of ovulation, intrauterine device [IUD], intrauterine hormone-releasing system [IUS], or sexual abstinence)
9. If male and sexually active, must have documented vasectomy or must practice birth control and not donate sperm during the study and for 3 months after the last study drug administration.
10. Must be up-to-date with all immunizations, in agreement with current local immunization guidelines for immunosuppressed subjects, before RI baseline (first administration of study drug).
11. Is able to adequately maintain a daily subject diary according to protocol.
12. Must be able to adhere to the study visit schedule and understand and comply with the other protocol requirements.
13. Agrees to refrain from making any new, major lifestyle changes that may affect pericarditis symptoms (e.g., changing exercise pattern) from the time of the ICF is signed through the end of the double-blind RW period.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Has a diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis; or systemic autoimmune diseases with exception of Still's disease.
2. Is pregnant, breastfeeding, or planning a pregnancy or fathering a child during the study or within 3 months after the last study drug administration.
3. Has a history of immunosuppression, including positive human immunodeficiency virus (HIV) test results.

4. Is currently receiving CS at a dose of >60 mg/day prednisone (or equivalent) for adult subjects, or >0.5 mg/kg/day (or >60 mg/day, whichever is lower) prednisone (or equivalent) in pediatric subjects (≥12 and <18 years old).
5. Has ever received cytotoxic drugs, including cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.
6. Has ever received agents that deplete B or T cells (e.g., rituximab, alemtuzumab).
7. Has received systemic immunomodulatory agents (with exception of CS) within the following time frames prior to RI baseline (first administration of study drug):
    a. Azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, or mercaptopurine within 24 weeks.
    b. TNF inhibitors, IL-6 inhibitors, or janus-activating kinase inhibitors within 12 weeks.
    c. Canakinumab within 12 weeks. Canakinumab could not have been discontinued due to safety unless it was discontinued due to local injection site reactions.
    d. Rilonacept within 6 weeks. Rilonacept could not have been discontinued due to lack of efficacy or due to safety.
    e. Methotrexate within 2 weeks.
    f. Anakinra within 5 days. Anakinra could not have been discontinued due to lack of efficacy or due to safety unless it was discontinued due to local injection site reactions.
8. Has a history of myeloproliferative disorder.
9. Has a history of demyelinating disease or symptoms suggestive of multiple sclerosis.
10. Meets the following TB criteria:
    a. History of active TB prior to screening OR
    b. History of latent TB that was not adequately treated prior to screening OR
    c. Signs or symptoms suggestive of active TB (e.g., new cough of >14 days in duration or a change in chronic cough, persistent fever, unintentional weight loss, or night sweats) upon review of medical history and/or physical examination at screening OR
    d. Recent close contact with a person with active TB OR
    e. Positive or indeterminate Interferon Gamma Release Assay (IGRA) test results or results from another positive TB test at screening based on acceptable clinical practice for the country in which the subject is enrolling.
11. Has chest x-ray (posterior-anterior view) at screening (or history of results within 12 weeks before receiving first administration of study drug), with evidence of malignancy or abnormality consistent with prior or active TB infection.

12. Has received immunization with a live (attenuated) vaccine within 12 weeks before screening or is expected to receive live (attenuated) vaccine during the study or within 12 weeks after the last study drug administration.
13. Has a history of positive or intermediate results for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening.
14. Has an estimated glomerular filtration rate (eGFR) <30 ml/min.
15. Has a history of malignancy of any organ system within the past 5 years before screening (other than a successfully treated non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
16. Has a known or suspected current active infection or a history of chronic or recurrent infectious disease, including, but not limited to, chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, or an open, draining infected skin wound.
17. Has had a serious infection, has been admitted to the hospital for an infection, has been treated with oral antibiotics within 2 weeks of RI baseline (first administration of study drug), or has been treated with IV antibiotics for an infection within 8 weeks of RI baseline.
18. Has had an organ transplant.
19. Has screening laboratory test results meeting any of the following criteria:
    a. Hemoglobin level <10.0 g/dL;
    b. WBC count $<3.0 \times 10^3/\mu L$
    c. Neutrophil count $<1.5 \times 10^3/\mu L$
    d. Platelet count $<100 \times 10^3/\mu L$
    e. Total bilirubin level >1.5 × the upper limit of normal (ULN) unless the test results are consistent with those for Gilbert's syndrome
    f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 × ULN
20. In the investigator's opinion, has a history of alcoholism or drug/chemical abuse within 2 years before screening.
21. Has a known hypersensitivity to ARCALYST® (rilonacept) or to any of its excipients.
22. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before screening or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
23. In the investigator's opinion, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations. This includes significant concomitant illnesses such as, but not limited to, cardiac, renal, neurological, endocrinological, metabolic, pulmonary, GI, or psychiatric diseases.

24. In the opinion of the investigator, is not likely to be compliant with the study protocol.
25. In the opinion of the investigator, should not participate in this study.

4.2 Subject Completion, Withdrawal from Study, and Study Drug Discontinuation

4.2.1 Completion

A subject will be considered to have completed the study if she/he has completed the RW period and has completed assessments at the EORW visit. At the EORW visit, subjects who were randomly assigned to rilonacept or subjects who transitioned to open-label rilonacept upon protocol-defined pericarditis recurrence (Section 6.2.3) in the RW period will be offered an opportunity to receive an additional 24 weeks of open-label rilonacept treatment based on their clinical status and at the discretion of the investigator, and after signing the LTE informed consent.

At the EORW visit, subjects who were randomly assigned to placebo and did not transition to bailout rilonacept will be offered an opportunity to receive an additional 24 weeks of open-label rilonacept treatment based on their clinical status and at the discretion of the investigator, after signing the LTE informed consent.

Any subject who in the opinion of investigator should not continue open-label rilonacept in LTE will be offered the opportunity to continue follow-up off study drug treatment in LTE, after signing the LTE informed consent.

Subjects who elect not to enter LTE will be followed for 6 weeks after receiving the last study drug administration.

4.2.2 Reasons for Discontinuation of Study Drug and Study Withdrawal

Subjects have the right to stop taking study drug before the end of the study or to withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject also may be asked to stop study drug at the investigator's discretion. In the event that a subject permanently discontinues study drug but does not withdraw the informed consent, the investigator should continue to follow up with the subject by telephone contact (TC) visits, in the clinic, or by other means through the EORW visit if the subject discontinues in RI or RW, or through the end of LTE-FUP if the subject discontinues in LTE-TP, unless consent is withdrawn.

The reasons for premature study drug discontinuation will be recorded in the electronic case report form (eCRF).

4.2.2.1 Discontinuation of Study Drug

The study drug dosing will be permanently stopped if any of the following occurs:

- The subject develops a serious or intolerable AE, TB, or malignancy, excluding non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma

- Initiation of protocol-prohibited medication (Section 5.8.6)
- Subject requires treatment with CS for pericarditis during RW or LTE-TP periods of the study
- Pregnancy or pregnancy planned during the study or within 3 months after the last study drug administration
- ALT or AST values ≥3 × ULN associated with total bilirubin ≥2 × ULN, with no underlying medical conditions to explain the elevated values
- Treatment with a live (attenuated) vaccine during the study
- Investigator or Sponsor's medical monitor or [redacted] medical monitor decides that, for safety reasons, it is in the subject's best interest
- Termination of the study by Kiniksa Pharmaceuticals

Permanent or temporary study drug discontinuation should be strongly considered at the time if any of the following occurs:

- Subject develops an opportunistic infection.
- Subject develops moderate or severe infection
- Neutrophil count $<1.0 \times 10^3/\mu L$
- Isolated ALT or AST values >5 × ULN
- Surgical procedure

The Sponsor has the right to terminate the study at any time in case of safety concerns (e.g., suspected unexpected serious adverse reactions [SUSARs]) or if special circumstances concerning the study drug or the company itself occur. In this event, the investigator(s) will be informed of the reason for study termination.

4.2.2.2 Withdrawal from the Study

Subjects may withdraw from the study at any time and for any reason, without prejudice to their future medical care by the investigator or at the study site. However, prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow-up including options such as less frequent follow-up calls or visits, follow-up with a family member or friend, or follow-up through a local physician or medical records. Follow-up options will be summarized on a withdrawal of consent checklist source document that must be reviewed and signed by the investigator for any subject who withdraws consent for further participation in the study. The checklist must be completed for all enrolled subjects who have withdrawn consent. The reasons for a subject's withdrawal from the study are also required to be recorded in the eCRF.

A subject may be considered withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Documented withdrawal of informed consent
- Death

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and re-engage the subject in the study or determine the reason for withdrawal. The measures taken are to continue until study end and are required to be recorded in source documentation.

In subjects who are documented as having withdrawn consent from all study activities, no further study visits or study-related TCs can be conducted. All data collected prior to the date of the subject's confirmed withdrawal of consent will be included in the study, as specified in the subject's signed ICF.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

In the single-blind RI period, all subjects will receive blinded rilonacept at the same dose through Week 12; subjects will be blinded to the time of transitioning to RW. Subjects who stopped background SOC pericarditis therapy and who achieve Clinical Response on rilonacept at RI Week 12/RW baseline will be randomly assigned in a double-blind manner to continue to receive blinded rilonacept or matching placebo using a 1:1 allocation ratio. The definition of Clinical Response is provided in Section 6.2.2. An interactive web response system (IWRS) will be used to administer the randomization schedule. 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

5.2 Treatments Administered

Throughout this protocol, "study drug" refers to the investigational medicinal products: rilonacept and matching placebo. Both will be administered as applicable by SC injection.

Study drug administration will be performed once a week (every 7 ± 2 days). The interval between study drug administrations must be at least 5 days.

Study drug will be dosed as follows:

Adult Subjects (≥18 years old):

Rilonacept: Loading dose 320 mg administered as 2 SC injections, 160 mg each (2 ml) at RI baseline, followed by once-weekly SC injections of 160 mg (2ml).

Placebo: administered as once-weekly SC injections of 2 ml each in the RW period

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 320 mg administered as 2 SC injections, 160 mg each (2 ml) at the next scheduled study drug administration date, followed by once-weekly SC injections of 160 mg (2ml).

Pediatric Subjects (≥12 and <18 years old):

Rilonacept: Loading dose 4.4 mg/kg administered as 2 SC injections, 2.2 mg/kg each (maximum 160 mg each) at RI baseline, followed by once-weekly SC injections of 2.2 mg/kg (maximum 160 mg). The volume of injections will be based on the subject's weight (Table 5–1).

Placebo (in RW): once-weekly SC injections with volume based on the subject's weight (Table 5–1, maximum 2 ml).

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 4.4 mg/kg administered as 1 (maximum 2 ml) or 2 SC injections at the next scheduled study drug administration date, followed by once-weekly SC injections of 2.2 mg/kg (maximum 2 ml). The volume of injections will be based on the subject's weight (Table 5–1).

Study drug dose/volume will be calculated by the investigator or pharmacist during site clinic visits based on body weight (as specified in the Study Schedule of Activities) using a weight-based dosing chart in **kilograms** (Table 5–1).

Table 5–1: Study Drug Dose Volume (After Reconstitution) by Body Weight in Kilograms for Pediatric Subjects Aged ≥12 and <18 Years

Weight Range (kg)	Loading Dose Volume (ml)	Weekly Dose Volume (ml)
23.6 to 27.2	2 x 0.7	0.7
27.3 to 30.8	2 x 0.8	0.8
30.9 to 34.4	2 x 0.9	0.9
34.5 to 38.1	2 x 1.0	1.0
38.2 to 41.7	2 x 1.1	1.1
41.8 to 45.4	2 x 1.2	1.2
45.5 to 49.0	2 x 1.3	1.3
49.1 to 52.6	2 x 1.4	1.4
52.7 to 56.3	2 x 1.5	1.5
56.4 to 59.9	2 x 1.6	1.6
60.0 to 63.5	2 x 1.7	1.7
63.6 to 67.2	2 x 1.8	1.8
67.3 to 70.8	2 x 1.9	1.9
70.9 or greater	2 x 2.0	2.0

Study Drug Self-Administration

The first study drug dose on RI baseline will be administered at the study site. During this visit, the subject will be trained on study drug preparation and injection. In case the subject is unwilling or unable to prepare and self-inject the study drug, the subject's caregiver will be trained.

The first study drug administration for adult and pediatric subjects on RI baseline will consist of 2 SC injections, constituting a loading dose. The first injection will be prepared and administered by study site staff. The second injection will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration. If the subject or subject's caregiver is unable to prepare and inject the study dug, the subject may report for once-weekly injections to a study site, or injections can be administered by the visiting registered nurse (RN).

5.3 Identity of Investigational Medicinal Product

Rilonacept (KPL-914) is the drug being evaluated in the current study. Refer to Section 1.3 for a detailed description of rilonacept's mechanism of action.

Study drug (rilonacept or placebo) is supplied in a single-use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

Each placebo vial contains lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the placebo vial contains 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Product Packaging and Storage

Additional information regarding the preparation, dispensation, administration, and storage of rilonacept or placebo will be described in the Pharmacy Manual.

Study drug will be provided by Kiniksa Pharmaceuticals to the study sites in the lyophilized formulation in glass vials as described in Section 5.3. Each single-use vial will have a clinical label adhered to the vial. One labeled vial will be placed into a carton. Each carton will have a clinical label adhered to the outside of the carton. One tamper-evident seal will be placed on the top of the carton to securely close the lid.

Study drug is to be stored and shipped refrigerated at 2°C to 8°C (36°F to 46°F) inside the original carton to protect it from light.

5.4.2 Study Drug Accountability

The sites will receive study drug for on-site administration at study site visits. Upon receipt of study drug, the investigator (or delegate) will conduct an inventory of the supplies and verify that the supplies are received intact, at the appropriate temperature, and in the correct amounts prior to completing a supplies receipt. The investigator will confirm receipt of study drug in the IWRS and retain a copy of this receipt at the study site. The inventory of supplies at each study site will be reviewed by the study monitor.

Study drug will be dispensed to the study subjects for outpatient self-administration according to the supply chain described in the Pharmacy Manual.

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviating from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all used and unused study drug containers must be retained by the study site/clinic and subject for cataloguing and documentation of compliance. The full process for drug dispensing, documentation, and destruction will be described in the Pharmacy Manual.

A full drug accountability log will be maintained at the study site at all times.

5.4.3 Other Supplies

Rilonacept should be reconstituted with preservative-free WFI that will be provided by Kiniksa Pharmaceuticals or designee along with 27-gauge, ½-inch needles, 3-ml syringes, alcohol wipes, gauze pads, bandages, and a puncture resistant container for disposal of needles and syringes. Only the syringes and needles provided by the Sponsor or its designee should be used to prepare and inject the study drug. The Sponsor also will provide coolers and refrigerated gel packs to ensure that the subjects transport the study drug at the proper temperature. On occasion, sites may be asked to locally procure ancillary materials.

5.5 Study Drug Overdose

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose must be promptly reported to the [redacted] Pharmacovigilance (PVG) in the same way and using the same procedures as for a serious adverse event (SAE) (Section 6.4.6), regardless of whether any AEs are associated with the overdose.

If there are AEs associated with the overdose, these should be recorded on the relevant AE/SAE sections in the eCRF; however, overdoses without signs or symptoms do not need to be recorded as AEs in the eCRF.

5.5.1 Treatment of Study Drug Overdose

The maximum amount of rilonacept that can be safely administered has not been determined. Maximum once-weekly doses of rilonacept up to 320 mg have been administered SC for up to approximately 18 months in a small number of subjects with CAPS, and for up to 6 months in subjects in an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, rilonacept given IV at doses up to 2000 mg monthly for up to 6 months in another subject population was tolerated without dose-limiting toxicities (Rilonacept IB). In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of AEs and appropriate symptomatic treatment instituted immediately (Section 13.1, ARCALYST® Prescribing Information).

5.5.2 Other Study Drug Errors

To avoid study drug errors, it is important to note the following:

- In this study, rilonacept is designated for SC injections only. It should be taken only by the subjects participating in the study and as instructed by study site personnel.
- Guidelines regarding the management of temperature excursions during storage will be detailed in the Pharmacy Manual.
- Pediatric dosing is calculated based on body weight in **kilograms,** not pounds.

Any study drug error must be promptly reported to the [redacted] PVG, in the same way and using the same procedures as for an SAE (Section 6.4.6)

5.6 Transmission of Infectious Agents

The lyophilized study drug is to be stored refrigerated at 2°C to 8°C (36°F to 46°F) inside the original carton to protect it from light. Study drug should not be used beyond the date stamped on the label. After reconstitution, study drug may be kept at room temperature, should be protected from light, and should be used within 3 hours of reconstitution. Study drug does not contain preservatives; therefore, unused portions of study drug should be discarded.

5.7 Misuse for Illegal Purposes

Rilonacept does not have addicting potential, and the risk of misuse for illegal purposes is minimal.

5.8 Prior and Concomitant Medications

Use of all concomitant medications and any changes in concomitant medications will be recorded in the subject's eCRF. The minimum requirement is that drug name and dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF. The initiation of protocol prohibited medication (Section 5.8.6) requires discontinuation of study drug.

Guidelines regarding the use of concomitant medication will be detailed in the Pharmacy Manual and are summarized in the following sections.

5.8.1 Screening

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine, and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs), in the opinion of the investigator, are not anticipated to significantly alter assessments of baseline disease activity.

Analgesics can be used at the discretion of the investigator during screening activities prior to the first study drug dose, but only after the subject has documented a pericarditis pain level ≥4 on the 11-point NRS within 7 days prior to and including RI baseline (first administration of study drug).

Subjects can enter the study on prednisone (or equivalent dose) not exceeding 60 mg/day for adults and not exceeding 0.5 mg/kg/day (with a maximum dose of 60 mg/day) in pediatric subjects.

5.8.2 Single-blind RI Period

- 1-week Stabilization period, during which rilonacept is administered in addition to SOC pericarditis therapy and ongoing pericarditis episode is treated. All concomitant pericarditis medications including NSAIDs, analgesics, colchicine and CS will remain stable, unless the dosing must be decreased or stopped in the judgement of the investigator due to an AE.
- 9-week background medication Weaning period, during which subjects are weaned off background SOC pericarditis therapy, as applicable, while treatment with blinded rilonacept continues. The guidelines for background medication taper and discontinuation will be provided in the Pharmacy Manual.

  Corticosteroids

  Starting at Week 1 and through Week 10, CS will be tapered and discontinued at a rate dependent on the dose at study entry.

  Analgesics

  Starting at Week 1 and through Week 10, analgesics (non-opioid and opioid) will be tapered and discontinued. Opioid analgesics can continue beyond Week 10 at stable doses through the end of the RW period if it is not feasible to discontinue them without causing withdrawal symptoms.

  NSAIDs and Colchicine

  Starting at Week 4 and through Week 10, NSAIDs and colchicine will be tapered and discontinued.

- 2-week Monotherapy period during which rilonacept administration continues: Subjects are required to be off all background SOC pericarditis therapy, with the exception of opioid analgesics if their discontinuation is not feasible.

5.8.3 Double-blind Placebo-controlled RW Period

During the RW period, subjects should not be receiving any concomitant medications for pericarditis, with the exception of opioid analgesics in case their taper down and discontinuation was not feasible in the RI period.

5.8.3.1 Concomitant Medication Upon Pericarditis Recurrence

Subjects meeting protocol criteria for bailout rilonacept

Upon pericarditis recurrence and meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) and completing the diagnostic workup as confirmed by the [redacted] medical monitor, subjects will be transitioned to open-label rilonacept, as described in Section 3.1. Because open-label rilonacept can be administered only if at least 5 days have passed from the last blinded study drug administration, the investigators are allowed to use sequential ORT, i.e., analgesics, NSAIDs, and colchicine if necessary at their discretion. The use of those medications will be detailed in the Pharmacy Manual; it is briefly given as follows:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to open-label rilonacept based on the subject's clinical status and at the discretion of the investigator.
- If, after transition to open-label rilonacept, the investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from rilonacept and followed through the EORW visit.

Subjects not meeting protocol criteria for bailout rilonacept

If, based on the investigator's judgement, the subject is experiencing pericarditis recurrence that does not meet the protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) but does require additional treatment, the subject will continue blinded study drug, and the investigator should manage the pericarditis recurrence using sequential ORT for pericarditis, i.e., analgesics, NSAIDs, colchicine as described in the Pharmacy Manual and outlined briefly below:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to blinded study drug based on the subject's clinical status and at the discretion of the investigator.
- If, after the addition of NSAIDs and colchicine, the investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from blinded study drug and followed through the EORW visit.

5.8.4 Long Term Extension Treatment Period (LTE-TP)

Subjects who opt to continue open-label rilonacept in the LTE-TP will have their concomitant pericarditis medications managed at the discretion of the investigator and based on the subject's clinical status. If CS are required in addition to rilonacept to manage recurrent pericarditis, rilonacept should be discontinued.

5.8.5 Long Term Extension Follow-Up Period (LTE-FUP)

During LTE-FUP, pericarditis medication can be managed at the investigator's discretion.

5.8.6 Prohibited Concomitant Medicines During the Study

Prohibited medications during the study and throughout the end of LTE-TP include the following:

- Interleukin (IL) blockers other than rilonacept
- IL-6 blockers
- Janus-activating kinase inhibitors
- TNF inhibitors
- Potent immunosuppressants (azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, mercaptopurine, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents, agents that deplete B or T cells [e.g., rituximab, alemtuzumab])
- Live (attenuated) vaccines, which are prohibited during the study and within 12 weeks after the last study drug administration

5.9 Blinding

In the single-blind RI period, all subjects will receive rilonacept but will be blinded to the duration of the RI period and the timing of randomization.

The RW period is a double-blind period in which rilonacept and placebo are identical in appearance. Neither the subject nor any of the investigator/site staff, [redacted] or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Council for Harmonisation [ICH] E9).

In the event of a pericarditis recurrence that meets the criteria for bailout rilonacept (Sections 3.1 and 6.2.3), the subject will be transitioned to open-label rilonacept but will remain blinded to their prior RW treatment assignment.

At the end of the RW period, all sites and subjects will be unblinded. Subjects will be offered participation in the LTE-TP, in which once-weekly open-label rilonacept can be continued for an additional 24 weeks.

5.9.1 Breaking the Blind

A subject's treatment assignment will not be broken until the end of the RW period.

If the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the Sponsor must be notified immediately. If the investigator intends to unblind treatment allocation for a subject, then the Sponsor should be notified immediately. The investigator may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study drug is essential for the appropriate clinical management or welfare of the subject. In most cases, the management of a medical emergency would be the same, regardless of whether the subject received active drug. The treatment assignment will be unblinded through the IWRS. The investigator must notify Kiniksa Pharmaceuticals and [redacted] medical monitors as soon as possible but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the eCRF.

The [redacted] PVG staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the blinded report may be sent to clinical investigators in accordance with local regulations.

5.10 Treatment Compliance

Subjects will record the administration of all doses of study drug (whether as an outpatient or in the clinic) in a subject's diary. In addition, throughout all study periods, adherence to study drug administration will be assessed by the study site in collaboration with the visiting RN (Section 6).

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will provide informed consent or an assent, if applicable. Potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all questions answered for them. Subjects will undergo screening procedures specific to the study only after the ICF has been provided by the subject unless performed as part of SOC practice. The investigator or designee will also sign the ICF.

6.1 Study Visits

The schedule of assessments for the study site visits is summarized in the Study Schedule of Activities. Following screening assessments, qualifying subjects will be enrolled and enter the RI period. Subjects who stop background pericarditis medications and achieve Clinical Response at RI Week 12 (Section 6.2.2), will be randomized and enter the RW period. During both the RI and RW period, a combination of clinic and outpatient visits will occur. Outpatient visits may consist of telephone or virtual contacts as well as home visits conducted by a visiting nurse. For each scheduled visit of the study (including outpatient and clinic), assessments should occur prior to scheduled injections of study drug. Subjects can be brought to the clinic in place of a scheduled outpatient visit or for an unscheduled visit at the discretion of the investigator.

The visit schedule is derived from the day of the RI baseline visit. One week is equal to 7 calendar days. Although visits do not occur every week, subjects are required to record pericarditis pain NRS measurements on a daily basis in their study device and to administer study drug on a once-weekly basis and record it in their study electronic diary (eDiary). If a subject is unable to independently complete the daily eDiary, a caregiver may help enter the data.

Upon completion of the RI and RW periods, all subjects will have the opportunity to continue participating in the LTE. This will require each subject again providing informed consent prior to LTE participation. The LTE period will have a treatment period (LTE-TP) and an off treatment follow-up period (LTE-FUP).

Any subject who prematurely discontinues study drug will be followed for the duration of the trial as specified in Section 4.2.2. In addition, throughout all study periods, compliance with study drug administration will be assessed by the site in collaboration with the visiting RN.

6.1.1 Screening: Clinic and Remote as Needed

A study screening eCRF is required to be completed for every subject with a signed ICF. For each subject, the subject identification is obtained from the IWRS.

It is anticipated that some subjects may have a portion of the study screening procedures done as part of routine care outside the auspices of this study. As long as these procedures were done within the

allotted screening period timeframe, the results of these procedures may be used to support study screening and completion of the study screening eCRF. Any protocol-specified study qualification procedures/tests not already done as part of routine care will need to be conducted after the subject provides informed consent and before enrollment. It is possible that the screening and enrollment visit will occur on the same day.

The below procedures are required to be completed to screen a subject ≤28 days prior to enrollment. All assessments and procedures are not required to be completed on-site; however, the site is expected to obtain the medical records for subject source documentation.

- Obtain the ICF.
- Enter the subject into the IWRS.
- Review inclusion/exclusion criteria; ensure that the subject has a diagnosis of recurrent pericarditis based and is presenting with at least the **third** pericarditis episode.
- Record: demographic information, medical/surgical history, concomitant medications, all prior and current concomitant pericarditis medications, a detailed pericarditis history including all recurrent pericarditis events.
- Perform a full physical examination (may be performed by an investigator or other healthcare provider designated by the investigator).
- Perform/obtain:
  - 11-point pericarditis pain NRS assessment – required to be ≥4 within 7 days prior to and including the day of RI baseline. The qualifying NRS assessment and CRP are not required to occur on the same day.
  - CRP (mg/dL) – required within 7 days prior to and including the day of RI baseline. For study qualification purposes, the CRP may be assessed using 1 of 4 approaches:
    - Point of care (POC) device provided by Sponsor (preferred method)
    - Blood sample sent to the local laboratory
    - CRP measurement taken as part of the subject's routine care (e.g., not specifically obtained for this study)
    - Blood sample sent to the central laboratory
  - Local laboratory hematology, chemistry, IGRA, hepatitis serology, HIV
  - Chest x-ray (unless performed and available within the past 12 weeks)
  - Local or central laboratory urine pregnancy test for women of childbearing potential
  - AE collection

6.1.2 Single-blind Treatment: Run-In

6.1.2.1 Enrollment (RI Baseline): Clinic Visit

For subjects who meet study entry criteria, enrollment commences at the RI baseline visit. The following procedures occur:

- Review inclusion and exclusion criteria to confirm subject qualification.
- Review and record updates to recurrent pericarditis history since the screening visit.
- Revise IWRS status change to enrollment.
- Assess and record all concomitant medications as well as all prior and concomitant pericarditis medication.
- Perform an abbreviated physical examination, height and body weight.
- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; the ECHO is to be read locally prior to sending to the core lab.
- Perform cardiac MRI (for substudy participants only).
- Provide the subject with their study device and complete the following:
  - For subjects ≥18 years, have them complete the 36-Item Short Form Health Survey (SF-36), 5-level EuroQoL-5D (EQ-5D-5L), Insomnia Severity Index (ISI)
  - For all subjects, instruct how to complete the 11-point pericarditis pain NRS (as outlined in Section 6.2.1.2) and the medication diary.
  - Have all subjects complete the Patient Global Impression of Pericarditis Severity (PGIPS) score.
- The investigator is to complete the Physician Global Assessment of Pericarditis Activity (PGA-PA).
- Obtain the Pharmacogenomics ICF.
- Obtain a local or central laboratory urine pregnancy test for women of childbearing potential.
- Obtain central laboratory chemistry, hematology, lipid panel, CRP, anti-drug antibodies (ADAs), biomarkers, and urinalysis (laboratory tests should be drawn prior to the first study drug administration, but results of those tests are not required before enrollment).
- AE reporting.
- Additional discussion/assessment as needed.

Upon completion of the above study activities, study drug dispensing can commence. The following procedures occur:

- Complete the IWRS to dispense assigned study drug; record the amount (number of vials) dispensed.
- Explain the study drug, proper once-weekly dosing, proper study drug administration technique, study drug administration documentation, and confirm that the subject (and subject's caregiver as applicable) understands.
- For pediatric subjects, body weight (in kilograms) obtained at the RI baseline visit is to be used to determine appropriate study drug dosing in the RI period. Please refer to the pediatric study drug dosing Table 5–1 as well as the Study Schedule of Activities for subsequent visits with weight assessments for pediatric dosing.
- Prepare and administer the first injection of study drug and train the subject or caregiver to prepare and administer the second dose of study drug.
- Instruct the subject to bring to each clinic visit all medications the subject is taking, including used and unused study drug vials.
- Arrange upcoming study visits (as many visits as possible that can be arranged ahead of time is advised).

6.1.2.2 RI Day 2: Clinic Visit (24-hour PK Sub-study Participants Only)

The RI Day 2 visit includes a PK sample that is collected 24 hours after the loading dose of study drug and then sent to the central laboratory.

6.1.2.3 RI Day 4: TC/RN Visit

The timing of the site TC visit on the RI Day 4 visit can occur independently of the RN visit. During the site TC visit, the subject is contacted to assess for AEs in follow-up to the initial injections received, to review the daily input of the pericarditis pain NRS score, as well as to review all concomitant medications, including concomitant pericarditis medication. The site then dispenses study drug (along with ancillary supplies) through the IWRS and coordinates shipment as outlined in the Pharmacy Manual. During the visiting RN visit, a CRP sample is drawn and sent to the central lab.

6.1.2.4 RI Week 1: TC/RN Visit

It is preferred that the site TC occur prior to the RN visits. It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 1 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Provide instruction on the pericarditis concomitant medication oral corticosteroid tapering if applicable.
- Confirm and review upcoming visit arrangements.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

RN home visit:

- Obtain the central laboratory samples for CRP, PK, and biomarkers (these are collected prior to study drug administration).
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Ensure the subject records study drug administration in the medication diary.
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.5 RI Week 2: TC/RN Visit

It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 2 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the oral pericarditis corticosteroid tapering, if applicable.
- Review study drug administration and documentation compliance.
- Confirm and review upcoming visit arrangements.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

RN home visit:

- Record study drug dispensing to the subject.
- Obtain central laboratory samples for CRP, PK, and ADAs (these are drawn prior to study drug administration).
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.6 RI Week 4: TC/RN Visit

It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 4 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the oral corticosteroid tapering if applicable and provide instruction on NSAID and/or colchicine tapering if applicable.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm and review upcoming visit arrangements.
- Instruct the subject to bring used and unused study drug vials (those not yet obtained by the visiting RN) to the next clinic visit.

RN home visit:

- Obtain central laboratory samples for CRP, PK, and biomarkers (these are drawn prior to study drug administration).
- Obtain a pharmacogenomics sample for those subjects who have provided informed consent.
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.7 RI Week 6: Clinic Visit

The RI Week 6 visit in the clinic includes the following assessments and procedures:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the concomitant oral corticosteroid, NSAID and/or colchicine tapering if applicable.
- Obtain used and unused study drug vials for study drug compliance evaluation.
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for hematology, chemistry, CRP, and ADAs.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur:

- Have the subject administer the next scheduled injection of study drug (if within the study drug window) and have the subject record in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming visit arrangements.

6.1.2.8 RI Week 10: TC Visit

The following assessments and procedures are to be completed:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess concomitant oral corticosteroid, NSAID and/or colchicine tapering completion.
- Assess study drug administration documentation.
- Confirm the RI Week 12/RW baseline clinic visit arrangements.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).

6.1.2.9 Randomization (RI Week 12/RW Baseline): Clinic Visit

The following assessments and procedures are conducted at the RI Week 12 visit, **prior to randomization**:

- CRP assessment (local and central) (the POC device provided for the study is the preferred method for local laboratory CRP assessment).
- Obtain a pericarditis pain NRS average score for the prior 7 days, including the day of the visit (4 missing NRS values within this week may result in an inability to move forward with randomization).
- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; ECHO is read locally prior to submission to the core lab.
- Abbreviated physical examination, height and body weight.
- For subjects ≥18 years, complete on their device SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, PK, and ADAs.
- Evaluate concomitant medications including pericarditis concomitant medication.
- Assess for AEs.
- Obtain used and unused study drug vials for study drug compliance evaluation.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Assess for Clinical Response (refer to Section 6.2.2).

For subjects who have successfully completed the RI period and are assessed as achieving Clinical Response at the RI Week 12 visit, the RW baseline visit commences.

The following assessments and procedures are conducted at the RW baseline visit:

- Update the subject status in the IWRS by randomizing the subject in the IWRS.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1). Please refer to the pediatric study drug dosing Table 5–1 as well as the Study Schedule of Activities for subsequent visits with weight assessments for pediatric dosing during RW.
- Dispense study drug and record the amount (number of vials) dispensed.

- Have the subject administer the study drug and record in the diary (if within the study drug window).
- Instruct the subject to bring all medications including used and unused study drug to each clinic visit.
- Instruct the subjects on the process to follow for a pericarditis recurrence event.
- Arrange upcoming visits.

For subjects that do not qualify for randomization per the IWRS, the [redacted] medical monitor is to be immediately contacted to evaluate the reasons for non-qualification. Following medical monitor consultation, if the subject is deemed to not be a treatment responder, the RI Week 12 visit will be completed, study drug will be discontinued, and the subject will not proceed to randomization. The subject will be requested to perform a 6-week safety follow-up (SFU) visit after his/her last dose of study drug as well as continue with follow-up as agreed upon until the EORW period.

6.1.3 Randomized-Withdrawal (RW) Period

During the RW period, subjects will continue with once-weekly study drug administration as well as daily 11-point pericarditis pain NRS scoring. Visits will occur every 4 weeks, alternating TC/RN visits and clinic visits, with the first visit during the RW period (RW Week 4) being a TC/RN visit. Additional unscheduled visits may occur at any time for evaluation of suspected pericarditis recurrence (Section 6.1.6.1) or for other reasons as deemed necessary by the study investigator.

The following procedures are to occur during the TC/RN visits:

Site TC visits:

- Assess for AEs.
- Assess for suspected pericarditis recurrence events.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Additional discussion/assessment as needed.
- Confirm and review upcoming visit arrangements.
- Instruct the subject to bring used and unused study drug vials (those not yet obtained by visiting RN) to the next clinic visit.

RN home visits:

- Obtain central laboratory samples for CRP.
- Provide review of self-administration of the study drug as needed.

- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.

The following procedures are to occur during the clinic visits (except for Week 24; see below):

- Assess for AEs.
- Assess for suspected pericarditis recurrence events.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Record height and body weight.
- Obtain central laboratory samples for chemistry, hematology, and CRP.
- Obtain central laboratory sample for PK and biomarkers (Weeks 8 and 24 only).
- Obtain central laboratory sample for ADAs (Week 24 only).
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS entry).
- Obtain used and unused study drug vials for study drug compliance evaluation.

Upon completion of the above study activities, study drug dispensing can commence. The following procedures occur:

- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Monitor administration of the study drug dose (whenever possible) and have the subject record in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming visit arrangements.

6.1.3.1 RW WEEK 24: Clinic Visit

The Week 24 visit in the clinic includes the following assessments and procedures:

- Assess for AEs.
- Assess for suspected pericarditis recurrences.

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Perform a full physical examination, height and body weight.
- Acquire a 12-lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the ECHO is to be read locally before sending to the core lab.
- Obtain an MRI (for substudy participants only).
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, and biomarkers.
- Obtain used and unused study drug vials for study drug compliance evaluation.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur:

- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Have the subject administer the RW Week 24 study drug dose (if within the study drug window) and have the subject record it in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming study visits.

6.1.3.2 EORW (End of RW Period/LTE Baseline): Clinic Visit

The EORW visit will be same day as LTE-TP baseline visit.

All randomized subjects, including those that have had pericarditis recurrence or have permanently discontinued study drug will have an EORW visit at the end of the RW period. The EORW activities are listed below:

- Evaluate concomitant medications as well as pericarditis concomitant medications.

- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; the EHCO is to be read locally prior to submission to the core lab.
- Perform a full physical examination, height and body weight.
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrences.
- Obtain informed consent for participation in the LTE period.
- Additional discussion/assessment as needed.

Upon completion of the EORW visit procedures and obtaining subject informed consent to participate in the LTE period, the LTE baseline visit procedures are as follows:

- Change the subject's status in the IWRS and obtain unblinding information; proceed with subject unblinding.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Dispense study drug and record the amount (number of vials) dispensed.
- Have the subject administer the LTE-TP Day 1 study drug dose as applicable (if within the study drug window) and have the subject record it in the medication diary.
- Instruct subjects on continuing the 11-point pericarditis pain NRS score daily entry.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm the upcoming study visits.

6.1.4 Long Term Extension

6.1.4.1 LTE Weeks 8 and 16: Clinic Visit

The LTE Weeks 8 and 16 clinic visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, and CRP.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm upcoming visit arrangements.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Have the subject administer the regularly scheduled study drug dose as applicable (if within the study drug window) and have the subject record it in the medication diary.
- Confirm the upcoming study visits.

6.1.4.2 LTE Week 24 Clinic Visit

The LTE Week 24 visit is the final visit of the LTE-TP. However, if at any time throughout the course of the study a subject prematurely discontinues study drug, an End of Treatment (EOT) visit is to occur. The visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Acquire a 12-lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the EHCO is to be read locally prior to submission to the core lab.
- Obtain cardiac MRI (substudy participants only).
- Perform a full physical examination.
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.

- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, biomarkers, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Have the subject administer the regularly scheduled study drug as applicable (if within study drug window), and have the subject record it in the medication diary.
- Change the subject status in the IWRS.
- Arrange an LTE Week 30 visit.

6.1.5 LTE Follow-Up Period

Upon completion of the LTE Week 24 EOT visit, subjects continue long term follow-up until the end of the study (EOS). The LTE-FUP includes 2 visits.

6.1.5.1 LTE Week 30 Visit: Clinic

The LTE Week 30 visit is a clinic visit. Visit activities are as follows:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess for pericarditis recurrence events.
- Additional discussion/assessment as needed.
- Obtain central laboratory samples for CRP, ADAs, and urine pregnancy test.
- Any left-over ancillary supplies are to be returned to the site.

6.1.5.2 LTE Week 48 End of Study Visit: TC

The LTE Week 48 EOS TC visit procedures are as follows:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess pericarditis recurrence.

6.1.6 Supplemental Visits

6.1.6.1 Pericarditis Recurrence Assessment: Clinic Visit

If a subject experiences symptoms consistent with pericarditis recurrence, he/she should contact the study investigator immediately for evaluation. It is possible that a subject may have assessments performed remotely, however, assessments are also expected be performed at the study site as soon as possible. Required assessments include:

- Evaluate pericarditis pain on the 11-point NRS.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Obtain laboratory samples for CRP (local and central) (the POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment).
- Acquire a 12 lead ECG.
- Acquire a cardiac ECHO per core laboratory imaging parameters; this ECHO is read locally for the purpose of pericarditis recurrence assessment and is then submitted to the ECHO core laboratory for central review.
- Perform an abbreviated physical examination, height and body weight.
- For subjects >18 years, complete the SF 36, EQ-5D 5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA PA.
- Obtain central laboratory samples for PK, ADAs, and biomarkers.
- Other procedures deemed necessary per the investigator or delegated site personnel.

Upon having completed the evaluation, if the investigator makes a clinical diagnosis that the subject is having a pericarditis recurrence event, he/she should contact the [redacted] medical monitor to review and confirm that all assessments have been performed and collected. Upon [redacted] medical monitor confirmation of completion of the assessment, the investigator commences as described in Section 6.2.3.

Subjects treated for a pericarditis recurrence event will continue to follow the same visit schedule described for the RW period (Section 6.1.3).

Source documentation including the assessments and evaluations used to confirm a pericarditis recurrence event, are required to be sent to CEC.

6.1.6.2 End of Treatment Visit: Clinic

The EOT visit is to be conducted when a subject permanently discontinues study drug. For subjects who complete the RW period but do not consent to participate in the LTE period, the EORW and EOT visit can be combined. For those subjects who do consent to participate in the LTE period, the EOT visit can be combined with the LTE Week 24 visit. In the event that a subject prematurely discontinues study drug, it is expected that the subject will have an EOT visit as soon as possible and continue to be followed as described in Section 4.2.2.

The EOT visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Acquire a 12 lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the ECHO is to be read locally prior to submission to the core lab.
- Perform a cardiac MRI (for sub-study participants only) only if the previous MRI was done longer than 6 months ago.
- Perform a full physical examination.
- For subjects >18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, biomarkers, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Arrange SFU visit.

6.1.6.3 Safety Follow-Up Visit: Clinic or TC/RN

The SFU visit is to be conducted 6 weeks after the last dose of study drug. For those subjects who discontinue study drug at the LTE Week 24 visit, the SFU visit is to occur as a clinic visit. However, for those subjects who prematurely discontinue study drug during the study, the visit may be conducted in the clinic or as an outpatient (TC/RN visit) based on investigator discretion. The visit activities are as follows:

Site TC visit:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess for pericarditis recurrence events.
- Remind the subject to continue daily pericarditis pain NRS input if the SFU is occurring prior to the LTE Week 24 visit.
- Additional discussion/assessment as needed.

RN home visit:

- Obtain central laboratory samples for CRP, ADAs, and urine pregnancy test.
- Collect any leftover ancillary supplies and return to the site.

When the visit is conducted as a clinic visit, all of the RN visit activities are to be performed during the clinic visit.

6.2 Efficacy Assessments

Efficacy assessments to be performed at study visits are summarized in the Study Schedule of Activities and include: CRP, daily pericarditis pain assessment (11-point NRS), ECG, ECHO, Patient Global Impression of Pericarditis Severity (PGIPS), Physician Global Assessment of Pericarditis Activity (PGA-PA), and subject's quality of life assessments (SF-36, EQ-5D-5L) and insomnia questionnaire (ISI). In a substudy at selected sites in approximately 10 subjects, a cardiac MRI will be performed.

Note that in case the electronic versions of the PROs and assessments/questionnaires (PGIPS, PGA-PA, SF-36, EQ-5D-5L, and ISI) are not available, the paper forms must be completed until the electronic versions are available again.

6.2.1 Individual Efficacy Assessments

6.2.1.1 C-Reactive Protein

Central and local laboratory assessments of CRP will be performed at study visits as described in the Study Schedule of Activities. Centrally assayed CRP values will be used for statistical evaluations of changes from baseline. Locally assayed CRP will be used for screening, evaluation of treatment response prior to randomization, and assessment of suspected pericarditis recurrence in the RW period. The POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment.

6.2.1.2 11-Point Pericarditis Pain Numerical Rating Scale

Subjects will be asked to provide a daily assessment of pericarditis pain starting at RI baseline. A validated 11-point pericarditis NRS (Section 13.2) will be used to measure the subject's level of pain intensity on a daily basis throughout the study (Hawker et al 2011; Mannion et al 2007; Dworkin et al 2005).

It is recommended that daily pericarditis pain measurements using the 11-point NRS are performed by subjects at the same time of the day each day, and prior to study drug injection on days with study drug administration.

6.2.1.3 Electrocardiogram

Twelve-lead ECGs will be performed at study visits as described in the Study Schedule of Activities. Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-segment elevation or PR-segment depression.

6.2.1.4 Echocardiogram

Echocardiographic assessment of presence of pericardial effusion including new or worsening of pericardial effusion should be obtained at study visits as described in the Study Schedule of Activities. Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart, and pericarditis is one of the main causes of pericardial effusion. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening. Echocardiograms are to be acquired per the ECHO core imaging parameters. Upon local assessment and interpretation, the ECHO is then to be submitted to the designated central imaging laboratory.

6.2.1.5 Patient Global Impression of Pericarditis Severity

Patient Global Impression questionnaires have been developed for a variety of indications. The PGIPS is a single-item PRO measure that assesses the subject's impression of overall severity of pericarditis symptoms at the time the questionnaire is administered, using a 7-point rating scale ranging from absent (no recurrent pericarditis symptoms) to very severe (recurrent pericarditis symptoms cannot be ignored) (Guy 1976). The PGIPS can be completed in less than 30 seconds.

The subject will select the box that best describes the severity of pericarditis symptoms right now:

- ☐ Absent: no symptoms
- ☐ Minimal: can be easily ignored without effort
- ☐ Mild: can be ignored with effort
- ☐ Moderate: cannot be ignored but does not influence my daily activities
- ☐ Moderately severe: cannot be ignored and occasionally limits my daily activities

- ☐ Severe: cannot be ignored and often limits my concentration on daily activities
- ☐ Very severe: cannot be ignored and markedly limits my daily activities

The PGIPS will be collected as described in the Study Schedule of Activities.

6.2.1.6 Physician Global Assessment of Pericarditis Activity

Physician Global Assessment questionnaires have been developed for a variety of indications. The PGA-PA is a single-item clinician-reported outcome measure that investigators use to rate their impression of the patient's overall pericarditis disease activity at the time the assessment is completed, using a 7-point rating scale ranging from absent to very severe (Guy 1976). Like the PGIPS, the PGA-PA can be completed in less than 30 seconds.

The investigator will select the box that best describes subject's pericarditis activity right now.

- ☐ Absent
- ☐ Minimal
- ☐ Mild
- ☐ Moderate
- ☐ Moderately severe
- ☐ Severe
- ☐ Very severe

The PGA-PA will be collected as described in the Study Schedule of Activities.

6.2.1.7 36-Item Short Form Health Survey

The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. The SF-36 was developed at RAND Corporation as part of its Medical Outcomes Study. The SF-36 assesses 8 health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health.

SF-36 will be collected in subjects ≥18 years or older as described in the Study Schedule of Activities.

6.2.1.8 EQ-5D-5L

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The rating scale records the subject's self-rated health on a vertical VAS. This can be used as a quantitative

measure of health outcome that reflects the subject's own judgement. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles (https://euroqol.org/eq-5d-instruments).

The EQ-5D-5L will be collected in subjects ≥18 years or older as described in Study Schedule of Activities.

6.2.1.9 Insomnia Severity Index

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. The total score is interpreted as follows: no clinically significant insomnia (0–7); subthreshold insomnia (8–14); clinical (moderate) insomnia (15–21); and clinical (severe) insomnia (22–28) (Morin et al 2011).

The ISI will be collected in subjects ≥18 years or older as described in Study Schedule of Activities.

6.2.1.10 Cardiac MRI

Cardiac MRI will be performed as described in the Study Schedule of Activities at selected sites in approximately 10 subjects in the cardiac MRI substudy. Cardiac MRI will be performed to assess any changes in pericardial inflammation. Cardiac MRI readings will be performed by a central imaging laboratory. The study site/clinic reading of the MRI at the time of the examination may be used by the investigator for clinical decision-making.

6.2.2 Assessment of Clinical Response at the End of the Run-In Period Week 12/RW Baseline

At RI Week 12/RW baseline visit, all subjects receiving rilonacept who are able to discontinue background SOC pericarditis therapy during the RI period (Section 3.1) are assessed for Clinical Response. Only subjects who achieve Clinical Response at RI Week 12 and have discontinued background medications for pericarditis are eligible for randomization in the RW period.

Clinical Response at RI Week 12 is defined as follows:

- A weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS during the 7 days prior to and including the day of randomization, **AND**
- CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.

6.2.3 Management of Suspected Pericarditis Recurrence in the RW Period

Pericarditis Recurrence Definition: Pericarditis recurrence, for the purpose of the protocol, is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis.

At any time point during the RW period, subjects who experience suspected recurrence of their pericarditis will have been instructed to inform their site investigator as soon as possible. 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 (Section 6.1.6.1). The investigator will evaluate all assessments performed for a diagnostic workup, whether at the study site or at locations outside.

Upon completion of pericarditis workup, the investigator is required to contact the [redacted] medical monitor to confirm that the protocol required diagnostic workup is complete prior to implementing treatment for the event.

Following communication with the [redacted] medical monitor, if the event meets the criteria for bailout rilonacept (at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and one CRP value ≥1 mg/dL either on the same day or separated by no more than 7 days), and after the [redacted] medical monitor has confirmed with the investigator that the diagnostic workup is complete, the attainment of bailout criteria is confirmed in the IWRS, blinded study drug is discontinued, and open-label rilonacept treatment is dispensed. If needed, sequential ORT is allowed as outlined in Section 5.8.3. The subject will continue to be followed up according to the Study Schedule of Activities for the RW period.

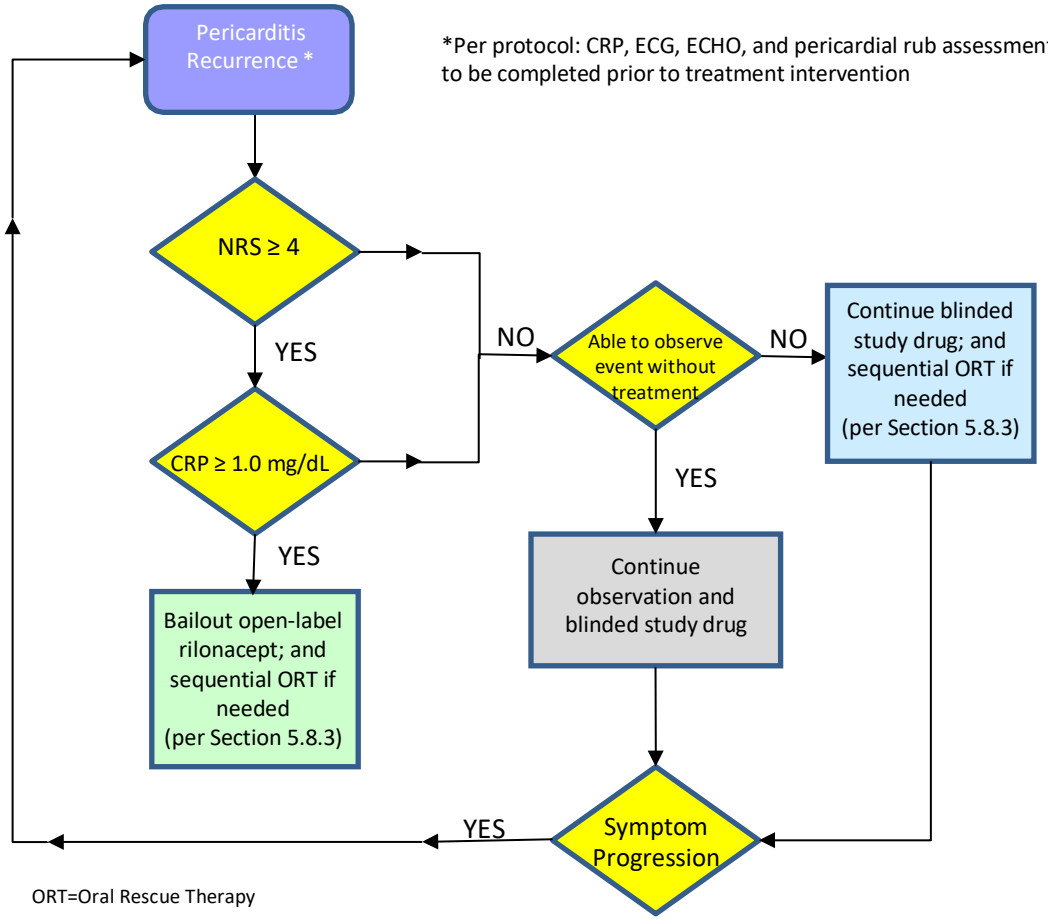
Following communication with the [redacted] medical monitor, if the event does not meet the protocol criteria for bailout rilonacept but in the judgement of investigator requires treatment, after the [redacted] medical monitor has confirmed with the investigator that the diagnostic workup is complete, the investigator is allowed to add sequential ORT to blinded study drug, and as outlined in Section 5.8.3. Blinded study drug treatment will continue until a pericarditis recurrence that meets criteria for bailout rilonacept, or until the end of the RW period.

For a summary of management of suspected pericarditis recurrence, refer to Figure 3.

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. The event package will include, but may not be limited to, data on the subject's pericarditis pain level, CRP value, ECG tracing, ECHO result, the presence or absence of pericardial rub, and any additional source documentation relevant to

the assessment of the suspected event. Details on endpoint package requirements will be described in the CEC charter. The CEC-confirmed pericarditis recurrences will be used for Primary Endpoint efficacy analysis. For more details on the CEC, refer to Section 6.7.2

Figure 3: Management of Suspected Pericarditis Recurrence in the Randomized-Withdrawal Period



6.3 Safety Assessments

Safety assessments to be performed at study visits are summarized in Study Schedule of Activities and include: assessment of AEs (Section 6.4), physical examinations (full and abbreviated) including vital signs measurements, chest x-ray, TB screening, and clinical laboratory tests (serology, hematology, chemistry, urinalysis) (Section 6.6). A pregnancy test (Section 6.6.6) will be conducted at screening and as needed during the study and must be performed 6 weeks after the last study drug administration.

6.3.1 Physical Examination

A full physical examination should include at minimum an evaluation of vital signs, head, eyes, ears, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. Body weight and height will be measured as per the Study Schedule of Activities and will be recorded in the eCRF. Any abnormality identified at baseline should be recorded on the medical history and physical examination eCRFs. At selected visits as specified in the Study Schedule of Activities, an abbreviated physical examination will be performed to evaluate vital signs, lung and heart sounds, including evaluation for pericardial rub.

At all visits at the study site, limited symptom-directed physical examinations may need to be performed in order to determine changes from baseline or abnormalities and should be recorded in the subject's trial notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

6.3.2 Vital Signs

Vital signs include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Blood pressure measurements should be obtained after the subject has been seated for at least 5 minutes.

6.3.3 Chest X-ray

Chest x-rays in accordance with local requirements will be obtained at screening (or an existing chest x-ray within 12 weeks of first study drug administration can be used) according to the Study Schedule of Activities. Chest x-rays should be reviewed by a qualified radiologist for clinically significant abnormalities and evidence of pulmonary disease that would exclude the potential subject.

6.3.4 Tuberculosis Screening

An IGRA test or another TB test based on acceptable clinical practice in each country will be performed in order to evaluate for the presence of active or latent TB infection at screening.

6.4 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

6.4.1 Definitions

6.4.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the reporting investigator to be clinically significant; and any untoward medical occurrence.

6.4.1.2 Treatment-emergent Adverse Event

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to the study drug or any event already present that worsens in either intensity or frequency after exposure to the study drug.

6.4.1.3 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence or effect that, at any dose:

- Results in *death*. Includes all deaths, even those that appear to be completely unrelated to the study drug (e.g., car accident where the subject is a passenger).
- Is *life-threatening*. In the view of the investigator, the subject was at immediate risk of death from the event at the time of the event (i.e., it does not include an AE that might have caused death if it had occurred in a more serious form).
- Requires *in-patient hospitalization* or prolongs an existing hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such pre-existing condition must be recorded on the medical history or physical examination page of the eCRF. Hospitalization is defined as an admission to the hospital ward, a short-stay type unit, or Emergency Room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay longer than originally anticipated for the event or development of a new AE as determined by the Investigator or treating physician.)
- Results in *persistent or significant disability/incapacity*. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.)
- Is a congenital anomaly/birth defect.
- Is an *important medical event*. Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above, i.e., any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the study drug.

All SAEs that occur after signing of study-related informed consent, whether or not the SAEs are related to the study drug or study procedures, must be reported.

6.4.1.4 Adverse Event of Special Interest

An adverse event of special interest (AESI) is defined as an AE of scientific and medical interest specific to the understanding of the study drug and requiring close monitoring and rapid communication by the investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of the study drug.

Treatments with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies. Therefore, malignancy is an AESI for rilonacept. Any AE of malignancy (excluding basal cell carcinoma of the skin) requires reporting to the [redacted] Pharmacovigilance (PHV) within 24 hours after the time the site personnel first learn about the event, following the process as described in Section 6.4.6.

6.4.1.5 Adverse Reaction

Any noxious and unintended response to the study drug (i.e., where a causal relationship between the study drug and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reaction.

6.4.1.6 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction that is "unexpected", i.e., it is not listed (or not listed at the severity that has been observed) in the designated Reference Safety Information of the Investigator's Brochure. Evaluation and reporting requirements for SUSARs are detailed in Section 6.4.8.

6.4.2 Assessing Adverse Events

6.4.2.1 Relationship to Study Drug

The investigator's assessment of an AE's relationship to the study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized by investigator using the following classification and criteria:

- **Not Related**: when the AE is definitely caused by the subject's clinical state or the study procedure/conditions
- **Unlikely Related**: when the temporal association between the AE and the study drug is such that the drug is not likely to have any reasonable association with the AE
- **Possibly Related**: when the AE follows a reasonable temporal sequence from the time of study drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- **Related**: when the AE follows a reasonable temporal sequence from administration of the study drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced

6.4.2.2 Intensity

The severity of an AE will be recorded as one of the following:

- **Mild**: easily tolerated, does not interfere with normal daily activities, does not require intervention
- **Moderate**: causes some interference with daily activities; minimal, local, or noninvasive intervention indicated
- **Severe**: as a consequence of the event, daily activities are limited or completely halted; hospitalization or prolongation of hospitalization indicated

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.3 Recording Adverse Events

Each subject should be monitored for the development of any AEs. This information should be collected by asking nonleading questions (such as "How are you feeling?") and from observations of and conversations with patients. AEs may also be collected by direct physical exam, diagnostic procedures, or any other appropriate source.

At every study visit (telephone or at the site), subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been admitted to the hospital, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

All AEs (serious and non-serious) will be documented in the subject's source documents and recorded in the eCRF. Any clinically relevant (as determined by the investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the subject's source documents and in the eCRF.

The AE term should be reported in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Information to be collected includes the following:

- Event term
- Date and time of onset
- Investigator-specified assessment of severity and relationship study drug
- Date of resolution of the event
- Seriousness
- Any required treatment or actions
- Outcome
- Whether or not it caused the subject to discontinue the study drug.
- Whether or not the AE is an Injection Site Reaction (ISR). ISR is defined as any AE that occurs at the study drug injection site. If an ISR is observed, the subject may be treated at the discretion of the investigator.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the condition deteriorates at any time during the study, it should be recorded as an AE.

6.4.3.1 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.3.2 Adverse Events Based on Examinations and Tests

If an abnormal laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical rather than the laboratory term (e.g., anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically significant findings on examinations and tests should be reported as AEs.

Any new or aggravated clinically significant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4.3.3 Pericarditis Disease Related Events

Signs, symptoms, and abnormal findings associated with pericarditis are to be captured as a pericarditis recurrence event rather than as an AE unless the event is more severe than expected for the subject. In any case, pericarditis recurrence is required to be captured in the eCRF (see Section 6.2.3) within 24 hours of learning of the event.

6.4.4 Time Period for Collection of Adverse Events

Adverse events will be assessed from the time the subjects signs the ICF and through the duration of the study, or at least through the SFU period (6 weeks after the last dose of study drug).

6.4.5 Follow-Up of Unresolved Adverse Events

Every reasonable effort will be made to follow subjects who have AEs.

Any AEs that are unresolved at the subject's SFU visit are to be followed up by the investigator until resolution or for as long as medically indicated. Additional information for any subject with an ongoing AE at the end of the SFU period may be requested by the [redacted] PHV, as needed.

6.4.6 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.4.1.3) must be reported to the [redacted] PHV using the EDC system, immediately (i.e., within 24 hours) after the time site personnel first learn about the event.

In the event the EDC entry is not possible (e.g., system failure or access problems), the study site should complete the paper SAE report form and fax the form to the [redacted] PHV within 24 hours of awareness. The EDC system should be updated as soon as it is available.

A full description of every SAE will need to be provided to the [redacted] PHV (this may be supported by source documentation such as discharge summary or laboratory report should these documents be requested by the [redacted] PHV). Additional follow-up information, if required or available, should be sent to the [redacted] PHV as soon as possible and placed with the original SAE information.

The following contact information is to be used for SAE reporting:

Telephone: [redacted]

Telephone: [redacted]

Fax: [redacted]

Information on non-serious AEs that become serious must also be reported to the [redacted] PHV as soon as it is available.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as applicable per institutional policy.

The Sponsor or designee will provide regulatory authorities, IRBs, IECs, and principal investigators with clinical safety updates/reports according to local requirements.

6.4.6.1 Other Reasons for Immediate Reporting

The following events require reporting to the [redacted] PHV within 24 hours after the time the site personnel first learn about the event:

- Pregnancy in subject or female partner of male subject
- Overdose of the study drug or concomitant medication, regardless of whether it is considered AE
- Other study drug errors
- Any AE of malignancy (excluding basal cell carcinoma of the skin)

6.4.7 Pregnancy

Pregnancy is regarded as an AE only if there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. Nonetheless, any pregnancy that occurs during study participation (including pregnancy in a female partner of a male subject) must be reported to the [redacted] PHV in the same way and using the same procedures as for an SAE (Section 6.4.6). The subject with pregnancy must not receive (additional) study drug. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriage must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study, and considered by the investigator as possibly related to the study drug, must be promptly reported to the [redacted] PHV.

In the event that a subject is found to be pregnant after having received at least 1 study drug dose, the study drug must be discontinued, and the pregnancy will be followed to term and the status of mother and child will be reported to the [redacted] PHV after delivery. Instances of perinatal death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of study drug, will be reported to the [redacted] PHV within 24 hours.

6.4.8 Evaluating and Reporting SUSARs

[redacted] Pharmacovigilance will promptly evaluate all SUSARs and nonserious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, [redacted] PHV staff in collaboration with Kiniksa Pharmaceuticals will assess the expectedness of these events using the Reference Safety Information (Section 6.2) of the rilonacept Investigator's Brochure.

[redacted] PHV will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by [redacted] PHV and Kiniksa Pharmaceuticals as needed.

All relevant information about suspected SUSARs that are fatal or life-threatening will be recorded and reported to the competent authorities in all the applicable countries, and IRBs/IECs in conjunction with Directive 2001/20/EC.

6.5 Other Assessments

6.5.1 Pharmacokinetic Sample

All subjects will have PK samples obtained according to the Study Schedule of Activities. For PK analyses, it is important that the exact time of the SC injection is recorded for each subject. When PK samples are to be collected on dosing days, serum will be collected pre-dose to measure rilonacept concentrations. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

A PK substudy will be conducted in a subset of subjects agreeing to provide a PK sample 24 hours after the first dose of study drug in the RI period. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

6.5.2 Anti-Drug Antibodies (ADAs) against Rilonacept (KPL-914)

Serum samples to measure the presence of ADAs against rilonacept will be collected according to the Study Schedule of Activities. Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the site.

6.5.3 Biomarkers

Serum and plasma will be collected according to the Study Schedule of Activities for biomarker analysis.

6.5.4 Pharmacogenomics

Whole blood for peripheral blood mononuclear cell (PBMC) isolation will be collected for pharmacogenomics assessments after signing the separate Pharmacogenomics ICF.

6.6 Laboratory Analyses

Any abnormal laboratory test results (hematology, chemistry, or urinalysis) or other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

Laboratory assessments will be performed at study visits as summarized in Study Schedule of Activities. Unscheduled laboratory assessments for safety issues are permitted as deemed necessary by the investigator.

Whenever possible in pediatric subjects, local laboratory tests should be drawn using pediatric tubes.

6.6.1 Serology

Samples for local laboratory assessment of hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and HIV levels will be collected at screening. If clinically indicated, those tests may be also collected during the study.

6.6.2 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.

6.6.3 Chemistry

Blood chemistry tests performed in the central study laboratory include albumin, total protein, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, total bilirubin, bicarbonate, chloride, potassium, sodium, creatinine, glucose.

In addition, the following chemistry tests may be performed together with local CRP measurement when using POC device: chloride, creatine kinase, creatinine, glucose, potassium, sodium, total carbon dioxide, blood urea nitrogen.

6.6.4 Non-fasting Lipid Panel

Subjects treated with rilonacept may experience increases in their lipids, including total cholesterol, LDL, 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 Study Schedule of Activities.

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.

6.6.5 Urinalysis

Urinalysis performed by the central study laboratory includes specific gravity, pH, protein, urobilinogen, ketones, glucose, blood, bilirubin, nitrites, leukocyte esterase. It will be performed as described in the Study Schedule of Activities.

6.6.6 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. The purpose of pregnancy test is to prevent embryo/fetal exposure to study drug. Subjects with positive or indeterminate pregnancy test during the screening are not eligible for the study.

6.6.7 Sample Collection

The procedures for the collection, handling, and shipment of laboratory samples are specified in the Laboratory Manual supplied to sites by the central laboratory.

6.7 Committees

6.7.1 Independent Data Monitoring Committee (DMC)

A DMC will be utilized in this study to ensure external objective medical and/or statistical (if needed) review of safety data in order to protect the ethical and safety interests of subjects. The DMC will review unblinded aggregate (and, where necessary, individual) subject safety data at pre-defined intervals according to a DMC charter. The analysis plan for the DMC review will be described in the DMC charter, which will also contain details of the composition and the responsibilities of the DMC.

6.7.2 Clinical Endpoint Committee (CEC)

An independent CEC will review and adjudicate all suspected recurrent pericarditis events that occur during the RW period of the study. The procedures for adjudicating events will be described in the CEC Charter. This will be done independent of the investigators, and in a manner blinded to treatment assignment. The CEC will complete assessments on an ongoing basis.

7 Statistical and Analytical Plan

7.1 Primary Efficacy Endpoint

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.

A sensitivity analysis will be done based on the investigator's assessment of the event.

Pericarditis recurrence is defined in Section 6.2.3.

Subjects who do not have a pericarditis recurrence will be censored at the date of the last available assessment during the RW period before data cutoff. Detailed censoring rules will be specified in the Statistical Analysis Plan (SAP).

7.2 Secondary Efficacy Endpoints for the RW Period

This section defines secondary efficacy endpoints for the RW period. Endpoints for the RI period and for the LTE-TP are defined in Section 7.3.

7.2.1 Major Secondary Efficacy Endpoints

1. Proportion of subjects who maintained Clinical Response at Week 24 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.

2. Percentage of days with no or minimal pain in the first 24 weeks of the RW period. No or minimal pain is defined as non-missing NRS ≤1.
3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period.

7.2.2 Other Secondary Endpoints

All time-to-event endpoints start from the day of randomization. The following variables will be analyzed:

- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)
- Number (percentage) of subjects with absent or minimal pericarditis activity based onPGA- the PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in EQ-5D-5L. There are 6 questions in this instrument (Section 6.2.1.8). Each of the first 5 questions has 5 levels, from level 1 (best) to level 5 (worst). They are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The sixth question is the health on the day, from 0 (the worst) to 100 (the best) (van Reenen and Janssen 2015). The levels of the first 5 questions (EQ-5D-5L profile) will be converted to an index value. Change from baseline in each one of these 7 values will be an endpoint.
- Change over time in subject's sleep quality assessed with the ISI (Section 6.2.1.9). There are 7 items in the ISI. Change in ISI total score, which is the sum of the 7 items over time, will be the endpoint.
- Change over time in ISI categories. The ISI total scores are divided to 4 categories:
  - 0–7 = No clinically significant insomnia
  - 8–14 = Subthreshold insomnia

- 15–21 = Clinical insomnia (moderate severity)
- 22–28 = Clinical insomnia (severe)

- Number (percentage) of subjects who receive sequential ORT for pericarditis (analgesics, NSAIDs, and/or colchicine) in the RW period

7.3 Other Endpoints

These include efficacy endpoints in the RI period and the LTE-TP. Since there is no control arm in these 2 periods, only descriptive statistics will be provided. All time-to-event endpoints start from the day of receiving rilonacept in that period.

7.3.1 Efficacy Endpoints for the RI Period

The following efficacy endpoints are included in this period:

- Proportion of subjects who achieved Clinical Response at the RI Week 12/RW baseline visit. Clinical Response is defined as a weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS and CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.
- Time to CRP normalization (≤0.5 mg/dL)
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12
- Change from baseline in CRP level at RI Week 12
- Resolution of ECHO and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L (Section 7.2.2 contains details about calculation)
- Change over time in the subject's sleep quality assessed with the ISI (Section 7.2.2 contains details about calculation)
- Change over time in ISI categories
- Number (percentage) of subjects who were off background pericarditis medication at RI Week 12

7.3.2 Efficacy Endpoints for the LTE-TP

The efficacy endpoints below are included in this period. Each endpoint will be summarized through Week 24, by subjects who did and did not have an adjudicated pericarditis recurrence in the RW period, respectively, and overall:

- Number (percentage) of subjects with pericarditis recurrences
- Proportion of subjects with Clinical Response
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L (Section 7.2.2 contains details about calculation)
- Change over time in the subject's sleep quality assessed with the ISI (Section 7.2.2 contains details about calculation)
- Change over time in ISI categories
- Number (percentage) of subjects requiring addition of SOC pericarditis therapy

7.4 Sample Size Calculations

For the purpose of sample size estimation, 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) 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.

Patient 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 patients 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 patients may be enrolled and/or randomized at Kiniksa Pharmaceutical's discretion. However, at this time it is anticipated that no more than 75 subjects will be enrolled into this study. Since the data cutoff will be the event date of the 22nd adjudicated pericarditis recurrence AND all subjects still in the RW period have been treated for 24 weeks, the actual power could be higher if the assumed hazard ratio holds.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

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

Safety Analysis Set: 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.

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

Per-protocol Analysis Set: The per protocol (PP) analysis set is a subset of the ITT analysis set with the exclusion of subjects with major 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.

Pharmacokinetic Analysis Set: The PK analysis set includes subjects who receive at least 1 dose of study drug and have at least 1 PK sample. The PK analysis set will be used for all PK analyses.

7.6 Description of Subgroups to be Analyzed

Subgroup analyses for the primary endpoint will be performed by the stratification variable for randomization, as well as by important variables for baseline demographics and patient characteristics. These analyses are for the RW period only. Details will be provided in the SAP.

7.7 Statistical Analysis Methodology

This section outlines the overall methodologies. Details of the statistical analyses, methods, and data conventions will be described in the SAP.

7.7.1 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 each of RI and RW periods and in the LTE-TP, 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.

7.7.2 Stratified Analysis

There will be 2 stratification variables for randomization:

- Oral CS use at RI baseline: yes or no
- Diagnosis of recurrent idiopathic pericarditis at RI baseline: yes or no

When a stratified analysis is used in the analysis and a stratum has no event of interest or no responder, the stratum will be pooled with the other stratum in the same stratification variable.

7.7.3 Testing Hypotheses and Multiplicity Adjustment

All statistical tests for the treatment comparison of efficacy endpoints in the RW period will be based on the ITT analysis set with 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 7.2.1 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 24 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 7.2.1 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.

7.7.4 Analysis of Primary Efficacy Endpoint

Primary analysis of this study will be done after 22nd CEC-confirmed pericarditis recurrence AND after all subjects in the RW period have been treated for 24 weeks. The log rank test will be the primary method for the analysis of time to recurrence, stratified by the stratification variables for randomization.

A sensitivity analysis will be performed based on the investigator's judgement of pericarditis recurrence. Additional sensitivity may be defined in the SAP.

7.7.5 Analysis of Secondary Efficacy Endpoints

7.7.5.1 Analysis of the Major Secondary Endpoints

1. Proportion of subjects who maintained Clinical Response at Week 24 of the RW period (defined as a weekly average of daily pericarditis pain ≤2.0 on the 11-point NRS and CRP ≤0.5 mg/dL at Week 24). The Cochran–Mantel–Haenszel (CMH) test will be used in this analysis, stratified by the stratification variables for randomization.
2. Percentage of days with minimal or no pain in the first 24 weeks post randomization. Minimal or no pain is defined as non-missing daily NRS ≤1. This endpoint will be analyzed with an analysis of covariance. In addition to treatment arm, the following covariates will be included in this analysis: the stratification variables for randomization, and baseline NRS weekly average in 2 categories: NRS ≤1 versus NRS >1.

3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period. The CMH test will be used in this analysis, stratified by the stratification variables for randomization.

7.7.5.2 Analyses of Other Secondary Endpoints in the RW Period

The following endpoints will be analyzed using the same method for the primary endpoint:

- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO

A mixed model with repeated measures (MMRM) will be used in the analysis of the endpoints below. 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, and the variables for stratification at randomization. The p-value for treatment comparison will be calculated at each scheduled assessment for at least 24 weeks as part of the summary statistics. This is done with the understanding that the comparison could be biased due to dropouts or subjects with pericarditis recurrence.

- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L: Health score and Index value, respectively
- Change over time in the subject's sleep quality: sum of the ISI scores.

The CMH test will be used in the analysis of the endpoints below, stratified by the stratification variables for randomization.

- Proportion of patients without pericarditis recurrence in the first 24 weeks of the RW period
- Number (percent) of subjects with absent or minimal pericarditis activity based on the investigator's assessment
- Number (percentage) of subjects who receive SOC pericarditis therapy in the RW period

The following endpoints will be analyzed using the Mantel-Haenszel test with 1 degree of freedom:

- Change in each 1 of the first 5 questions in the EQ-5D-5L, i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
- Change over time in ISI categories

[redacted]

7.7.6 Analyses of Other Endpoints

Endpoints listed in Section 7.3 for the RI period and the LTE-TP will be descriptive in nature since there is no control arm. Summary statistics will be generated following the methodologies stated in Section 7.7.

Other analyses include anti-rilonacept antibodies and biomarker analyses. These analyses will be described in the SAP.

7.7.7 Pharmacokinetic Analyses

For all subjects, serum samples will be collected at time points shown in the Study Schedule of Activities in order to quantify concentrations of rilonacept. Descriptive statistics will be calculated for the serum concentrations of rilonacept by visit. Individual listings of serum concentrations will be provided.

Pharmacokinetic data may be used in a subsequent population PK evaluation that will be conducted outside of this study and described in a separate report.

7.7.8 Safety Analyses

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 the most recent version of MedDRA. TEAEs will be analyzed for all subjects combined and by treatment group in the RW period. Further analyses by severity and relationship to study drug as well as analyses of serious TEAEs will be presented.

Descriptive statistics will be used to summarize safety endpoints by visit for all subjects combined in the RI period and by treatment group in the RW period. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for clinical laboratory analyses (including safety

laboratory measurements, ADAs, etc.), vital signs measurements, ECGs, and physical examination findings.

7.7.9 Interim Analyses

No interim analyses are planned for this study.

8 Data Quality Assurance

Assessment of subject compliance and adherence to study drug administration will be assessed by the site in collaboration with the visiting RN.

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management (ICH Q9).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

[redacted] will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant Standard Operating Procedures (SOPs) of [redacted].

Investigative site personnel will enter subject data into an EDC system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After the last study database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a Master DVD/CD-ROM copy of all of the site data from the study will be created and sent to Kiniksa for storage. [redacted] will maintain a duplicate Master DVD/CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to Kiniksa Pharmaceuticals.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Regulatory agencies and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, informed assent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by Kiniksa Pharmaceutical or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply Kiniksa Pharmaceutical or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Subject Information and Consent

A written informed consent in compliance approved by an IRB/IEC, as appropriate, at each center/country shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent for (or assent form, as applicable) template may be provided by Kiniksa Pharmaceutical or its designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by Kiniksa Pharmaceutical or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before screening, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the

subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

It should be emphasized to the subjects that they may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

For potential subjects under the age of 18, a parent or legal guardian is required to sign and date the ICF and the potential subject is also required to sign and date an informed assent form. The informed assent form explains the trial, it's purpose, procedures as well as risk and benefits in age-appropriate language. Both the ICF and informed assent form, as applicable, are required prior to participation in the trial. The investigator shall retain the signed original ICF(s)/assent form(s), as applicable, and give a copy of the signed original form to the subject or legal guardian.

For this study subjects will be required to sign and date the ICF (or assent form, if applicable) prior to entry to the study and prior to entry to LTE.

In addition, a separate ICF (assent, if applicable) will be needed for subjects participating in pharmacogenomic testing.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on local or country-specific industry and government standard operating procedures, working practice documents, or guidelines.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by Kiniksa Pharmaceuticals, its designee, the regulatory agencies/authorities, or the IRB/IEC.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Kiniksa Pharmaceuticals or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Kiniksa Pharmaceuticals or its designee to submit the complete and accurate certification or disclosure statements required under US Title 21 Code of Federal Regulations (CFR) Part 54. In addition, the investigator must provide to Kiniksa Pharmaceuticals a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 or local country-specific equivalent for outside the US
- Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572
- Financial disclosure information
- IRB/IEC-approved ICFs/assent forms, as applicable, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to [redacted] and/or IRB/IEC according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and Kiniksa Pharmaceuticals and regulatory authority(ies) with any reports required.

10.8 Records Retention

It is the responsibility of the investigator to ensure all essential trial documentation and source records (e.g., signed ICFs, study site/clinic files, subjects' hospital notes, copies of eCRFs) at their site are securely retained. The Sponsor will inform the investigator of the time periods for retaining study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations; otherwise, the retention period by default will be 15 years.

10.9 Publications

Kiniksa shall have the sole and exclusive right to publish information obtained from the study, including any data, results, and conclusions. Investigators are encouraged to participate in the study execution such that they may be invited to participate in the authorship of a potential publication in a manner commensurate with their participation in the study execution in accordance with International Committee of Medicinal Journal Editors standards. Any publication of the results will be subject to the terms and conditions provided in the study agreement.

11 Study Management

The administrative structure will include a Data Monitoring Committee (DMC) and a Clinical Endpoint Committee (CEC). Please refer to Section 6.7 for further details.

11.1 Monitoring

11.1.1 Monitoring of the Study

Data for each subject will be recorded in source records and in the eCRF. Data collection must be completed for each subject who signs an ICF.

For each subject enrolled, the investigator or designee will document in the source records of the subject that the subject is enrolled in this study along with all safety and efficacy information. The investigator is responsible for maintaining adequate case histories in the source records of each subject. Source data should be preserved for the maximum period of time permitted by the hospital/institution and made available by the investigator in the cases described above.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow Kiniksa Pharmaceuticals, representatives of Kiniksa Pharmaceuticals, or a regulatory agency(ies) access to all study records.

The investigator should promptly notify Kiniksa Pharmaceuticals and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Kiniksa Pharmaceuticals and [redacted].

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Sponsor initiated amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval and to the regulatory authorities, if required, before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is any change, divergence, or departure from the study design or procedures defined in the protocol. No waivers will be granted for exemptions to inclusion/exclusion criteria. The Investigator will conduct the study in compliance with the protocol agreed to with the Sponsor and, if required, the regulatory authorities, and which was given approval/favorable opinion by the IRB/IEC. In the event of a protocol deviation, the Sponsor or a designee must be notified.

The Investigator, or person designated by the Investigator, must document and explain any deviation from the approved protocol. The Investigator will notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

11.3 Study Termination

Although Kiniksa Pharmaceuticals has every intention of completing the study, Kiniksa Pharmaceuticals reserves the right to discontinue the study at any time in case of safety concerns (e.g., SUSARs) or if special circumstances concerning the study drug or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, Kiniksa Pharmaceutical will ensure that the clinical study report(s) are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified to approve the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, Kiniksa Pharmaceutical will provide the investigator(s) with the full summary of the study results. The investigator(s) are encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers, as applicable.

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13 Appendices

13.1 Appendix: ARCALYST® Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARCALYST safely and effectively. See full prescribing information for ARCALYST.

ARCALYST® (rilonacept)
Injection for Subcutaneous Use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. (1)

DOSAGE AND ADMINISTRATION

- Adult patients 18 yrs and older: Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg on the same day at two different sites. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. Do not administer ARCALYST more often than once weekly. (2)
- Pediatric patients aged 12 to 17 years: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. Do not administer ARCALYST more often than once weekly. (2)

DOSAGE FORMS AND STRENGTHS

Sterile, single-use 20-mL, glass vial containing 220 mg of rilonacept as a lyophilized powder for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Interleukin-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking ARCALYST. Discontinue treatment with ARCALYST if a patient develops a serious infection. Do not initiate treatment with ARCALYST in patients with active or chronic infections. (5.1)
- Hypersensitivity reactions associated with ARCALYST administration have been rare. If a hypersensitivity reaction occurs, discontinue administration of ARCALYST and initiate appropriate therapy. (5.5)
- Live vaccines should not be given concurrently with ARCALYST. Prior to initiation of therapy with ARCALYST, patients should receive all recommended vaccinations. (5.3)

ADVERSE REACTIONS

The most common adverse reactions reported by patients with CAPS treated with ARCALYST are injection-site reactions and upper respiratory tract infections. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-REGN-777 (1-877-734-6777) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with ARCALYST. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy – No human data. Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2016

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARCALYST® (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Injection for Subcutaneous Use Only.

2.2 Dosing

Adult patients 18 years and older: Treatment should be initiated with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg each given on the same day at two different sites. Dosing should be continued with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. ARCALYST should not be given more often than once weekly. Dosage modification is not required based on advanced age or gender.

Pediatric patients aged 12 to 17 years: Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. ARCALYST should not be given more often than once weekly.

2.3 Preparation for Administration

Each single-use vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection (supplied separately) is required prior to subcutaneous administration of the drug.

2.4 Administration

Using aseptic technique, withdraw 2.3 mL of preservative-free Sterile Water for Injection through a 27-gauge, ½-inch needle attached to a 3-mL syringe and inject the preservative-free Sterile Water for Injection into the drug product vial for reconstitution. The needle and syringe used for reconstitution with preservative-free Sterile Water for Injection should then be discarded and should not be used for subcutaneous injections. After the addition of preservative-free Sterile Water for Injection, the vial contents should be reconstituted by shaking the vial for approximately one minute and then allowing it to sit for one minute. The resulting 80-mg/mL solution is sufficient to allow a withdrawal volume of up to 2 mL for subcutaneous administration. The reconstituted solution is viscous, clear, colorless to pale yellow,

and essentially free from particulates. Prior to injection, the reconstituted solution should be carefully inspected for any discoloration or particulate matter. If there is discoloration or particulate matter in the solution, the product in that vial should not be used.

Using aseptic technique, withdraw the recommended dose volume, up to 2 mL (160 mg), of the solution with a new 27-gauge, ½-inch needle attached to a new 3-mL syringe for subcutaneous injection. EACH VIAL SHOULD BE USED FOR A SINGLE DOSE ONLY. Discard the vial after withdrawal of drug.

Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard.

2.5 Stability and Storage

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be protected from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded.

3 DOSAGE FORMS AND STRENGTHS

ARCALYST is supplied in sterile, single-use, 20-mL, glass vials. Each vial contains 220 mg of rilonacept as a white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted ARCALYST is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Interleukin-1 (IL-1) blockade may interfere with the immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking ARCALYST [*see Clinical Studies (14)*]. There was a greater incidence of infections in patients on ARCALYST compared with placebo. In the controlled portion of the study, one infection was reported as severe, which was bronchitis in a patient on ARCALYST.

In an open-label extension study, one patient developed bacterial meningitis and died [*see Adverse Reactions (6.3)*]. ARCALYST should be discontinued if a patient develops a serious infection. Treatment with ARCALYST should not be initiated in patients with an active or chronic infection.

In clinical studies, ARCALYST has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of an IL-1 blocker in combination with TNF inhibitors. **Taking ARCALYST with TNF inhibitors is not recommended because this may increase the risk of serious infections.**

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as ARCALYST that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ARCALYST.

5.2 Immunosuppression

The impact of treatment with ARCALYST on active and/or chronic infections and the development of malignancies is not known [*see Adverse Reactions (6.3)*]. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.

5.3 Immunizations

Since no data are available on either the efficacy of live vaccines or on the risks of secondary transmission of infection by live vaccines in patients receiving ARCALYST, live vaccines should not be given concurrently with ARCALYST. In addition, because ARCALYST may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ARCALYST. No data are available on the effectiveness of vaccination with inactivated (killed) antigens in patients receiving ARCALYST.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ARCALYST adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current Recommended Immunizations schedules at the website of the Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/schedules/index.html).

5.4 Lipid Profile Changes

Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted [*see Adverse Reactions (6.7)*].

5.5 Hypersensitivity

Hypersensitivity reactions associated with ARCALYST administration in the clinical studies were rare. If a hypersensitivity reaction occurs, administration of ARCALYST should be discontinued and appropriate therapy initiated.

6 ADVERSE REACTIONS

Six serious adverse reactions were reported by four patients during the clinical program. These serious adverse reactions were *Mycobacterium intracellulare* infection; gastrointestinal bleeding and colitis; sinusitis and bronchitis; and *Streptococcus pneumoniae* meningitis [*see Adverse Reactions (6.3)*].

The most commonly reported adverse reaction associated with ARCALYST was injection-site reaction (ISR) [*see Adverse Reactions (6.2)*]. The next most commonly reported adverse reaction was upper respiratory infection [*see Adverse Reactions (6.3)*].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described herein reflect exposure to ARCALYST in 600 patients, including 85 exposed for at least 6 months and 65 exposed for at least one year. These included patients with CAPS, patients with other diseases, and healthy volunteers. Approximately 60 patients with CAPS have been treated weekly with 160 mg of ARCALYST. The pivotal trial population included 47 patients with CAPS. These patients were between the ages of 22 and 78 years (average 51 years). Thirty-one patients were female and 16 were male. All of the patients were White/Caucasian. Six pediatric patients (12-17 years) were enrolled directly into the open-label extension phase.

6.1 Clinical Trial Experience

Part A of the clinical trial was conducted in patients with CAPS who were naïve to treatment with ARCALYST. Part A of the study was a randomized, double-blind, placebo-controlled, six-week study comparing ARCALYST to placebo [*see Clinical Studies (14)*]. Table 1 reflects the frequency of adverse events reported by at least two patients during Part A.

Table 1: Most Frequent Adverse Reactions (Part A, Reported by at Least Two Patients)

Adverse Event	**ARCALYST 160 mg (n = 23)**	**Placebo (n= 24)**
Any AE	17 (74%)	13 (54%)
Injection-site reactions	11 (48%)	3 (13%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Nausea	1 (4%)	3 (13%)
Diarrhea	1 (4%)	3 (13%)
Sinusitis	2 (9%)	1 (4%)
Abdominal pain upper	0	2 (8%)
Cough	2 (9%)	0
Hypoesthesia	2 (9%)	0
Stomach discomfort	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)

6.2 Injection-Site Reactions

In patients with CAPS, the most common and consistently reported adverse event associated with ARCALYST was injection-site reaction (ISR). The ISRs included erythema, swelling, pruritus, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth and hemorrhage. Most injection-site reactions lasted for one to two days. No ISRs were assessed as severe, and no patient discontinued study participation due to an ISR.

6.3 Infections

During Part A, the incidence of patients reporting infections was greater with ARCALYST (48%) than with placebo (17%). In Part B, randomized withdrawal, the incidence of infections were similar in the ARCALYST (18%) and the placebo patients (22%). Part A of the trial was initiated in the winter months, while Part B was predominantly performed in the summer months.

In placebo-controlled studies across a variety of patient populations encompassing 360 patients treated with rilonacept and 179 treated with placebo, the incidence of infections was 34% and 27% (2.15 per patient-exposure year and 1.81 per patient-exposure year), respectively, for rilonacept and placebo.

Serious Infections: One patient receiving ARCALYST for an unapproved indication in another study developed an infection in his olecranon bursa with *Mycobacterium intracellulare*. The patient was on chronic glucocorticoid treatment. The infection occurred after an intraarticular glucocorticoid injection into the bursa with subsequent local exposure to a suspected source of mycobacteria. The patient recovered after the administration of the appropriate antimicrobial therapy. One patient treated for another unapproved indication developed bronchitis/sinusitis, which resulted in hospitalization. One patient died in an open-label study of CAPS from *Streptococcus pneumoniae* meningitis.

6.4 Malignancies

[*see Warnings and Precautions (5.2)*].

6.5 Hematologic Events

One patient in a study in an unapproved indication developed transient neutropenia (ANC < 1 x 10^9/L) after receiving a large dose (2000 mg intravenously) of ARCALYST. The patient did not experience any infection associated with the neutropenia.

6.6 Immunogenicity

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST. Nineteen of 55 patients (35%) who had received ARCALYST for at least 6 weeks tested positive for treatment-emergent binding antibodies on at least one occasion. Of the 19, seven tested positive at the last assessment (Week 18 or 24 of the open-label extension period), and five patients tested positive for neutralizing antibodies on at least one occasion. There was no correlation of antibody activity and either clinical effectiveness or safety.

The data reflect the percentage of patients whose test results were positive for antibodies to the rilonacept receptor domains in specific assays, and are highly dependent on the sensitivity and specificity of the assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is

highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to rilonacept with the incidence of antibodies to other products may be misleading.

6.7 Lipid Profiles

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with ARCALYST experienced increases in their mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were 19 mg/dL, 2 mg/dL, 10 mg/dL, and 57 mg/dL respectively after 6 weeks of open-label therapy. Physicians should monitor the lipid profiles of their patients (for example after 2-3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

7 DRUG INTERACTIONS

7.1 TNF-Blocking Agent and IL-1 Blocking Agent

Specific drug interaction studies have not been conducted with ARCALYST. Concomitant administration of another drug that blocks IL-1 with a TNF-blocking agent in another patient population has been associated with an increased risk of serious infections and an increased risk of neutropenia. The concomitant administration of ARCALYST with TNF-blocking agents may also result in similar toxicities and is not recommended [*see Warnings and Precautions (5.1)*]. The concomitant administration of ARCALYST with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of ARCALYST and other agents that block IL-1 or its receptors is not recommended.

7.2 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of ARCALYST, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of ARCALYST in pregnant women. Based on animal data, ARCALYST may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15 or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human doses of 160 mg based on body

surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100 or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). ARCALYST should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nonteratogenic effects. A peri- and post-natal reproductive toxicology study was performed in which mice were subcutaneously administered a murine analog of rilonacept at doses of 20, 100, 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F_1 offspring during maturation at all doses tested.

8.3 Nursing Mothers

It is not known whether rilonacept is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARCALYST is administered to a nursing woman.

8.4 Pediatric Use

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with ARCALYST at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24-weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g. Serum Amyloid A and C-Reactive Protein). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult patients.

The trough drug levels for four pediatric patients measured at the end of the weekly dose interval (mean 20 mcg/mL, range 3.6 to 33 mcg/mL) were similar to those observed in adult patients with CAPS (mean 24 mcg/mL, range 7 to 56 mcg/mL).

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

When administered to pregnant primates, rilonacept treatment may have contributed to alterations in bone ossification in the fetus. It is not known if ARCALYST will alter bone development in pediatric patients. Pediatric patients treated with ARCALYST should undergo appropriate monitoring for growth and development. [*see Use in Specific Populations (8.1)*]

8.5 Geriatric Use

In the placebo-controlled clinical studies in patients with CAPS and other indications, 70 patients randomized to treatment with ARCALYST were ≥ 65 years of age, and 6 were ≥ 75 years of age. In the CAPS clinical trial, efficacy, safety and tolerability were generally similar in elderly patients as compared to younger adults; however, only ten patients ≥ 65 years old participated in the trial. In an open-label extension study of CAPS, a 71 year old woman developed bacterial meningitis and died [*see Adverse*

Reactions (6.3)]. Age did not appear to have a significant effect on steady-state trough concentrations in the clinical study.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

There have been no reports of overdose with ARCALYST. Maximum weekly doses of up to 320 mg have been administered subcutaneously for up to approximately 18 months in a small number of patients with CAPS and up to 6 months in patients with an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, ARCALYST given intravenously at doses up to 2000 mg monthly in another patient population for up to six months were tolerated without dose-limiting toxicities. The maximum amount of ARCALYST that can be safely administered has not been determined.

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

ARCALYST is supplied in single-use, 20-mL glass vials containing a sterile, white to off-white, lyophilized powder. Each vial of ARCALYST is to be reconstituted with 2.3 mL of Sterile Water for Injection. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for subcutaneous administration only. The resulting solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Each vial contains 220 mg rilonacept. After reconstitution, each vial contains 80 mg/mL rilonacept, 46 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5 ± 0.3. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-

inflammatory Syndrome-1 [*CIAS1*]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

In most cases, inflammation in CAPS is associated with mutations in the NLRP-3 gene which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation.

Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1 receptor antagonist (IL-1ra) with reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.

12.2 Pharmacodynamics

C-Reactive Protein (CRP) and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Compared to placebo, treatment with ARCALYST resulted in sustained reductions from baseline in mean serum CRP and SAA to normal levels during the clinical trial. ARCALYST also normalized mean SAA from elevated levels.

12.3 Pharmacokinetics

The average trough levels of rilonacept were approximately 24 mcg/mL at steady-state following weekly subcutaneous doses of 160 mg for up to 48 weeks in patients with CAPS. The steady-state appeared to be reached by 6 weeks.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

No study was conducted to evaluate the effect of age, gender, or body weight on rilonacept exposure. Based on limited data obtained from the clinical study, steady state trough concentrations were similar between male and female patients. Age (26-78 years old) and body weight (50-120 kg) did not appear to have a significant effect on trough rilonacept concentrations. The effect of race could not be assessed because only Caucasian patients participated in the clinical study, reflecting the epidemiology of the disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of rilonacept. The mutagenic potential of rilonacept was not evaluated.

Male and female fertility was evaluated in a mouse surrogate model using a murine analog of rilonacept. Male mice were treated beginning 8 weeks prior to mating and continuing through female gestation day 15. Female mice were treated for 2 weeks prior to mating and on gestation days 0, 3, and 6. The murine analog of rilonacept did not alter either male or female fertility parameters at doses up to 200 mg/kg (this dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

14 CLINICAL STUDIES

The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS.

Part A was a 6-week, randomized, double-blind, parallel-group period comparing ARCALYST at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all patients received ARCALYST 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on ARCALYST 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with ARCALYST 160 mg weekly.

Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment.

The changes in mean symptom scores for the randomized parallel-group period (Part A) and the randomized withdrawal period (Part B) of the study are shown in Table 2. ARCALYST-treated patients had a larger reduction in the mean symptom score in Part A compared to placebo-treated patients. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on ARCALYST.

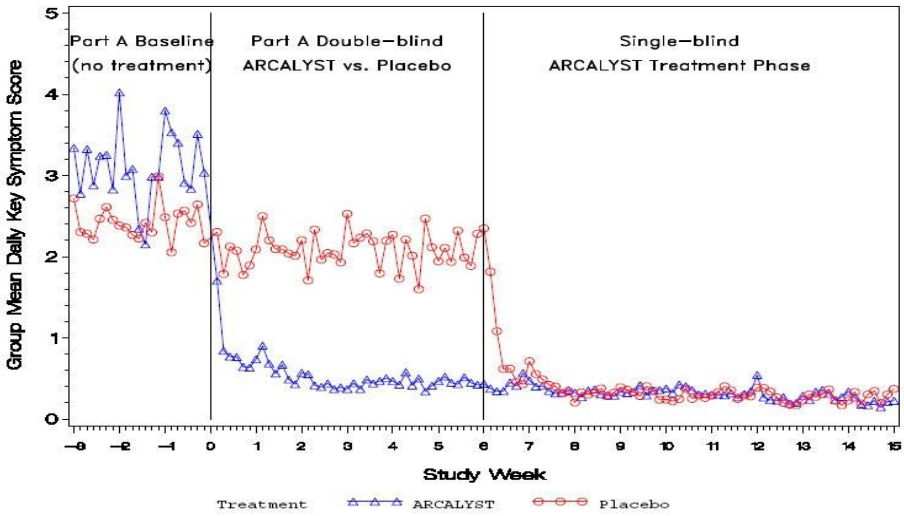
Table 2: Mean Symptom Scores

Part A	Placebo (n=24)	ARCALYST (n=23)	Part B	Placebo (n=23)	ARCALYST (n=22)
Pre-treatment Baseline Period (Weeks -3 to 0)	2.4	3.1	Active ARCALYST Baseline Period (Weeks 13 to 15)	0.2	0.3
Endpoint Period (Weeks 4 to 6)	2.1	0.5	Endpoint Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment groups	(-1.3, -0.4)**	

*Differences are adjusted using an analysis of covariance model with terms for treatment and Part A baseline.
**A confidence interval lying entirely below zero indicates a statistical difference favoring ARCALYST versus placebo.

Daily mean symptom scores over time for Part A are shown in Figure 1.

Figure 1: Group Mean Daily Symptom Scores by Treatment Group in Part A and Single-blind ARCALYST Treatment Phase from Week -3 to Week 15



Improvement in symptom scores was noted within several days of initiation of ARCALYST therapy in most patients.

In Part A, patients treated with ARCALYST experienced more improvement in each of the five components of the composite endpoint (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) than placebo-treated patients.

In Part A, a higher proportion of patients in the ARCALYST group experienced improvement from baseline in the composite score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%) and by at least 75% (70% vs. 0%) compared to the placebo group.

Serum Amyloid A (SAA) and C-Reactive Protein (CRP) levels are acute phase reactants that are typically elevated in patients with CAPS with active disease. During Part A, mean levels of CRP decreased versus baseline for the ARCALYST treated patients, while there was no change for those on placebo (Table 3). ARCALYST also led to a decrease in SAA versus baseline to levels within the normal range.

Table 3. Mean Serum Amyloid A and C-Reactive Protein Levels Over Time in Part A

Part A	ARCALYST	Placebo
SAA (normal range: 0.7 – 6.4 mg/L)	(n=22)	(n=24)
Pre-treatment Baseline	60	110
Week 6	4	110
CRP (normal range: 0.0 – 8.4 mg/L)	(n= 21)	(n=24)
Pre-treatment Baseline	22	30
Week 6	2	28

During the open-label extension, reductions in mean symptom scores, serum CRP, and serum SAA levels were maintained for up to one year.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each 20-mL glass vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. ARCALYST is supplied in a carton containing four vials (NDC 61755-001-01).

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be kept from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded. Discard the vial after a single withdrawal of drug.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

The first injection of ARCALYST should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer ARCALYST, he/she should be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously should be assessed to ensure proper administration of ARCALYST, including rotation of injection sites. (*See Patient Information Leaflet for ARCALYST®*). ARCALYST should be reconstituted with preservative-free Sterile Water for Injection to be provided by the pharmacy. A puncture-resistant container for disposal of vials, needles and syringes should be used. Patients or caregivers should be instructed in proper vial, syringe, and needle disposal, and should be cautioned against reuse of these items.

Injection-site Reactions: Physicians should explain to patients that almost half of the patients in the clinical trials experienced a reaction at the injection site. Injection-site reactions may include pain, erythema, swelling, pruritus, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Patients should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Infections: Patients should be cautioned that ARCALYST has been associated with serious, life-threatening infections, and not to initiate treatment with ARCALYST if they have a chronic or active infection. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ARCALYST. Treatment with ARCALYST should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ARCALYST, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ARCALYST with other IL-1 blocking agents, such as anakinra, is not recommended.

Vaccinations: Prior to initiation of therapy with ARCALYST physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ARCALYST.

REGENERON

Manufactured and distributed by:

Regeneron Pharmaceuticals, Inc.

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V 5.0

Patient Information

ARCALYST® (ARK-a-list)

(rilonacept)

Injection for Subcutaneous Use

Read the patient information that comes with ARCALYST before you start taking it and each time you refill your prescription. There may be new information. The information in this leaflet does not take the place of talking with your healthcare provider about your medical condition and your treatment.

What is the most important information I should know about ARCALYST?

ARCALYST can affect your immune system. ARCALYST can lower the ability of your immune system to fight infections. Serious infections, including life-threatening infections and death have happened in patients taking ARCALYST. **Taking ARCALYST can make you more likely to get infections, including life-threatening serious infections, or may make any infection that you have worse.**

You should not begin treatment with ARCALYST if you have an infection or have infections that keep coming back (chronic infection).

After starting ARCALYST, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have any open sores on your body, call your healthcare provider right away. **Treatment with ARCALYST should be stopped if you develop a serious infection.**

You should not take medicines that block Tumor Necrosis Factor (TNF), such as Enbrel® (etanercept), Humira® (adalimumab), or Remicade® (infliximab), while you are taking ARCALYST. You should also not take other medicines that block Interleukin-1 (IL-1), such as Kineret® (anakinra), while taking ARCALYST. Taking ARCALYST with any of these medicines may increase your risk of getting a serious infection.

Before starting treatment with ARCALYST, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as fever, cough, or flu-like symptoms
- have any open sores on your body
- have a history of infections that keep coming back
- have asthma. Patients with asthma may have an increased risk of infection.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis.
- have or have had HIV, Hepatitis B, or Hepatitis C
- take other medicines that affect your immune system

Before you begin treatment with ARCALYST, talk with your healthcare provider about your vaccination history. Ask your healthcare provider whether you should receive any vaccinations, including pneumonia vaccine and flu vaccine, before you begin treatment with ARCALYST.

What is ARCALYST?

ARCALYST is a prescription medicine called an interleukin-1 (IL-1) blocker. ARCALYST is used to treat adults and children 12 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle Wells Syndrome (MWS). ARCALYST can help lessen the signs and symptoms of CAPS, such as rash, joint pain, fever, and tiredness, but it can also lead to serious side effects because of the effects on your immune system.

What should I tell my healthcare provider before taking ARCALYST?

ARCALYST may not be right for you. **Before taking ARCALYST, tell your healthcare provider about all of your medical conditions, including if you:**

- are scheduled to receive any vaccines. You should not receive live vaccines if you take ARCALYST.
- are pregnant or planning to become pregnant. It is not known if ARCALYST will harm your unborn child. Tell your healthcare provider right away if you become pregnant while taking ARCALYST.
- are breast-feeding or planning to breast-feed. It is not known if ARCALYST passes into your breast milk.

See "What is the most important information I should know about ARCALYST?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take other medicines that affect your immune system, such as:

- other medicines that block IL-1, such as Kineret® (anakinra).
- medicines that block Tumor Necrosis Factor (TNF), such as Enbrel® (etanercept), Humira® (adalimumab), or Remicade® (infliximab).
- corticosteroids.

See "What is the most important information I should know about ARCALYST?"

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist every time you get a new prescription.

If you are not sure or have any questions about any of this information, ask your healthcare provider.

How should I take ARCALYST?

See the "Patient Instructions for Use" at the end of this leaflet.

- Take ARCALYST exactly as prescribed by your healthcare provider.
- ARCALYST is given by injection under the skin (subcutaneous injection) one time each week.
- Your healthcare provider will tell and show you or your caregiver:
    - how much ARCALYST to inject
    - how to prepare your dose
    - how to give the injection
- Do not try to give ARCALYST injections until you are sure that you or your caregiver understands how to prepare and inject your dose. Call your healthcare provider or pharmacist if you have any questions about preparing and injecting your dose, or if you or your caregiver would like more training.
- If you miss a dose of ARCALYST, inject it as soon as you remember, up to the day before your next scheduled dose. The next dose should be taken at the next regularly scheduled time. If you have any questions, contact your healthcare provider.
- If you accidentally take more ARCALYST than prescribed, call your healthcare provider.

What are the possible side effects of ARCALYST?

Serious side effects may occur while you are taking and after you finish taking ARCALYST including:

- **Serious Infections. See "What is the most important information I should know about taking ARCALYST?"** Treatment with ARCALYST should be discontinued if you develop a serious infection.
- **Allergic Reaction.** Call your healthcare provider or seek emergency care right away if you get any of the following symptoms of an allergic reaction while taking ARCALYST:
  - rash
  - swollen face
  - trouble breathing

Common side effects with ARCALYST include:

- **Injection-site reaction**. This includes: pain, redness, swelling, itching, bruising, lumps, inflammation, skin rash, blisters, warmth, and bleeding at the injection site.
- **Upper respiratory infection.**
- **Changes in your blood cholesterol and triglycerides (lipids).** Your healthcare provider will check you for this.

These are not all the possible side effects of ARCALYST. Tell your healthcare provider about any side effects that bother you or that do not go away. For more information ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ARCALYST?

- Keep ARCALYST in the carton it comes in.
- Store ARCALYST in a refrigerator between 36°F to 46°F (2°C to 8°C). Call your pharmacy if you have any questions.
- Always keep ARCALYST away from light.
- Refrigerated ARCALYST can be used until the expiration date printed on the vial and carton.
- ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing**.** Keep ARCALYST away from light.
- If you need to take ARCALYST with you when traveling, store the carton in a cool carrier with a cold pack and protect it from light.

Keep ARCALYST, injection supplies, and all other medicines out of reach of children.

What are the ingredients in ARCALYST?

Active ingredient: rilonacept.

Inactive ingredients: histidine, arginine, polyethylene glycol 3350, sucrose, and glycine.

General Information about ARCALYST

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use ARCALYST for a condition for which it was not prescribed. Do not give ARCALYST to other people even if they have the same condition. It may harm them.

This leaflet summarizes the most important information about ARCALYST. If you would like more information, speak with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ARCALYST that was written for healthcare professionals. For more information about ARCALYST, call 1-877-REGN-777 (1-877-734-6777), or visit www.ARCALYST.com.

Patient Instructions for Use

It is important for you to read, understand and follow the instructions below exactly. Following the instructions correctly will help to make sure that you use, prepare and inject the medicine the right way to prevent infection.

How do I prepare and give an injection of ARCALYST?

STEP 1: Setting up for an injection

1. Choose a table or other flat surface area to set up the supplies for your injection. Be sure that the area is clean or clean it with an antiseptic or soap and water first.
2. Wash your hands well with soap and water, and dry with a clean towel.
3. Put the following items on a table, or other flat surface, for each injection (see Figure 1):

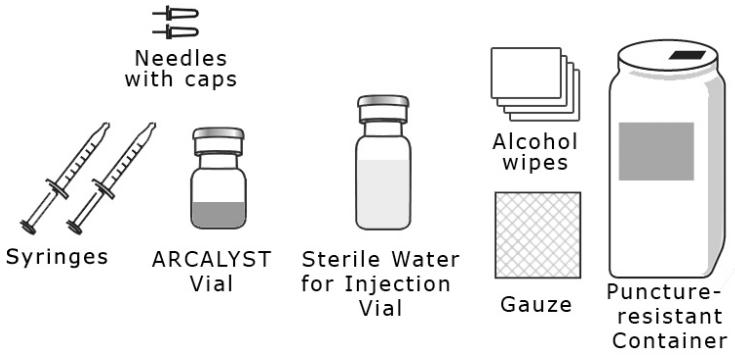

Figure 1

- 2 sterile, 3-milliliter (mL) disposable syringes with markings at each 0.1 mL (see Figure 2):
    - one needed for mixing (reconstitution) ARCALYST
    - one needed for injection

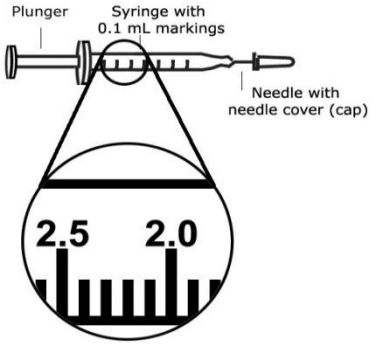

Figure 2

- 2 sterile disposable needles (27-gauge, ½-inch)
    - one needed for mixing
    - one needed for injection
- 4 alcohol wipes
- 1 2x2 gauze pad
- 1 vial of ARCALYST (powder in vial)
- 1 vial of preservative-free Sterile Water for Injection
- 1 puncture-resistant container for disposal of used needles, syringes, and vials

Note:

- Do not use Sterile Water for Injection, syringes or needles other than those provided by your pharmacy. Contact your pharmacy if you need replacement syringes or needles.
- Do not touch the needles or the rubber stoppers on the vials with your hands. If you do touch a stopper, clean it with a fresh alcohol wipe.
- If you touch a needle or the needle touches any surface, throw away the entire syringe into the puncture-resistant container and start over with a new syringe.
- **Do not reuse needles or syringes.**

- To protect yourself and others from possible needle sticks, it is very important to throw away every syringe, with the needle attached, in the puncture proof container right after use. ***Do not try to recap the needle.***

STEP 2: Preparing Vials

1. Check the expiration date on the carton of ARCALYST. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
2. Check the expiration date on the vial of Sterile Water for Injection. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
3. Remove the protective plastic cap from both vials.
4. Clean the top of each vial with an alcohol wipe. Use one wipe for each vial and wipe in one direction around the top of the vial (see Figure 3).

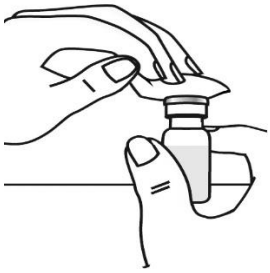

Figure 3

5. Open the wrapper that contains the 27-gauge needle by pulling apart the tabs and set it aside for later use. Do not remove the needle cover. This needle will be used to mix the water with powder. Open the wrapper that contains the syringe by pulling apart the tabs. Hold the barrel of the syringe with one hand and twist the 27-gauge needle onto the tip of the syringe until it fits snugly with the other hand (see Figure 4).

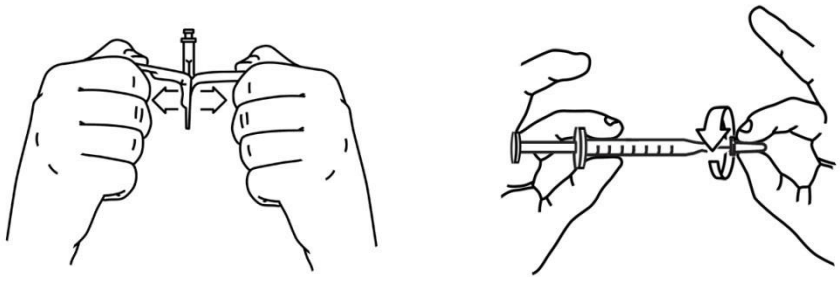

Figure 4

6. Hold the syringe at eye level. With the needle covered pull back the plunger to the 2.3 mL mark, filling the syringe with air (see Figure 5).

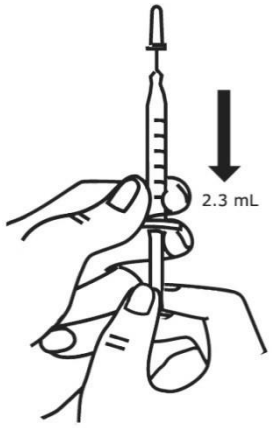

Figure 5

7. Hold the syringe in one hand, use the other hand to pull the needle cover straight off. Do not twist the needle as you pull off the cover. Place the needle cover aside. Hold the syringe in the hand that you will use to mix (reconstitute) your medicine. Hold the Sterile Water vial on a firm surface with your other hand. Slowly insert the needle straight through the rubber stopper. Do not bend the needle. Push the plunger in all the way to push the air into the vial (see Figure 6).

Figure 6

8. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up.
9. Make sure the tip of the needle is covered by the liquid and slowly pull back on the plunger to the 2.3 mL mark to withdraw the Sterile Water from the vial (see Figure 7).

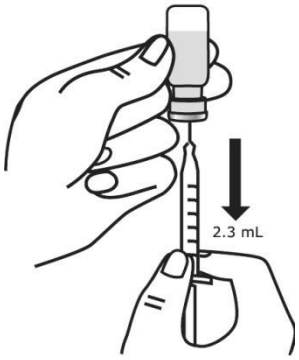

Figure 7

10. Keep the vial upside down and tap or flick the syringe with your fingers until any air bubbles rise to the top of the syringe.
11. To remove the air bubbles, gently push in the plunger so only the air is pushed out of the syringe and back into the bottle.
12. After removing the bubbles, check the syringe to be sure that the right amount of Sterile Water has been drawn into the syringe (see Figure 8).

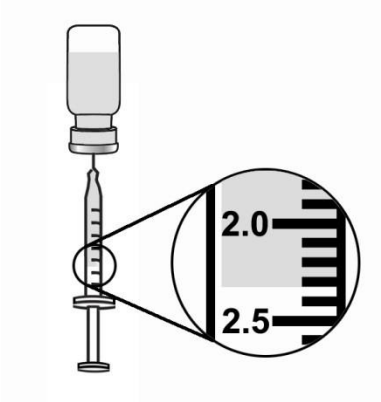

Figure 8

13. Carefully remove the syringe with needle from the Sterile Water vial. Do not touch the needle.

STEP 3: Mixing (Reconstituting) ARCALYST

1. With one hand, hold the ARCALYST vial on a firm surface.

2. With the other hand, take the syringe with the Sterile Water and the same needle, and slowly insert the needle straight down through the rubber stopper of the ARCALYST vial. Push the plunger in all the way to inject the Sterile Water into the vial.
3. Direct the water stream to gently go down the side of the vial into the powder (see Figure 9).

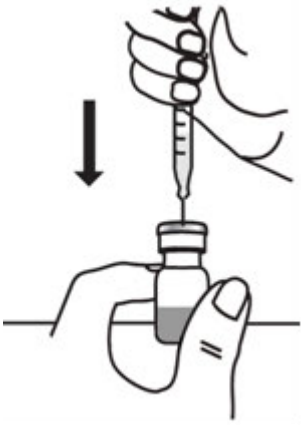

Figure 9

4. Remove the syringe and needle from the stopper and throw away the needle, syringe, and Sterile Water vial in the puncture-resistant container. Do not try to put the needle cover back on the needle.
5. Hold the vial containing the ARCALYST and sterile water for injection sideways (not upright) with your thumb and a finger at the top and bottom of the vial, and quickly shake the vial back and forth (side-to-side) for about 1 minute (see Figure 10).

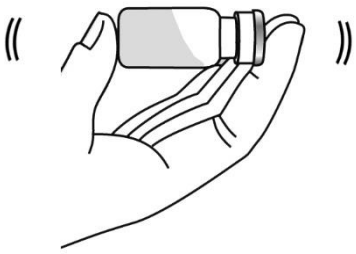

Figure 10

6. Put the vial back on the table and let the vial sit for about 1 minute.
7. Look at the vial for any particles or clumps of powder which have not dissolved.

8. If the powder has not completely dissolved, shake the vial quickly back and forth for 30 seconds more. Let the vial sit for about 1 minute.
9. Repeat Step 8 until the powder is completely dissolved and the solution is clear.
10. The mixed ARCALYST should be thick, clear, and colorless to pale yellow. Do not use the mixed liquid if it is discolored or cloudy, or if small particles are in it (see Figure 11).

    NOTE: Contact your pharmacy to report any mixed ARCALYST that is discolored or contains particles.

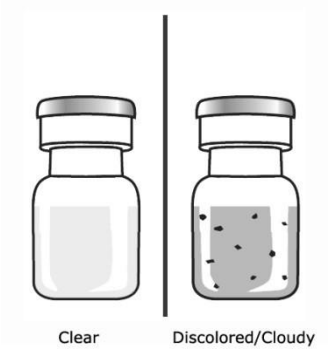

Figure 11

11. ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing. Keep ARCALYST away from light.

STEP 4: Preparing the injection

1. Hold the ARCALYST vial on a firm surface and wipe the top of the ARCALYST vial with a new alcohol wipe (see Figure 12).

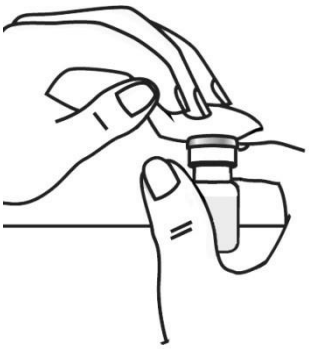

Figure 12

2. Take a new sterile, disposable needle and attach securely to a new syringe without removing the needle cover (see Figure 13).

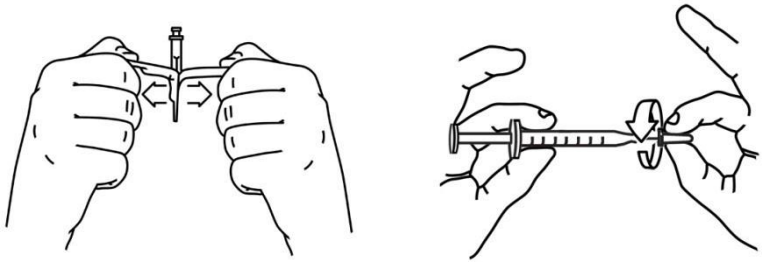

Figure 13

3. The amount of air you draw into the syringe should equal the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject.
4. To draw air into the syringe, hold the syringe at eye level. Do not remove the needle cover. Pull back the plunger on the syringe to the mark that is equal to the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject (see Figure 14).

Figure 14

5. Remove the needle cover and be careful not to touch the needle. Keep the ARCALYST vial on a flat surface and slowly insert the needle straight down through the stopper. Push the plunger down and inject all the air into the vial (see Figure 15).

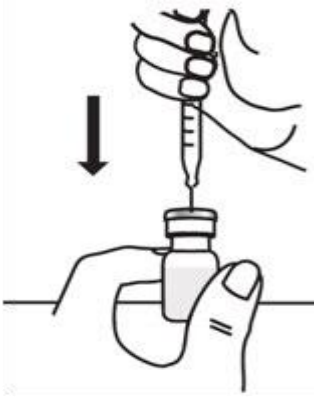

Figure 15

6. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up. Hold the vial at eye level.
7. Keep the tip of the needle in the liquid and slowly pull back on the plunger to the mark on the syringe that matches the amount of medicine prescribed by your healthcare provider (see Figure 16).

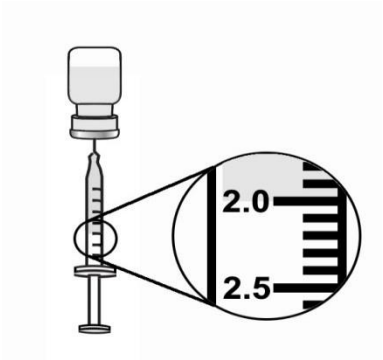

Figure 16

NOTE: The maximum adult dose of ARCALYST is 2 mL.

8. Keep the vial upside down with the needle straight up, and gently tap the syringe until any air bubbles rise to the top of the syringe (see Figure 17).

   It is important to remove air bubbles so that you withdraw up the right amount of medicine from the vial.

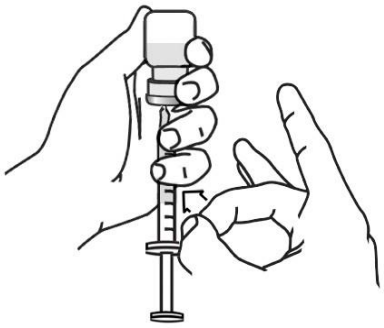

Figure 17

9. To remove the air bubbles, slowly and gently push in the plunger so only the air is pushed through the needle.
10. Check to make sure that you have the amount of medicine prescribed by your healthcare provider in the syringe.
11. Throw away the ARCALYST vial in the puncture-resistant container even if there is any medicine left in the vial (see Figure 18). Do not use any vial of ARCALYST more than one time.

Figure 18

STEP 5: Giving the Injection

1. ARCALYST is given by subcutaneous injection, an injection that is given into the tissue directly below the layers of skin. It is not meant to go into any muscle, vein, or artery.

   You should change (rotate) the sites and inject in a different place each time in order to keep your skin healthy.

Rotating injection sites helps to prevent irritation and allows the medicine to be completely absorbed. Ask your healthcare provider any questions that you have about rotating injection sites.

- Do not inject into skin that is tender, red, or hard. If an area is tender or feels hardened, choose another site for injection until the tenderness or "hardening" goes away.
- Tell your healthcare provider about any skin reactions including redness, swelling, or hardening of the skin.
- Areas where you may inject ARCALYST include the left and right sides of the abdomen, and left and right thighs. If someone else is giving the injection, the upper left and right arms may also be used for injection (see Figure 19):

  (Do not inject within a 2-inch area around the navel)

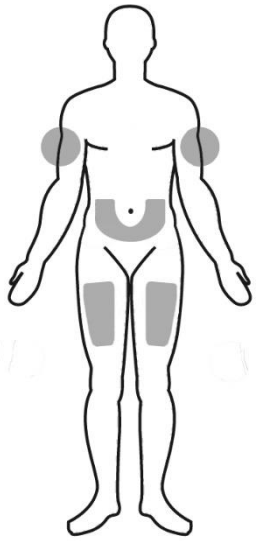

Figure 19

2. Choose the area for the injection. Clean the area in a circular motion with a new alcohol wipe. Begin at the center of the site and move outward. Let the alcohol air dry completely.
3. Take the cover off the needle and be careful not to touch the needle.
4. Hold the syringe in one hand like you would hold a pencil.
5. With the other hand gently pinch a fold of skin at the cleaned site for injection (see Figure 20).

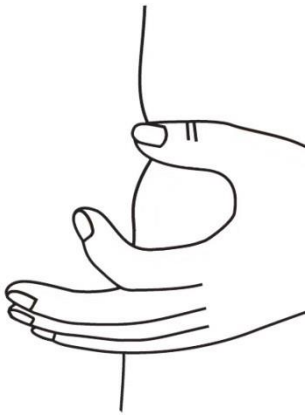

Figure 20

6. Use a quick "dart like" motion to insert the needle straight into the skin (90 degree angle) (see Figure 21). Do not push down on the plunger while inserting the needle into the skin.

   For small children or persons with little fat under the skin, you may need to hold the syringe and needle at a 45 degree angle (see Figure 21).

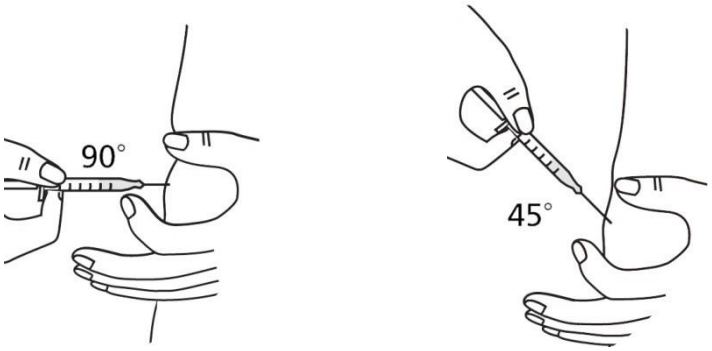

Figure 21

7. After the needle is completely in the skin, let go of the skin that you are pinching.
8. With your free hand hold the syringe near its base. Gently pull back the plunger. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle, discard the syringe and needle. Start over with "STEP 1: Setting up for an injection" using new supplies (syringes, needles, vials, alcohol swabs and gauze pad).
9. If no blood appears, inject all the medicine in the syringe at a slow, steady rate, pushing the plunger all the way down. It may take up to 30 seconds to inject the entire dose.
10. Pull the needle out of the skin, and hold a piece of sterile gauze over the injection site for several seconds (see Figure 22).

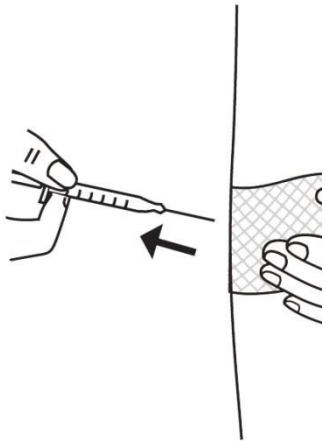

Figure 22

11. Do not replace the needle cover. Throw away the vials, used syringes and needles in the puncture-resistant container (see Figure 23). Do not recycle the container. DO NOT throw away vials, needles, or syringes in the household trash or recycle.

Figure 23

12. Keep the puncture-resistant container out of reach of children. When the container is about two-thirds full, dispose of it as instructed by your healthcare provider. Follow any special state or local laws about the right way to throw away needles and syringes.
13. Used alcohol wipes can be thrown away in the household trash.

Contact your healthcare provider right away with any questions or concerns about ARCALYST.

Notes: 1. Enbrel®, Humira®, Kineret®, and Remicade®, respectively, are trademarks of Immunex Corporation, AbbVie Biotechnology Ltd., Amgen Inc., and Janssen Biotech, Inc., respectively.

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V 4.0

13.2 Appendix: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Subjects will be asked to select the score that best describes their average level of pericarditis pain over the previous 24 hours using an 11-point NRS, where zero (0) indicates 'no pain' and ten (10) means indicates 'pain as bad as it could be'.

On this scale of 0-10, zero (0) indicates 'no pain' and ten (10) indicates 'pain as bad as it could be', please rate your pericarditis pain on average in the last 24 hours

Kiniksa Pharmaceuticals, Ltd.

CLINICAL STUDY PROTOCOL

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPEN-LABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – **R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY** **(RHAPSODY)**

VERSION 1.1, 05 October 2018

IND: **136,896**
EudraCT: **2018-002719-87**

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KPL-914-C002

Sponsor: [redacted]

Sponsor Study Contact: [redacted]

Sponsor Medical Contact [redacted]

Medical Monitor: [redacted]

Version of Protocol: Version 1.1

Date of Protocol: 05 October 2018

Protocol Approval - Sponsor Signatory

Study Title	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects \vith recurrent pericarditis **(RHAPSODY)**
Protocol Number	KPL-9 I 4-C002
Protocol Date	05 October 2018

Protocol accepted and approved by:

Chief Medical Officer

[redacted]

Protocol Approval - Lead Statistician

Study Title	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis **(RHAPSODY)**
Protocol Number	KPL-9I4-C002
Protocol Date	05 October 2018

Protocol accepted and approved by:

Lead Statistician

[redacted]

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis (RHAPSODY)" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1.1, dated 05 October 2018, the International Council for Harmonisation tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Kiniksa Pharmaceuticals or implement protocol changes without Institutional Review Board Independent Ethics Committee approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Kiniksa Pharmaceuticals.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

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PROTOCOL SYNOPSIS

Protocol Number:	KPL-914-C002
Title:	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis
Study Acronym:	**R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY** **RHAPSODY**
Sponsor:	[redacted]
Study Phase:	3
Study Sites:	Multicenter, global
Indication:	Recurrent pericarditis

Study Rationale:

Recurrent pericarditis is a rare autoinflammatory condition with no approved therapies. Current treatments, utilizing nonspecific inhibitors of inflammation (nonsteroidal anti-inflammatory drugs [NSAIDs], colchicine, corticosteroids [CS]), result in significant morbidity with chronic use. Some patients develop CS dependency or require surgical pericardiectomy to treat the symptoms of their disease.

The interleukin-1 (IL-1) pathway plays a major role in the pathophysiology of recurrent pericarditis. Rilonacept (KPL-914) is a recombinant fusion protein that blocks IL-1 signaling. It is currently approved for treatment of another autoinflammatory condition, Cryopyrin-Associated Periodic Syndrome (CAPS). Based on its IL-1–antagonistic properties and pharmacokinetics (PK), which allow for once-weekly subcutaneous (SC) injections, it is reasonable to evaluate the efficacy and safety of rilonacept in subjects with recurrent pericarditis to address the unmet need in treatment of this disease.

Study Objectives:

Primary:	To assess the efficacy of rilonacept treatment in subjects with recurrent pericarditis.
Secondary:	To assess the safety of rilonacept treatment in subjects with recurrent pericarditis.

Study Population:

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 prior pericarditis episodes (including the first episode and 1 recurrence). Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present at screening with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale (NRS) and C-reactive protein (CRP) value ≥1 mg/dL (either on the same day or separated by no more than 7 days) within 7 days prior to first study drug administration.

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to first administration of study drug, and that changes in medications made within this time period (for instance, 1-time use of NSAIDs) are not anticipated by the investigator to significantly alter assessments of baseline disease activity.

Study Design:

This study has 5 periods:

(1) Screening period, during which assessment of disease characteristics, baseline therapy, and the pre-treatment workup is completed (up to 4 weeks)

(2) Single-blind Run-In (RI) period (12 weeks), during which blinded rilonacept is administered SC once weekly in all subjects. 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 stopped background SOC pericarditis therapy and who achieve Clinical Response at RI Week 12, defined as the 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 Withdrawal (RW) baseline and a 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

Study Design Continued

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.

(3) Double-blind placebo-controlled RW period (pericarditis recurrence event-driven duration, with a minimum of 24 weeks), 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 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] 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.

(4) Long Term Extension Treatment Period (LTE-TP) (24 weeks), during which all subjects completing the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) will have an option to receive up to 24 weeks 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. Any subject who, in the opinion of investigator, should not continue open-label rilonacept will be offered participation in the LTE off study drug and after signing LTE informed consent.

(5) Long Term Extension Follow-Up Period (LTE-FUP) (24 weeks), during which all subjects in the LTE-TP will be followed in the LTE-FUP for safety and potential pericarditis recurrences.

Estimated Study Duration:

Subjects completing LTE-TP are projected to be dosed with rilonacept for a minimum of approximately 1.2 years and up to 3 years based on enrollment assumptions and pericarditis recurrence events accrual time.

Study Efficacy Assessments:

- Daily pericarditis pain on the 11-point NRS in the subject's electronic diary
- CRP level
- Electrocardiogram (ECG)
- Echocardiography (ECHO)
- Patient Global Impression of Pericarditis Severity (PGIPS)
- Physician Global Assessment of Pericarditis Activity (PGA-PA)
- 36-Item Short Form Health Survey (SF-36)
- 5-Level EuroQoL-5D (EQ-5D-5L)
- Insomnia Severity Index (ISI)
- Cardiac magnetic resonance imaging (in a substudy in approximately 10 subjects)

Study Pharmacokinetic or Pharmacodynamic Assessments:

Pharmacokinetic or pharmacodynamic assessments will include:

- PK analysis
- Anti-rilonacept antibodies
- Biomarkers
- Peripheral blood mononuclear cell isolation (for subjects who sign the separate informed consent for pharmacogenomics assessments)

Study Safety Assessments:

Safety assessments during the study will include:

- Physical examination
- Vital signs measurements
- Adverse event (AE) monitoring
- Chest x-ray
- Tuberculosis screening
- Laboratory tests

Investigational Medicinal Product, Dosage, and Route of Administration:

Rilonacept (KPL-914) is a recombinant fusion protein consisting of the extracellular domains of human IL-1 cytokine receptor and the Fc portion of human immunoglobulin G1 (IgG1). It acts as a soluble decoy receptor binding IL-1α/IL-1β and prevents their interaction with the IL-1 cell-surface receptor.

Study drug (rilonacept or placebo) is supplied in a single use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml of placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

The first injection of rilonacept loading dose at the RI baseline visit will be administered at the study site by study site staff. The second injection of rilonacept loading dose at the RI baseline visit will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration.

Sample Size:

Approximately 56 subjects (not to exceed 75 subjects) with recurrent pericarditis will be enrolled, which will allow approximately 50 subjects to be randomly assigned to blinded treatment.

Statistical Methods:

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 efficacy analysis. A sensitivity analysis will be done based on the investigator's assessment of the pericarditis recurrence.

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 efficacy endpoints.

Major secondary efficacy endpoints for the RW period include:

- Proportion of subjects who maintained Clinical Response at Week 24 of the RW period
- Percentage of days with no or minimal pain (pain ≤1 on the 11-point NRS) in the first 24 weeks of the RW period
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point rating scale of PGIPS) at Week 24 of the RW period

Other secondary efficacy endpoints for the RW period include:

- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to pericarditis pain NRS ≥4

Statistical Methods Continued:

- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO
- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain (weekly average)
- Proportion of subjects with absent or minimal pericarditis activity based on Physician Global Assessment of Pericarditis Activity (PGA-PA)
- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who receive sequential ORT therapy for pericarditis recurrence (analgesics, NSAIDs, and/or colchicine) in the RW period

Efficacy endpoints for the RI period include:

- Proportion of subjects who achieved Clinical Response at the RI Week 12 visit
- Time to CRP normalization
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12
- Change from baseline in CRP level at RI Week 12
- Resolution of echocardiographic and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on the PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who were off background SOC pericarditis therapy at RI Week 12

Efficacy endpoints for the LTE-TP include:

- Number (percentage) of subjects with pericarditis recurrences
- Proportion of subjects with Clinical Response
- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on PGA-PA

Statistical Methods Continued:

- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects requiring addition of SOC pericarditis therapy

Primary analysis of this study will be done after the 22nd CEC-confirmed pericarditis recurrence and after all subjects in the RW period have been treated for 24 weeks. Subjects who have not had an adjudicated pericarditis recurrence will be censored on the day of the last available assessment before data cutoff.

Details of the analyses will be specified in the Statistical Analysis Plan.

Protocol Version and Date:	Version 1.1 05 Oct 2018

STUDY SCHEDULE OF ACTIVITIES

Table 1–1 Study Schedule of Activities – Screening and Run-In Period (Part 1 of 2)

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]
EQ-5D		X								X
SF-36		X								X
ISI		X								X
PGIPS		X						X		X
PGA-PA		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

[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.

[m] All procedures are to be completed prior to study drug administration.

[q] The Randomization visit serves as both the RI Week 12 visit and the RW baseline visit.

Table 1–1 Study Schedule of Activities – Screening and Run-In Period (Part 2 of 2)

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
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, hepatitis serology, HIV (Local)	X									
Chest X-Ray	X									
Urine Pregnancy (Local or Central)[j]	X	X								
Urinalysis (Central)		X								
PK (Central)			X[i]		X	X	X			X
ADA (Central)		X				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
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.

[f] Both a documented CRP ≥ 1.0 mg/dL AND a pericarditis pain level of ≥ 4 is required 7 days prior to and including the Run-In Baseline visit. These are not required to occur on the same day.

[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.

Table 1–2 Study Schedule of Activities – Randomized Withdrawal (Part 1 of 2)

Trial Period	RANDOMIZATION WITHDRAWAL (minimum 24 weeks)[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

[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

[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.

[m] All procedures are to be completed prior to study drug administration.

[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.

Table 1–2 Study Schedule of Activities – Randomized Withdrawal (Part 2 of 2)

Trial Period	RANDOMIZATION WITHDRAWAL (minimum 24 weeks)[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
Hematology, Chemistry Labs (Central)		X		X		X		X	X
Lipid Panel (Central)[h]						X			X
CRP (Local)									
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)									
Urinalysis (Central)									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]
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.

[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.

[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 1–3 Study Schedule of Activities – Long Term Extension (Part 1 of 2)

Trial Period	LONG TERM EXTENSION (48 WEEKS)				
	Long Term Extension Treatment (24 Weeks)[m]			Long Term Extension Follow Up (24 Weeks)	
Visit Name	LTE Week 8	LTE Week 16	LTE Week 24	LTE Week 30	EOS/ LTE Week 48
Visit Window[b] (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2
Visit Type	Clinic	Clinic	Clinic	Clinic	TC
Concomitant medications	X	X	X	X	X
Pericarditis Concomitant medications	X	X	X	X	X
Full Physical Examination[c]			X		
12-Lead ECG			X		
Echo[e]			X		
MRI (substudy only)			X		
Pericardial pain (11-point NRS)	DAILY				
EQ-5D			X		
SF-36			X		
ISI			X		
PGIPS	X	X	X		
PGA-PA	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

[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.

[m] All procedures are to be completed prior to study drug administration.

Table 1–3 Study Schedule of Activities – Long Term Extension (Part 2 of 2)

Trial Period	LONG TERM EXTENSION (48 WEEKS)				
	Long Term Extension Treatment (24 Weeks)[m]			Long Term Extension Follow Up (24 Weeks)	
Visit Name	LTE Week 8	LTE Week 16	LTE Week 24	LTE Week 30	EOS/ LTE Week 48
Visit Window[b] (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2
Visit Type	Clinic	Clinic	Clinic	Clinic	TC
Hematology, Chemistry Labs (Central)	X	X	X		
Lipid Panel (Central)[h]			X		
CRP (Central)	X	X	X		
PK (Central)			X	X	
ADA (Central)			X	X	
Biomarkers (Central)			X		
Urine Pregnancy[j] (Local or Central)				X	
Urinalysis			X		
IWRS Subject Status Update			X		
IWRS Weight Input (pediatric only)	X	X			
IWRS Drug Dispensing	X	X			
In Clinic Study Drug Administration[o]	X	X	X		
Outpatient Study Drug Administration[o]	WEEKLY				
Study Drug Compliance Review	X	X	X		
Assessment of Pericarditis Recurrence	X	X	X	X	X
Adverse Event Reporting[l]	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.

[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.

Table 1–4 Study Schedule of Activities – Supplemental Visits (Part 1 of 2)

Trial Period	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	

[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

[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.

[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.

Table 1–4 Study Schedule of Activities – Supplemental Visits (Part 2 of 2)

Trial Period	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
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
Biomarkers (Central)	X		
Urine Pregnancy[j] (Local or Central)			X
Urinalysis (Central)		X	
IWRS Subject Status Update	X[s]	X	
IWRS Weight Input (pediatric only)	X		
IWRS Drug Dispensing	X		
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] Upon investigator confirmation of pericarditis recurrence, the IWRS is to be updated.

[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.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAPS	Cryopyrin Associated Periodic Syndrome
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CMH	Cochran–Mantel–Haenszel
CRP	C-reactive protein
CS	corticosteroids
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiography; echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EORW	End of Randomized-Withdrawal(visit)
EOS	End of Study
EOT	End of Treatment (visit)
EQ-5D-5L	5-level EuroQoL-5D
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG1	human immunoglobulin G1
IGRA	Interferon Gamma Release Assay
IL-1	interleukin-1
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ISR	injection site reaction
ITT	intent to treat
IV	intravenous(ly)
IWRS	interactive web response system
KPL-914	rilonacept

LDL	low-density lipoprotein
LTE-FUP	Long Term Extension Follow-Up Period
LTE-TP	Long Term Extension Treatment Period
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MWS	Muckle-Wells Syndrome
NSAID	nonsteroidal anti-inflammatory drug
NRS	Numerical Rating Scale
ORT	Oral Rescue Therapy
PHV	Pharmacovigilance
PGA-PA	Physician Global Assessment of Pericarditis Activity
PGIPS	Patient Global Impression of Pericarditis Severity
PK	pharmacokinetic(s)
POC	point of care
PRO	patient-reported outcome
RI	Run-In (period)
RN	visiting registered nurse
RW	Randomized-Withdrawal (period)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SF-36	36-Item Short Form Health Survey
SFU	safety follow-up
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TC	site telephone visit (telephone contact)
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell
WFI	Water for Injection

1 Introduction

Pericarditis is inflammation of the pericardium, the double-walled sac surrounding the heart. Etiologies of pericarditis include infectious causes (viral, bacterial, fungal, and parasitic) and non-infectious causes (idiopathic, autoimmune, neoplastic, metabolic, traumatic, post-surgical, and drug-related) (Adler et al 2015). In 80% of cases in developed countries, the cause of pericarditis is either post-viral or "idiopathic" in that it cannot be attributed to a specific condition (Imazio et al 2010; Zayas et al 1995).

The underlying pathogenesis of recurrent pericarditis remains unclear, although a growing body of evidence suggests that abnormal immune responses play a role in the pathogenic processes. While the adaptive immune system plays a role in autoimmune disorders that manifest with pericarditis as one of the many organ systems involved (such as in systemic lupus erythematosus or rheumatoid arthritis), the innate immune system, including interleukin 1 (IL-1) signaling, is often the major effector in autoinflammatory disorders, such as isolated pericarditis (Baskar et al 2016; Brucato et al 2016; Imazio et al 2016, Dinarello et al 2012).

Diagnosis of pericarditis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic changes, pericardial effusion, or elevated levels of inflammation markers (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Adler et al 2015). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define an acute pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rubs, new widespread ST-segment elevation or PR-segment depression based on electrocardiogram (ECG) findings, and pericardial effusion (new or worsening). Elevations of certain markers of inflammation (i.e., CRP, ESR, and WBC) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]) are used as supportive findings (Adler et al 2015).

Recurrent pericarditis is characterized by the recurrence of pericarditis signs and symptoms after a symptom-free period of at least 4 to 6 weeks (Adler et al 2015). Recurrent pericarditis affects 20% to 30% of patients with acute pericarditis (Imazio 2014) and can be debilitating for patients due to pain and limitations in physical function during pericarditis episodes. Pericarditis recurrences result in increased emergency room admissions and hospitalizations. In the United States, 5% of patients presenting to the emergency room with non-ischemic chest pain are diagnosed with pericarditis (Agarwal et al 2015).

The estimated prevalence of recurrent pericarditis in the US and Europe is 70,000 to 160,000 patients including approximately 8,000 to 21,000 patients who are refractory or intolerant to current therapies or who require long-term administration of corticosteroids (CS) to control their disease (Brucato et al 2016; Lazaros et al 2016; Imazio et al 2010; Khandaker et al 2010; Imazio et al 2008).

1.1 Current Therapeutic Management of Pericarditis

There are no approved therapies for the treatment of recurrent pericarditis. Current treatments include nonspecific inhibitors of inflammation, i.e., aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and CS (Lilly et al 2013).

Aspirin and other NSAIDs are the first-line approach. Because high doses of aspirin and NSAIDs are often required, consideration must be given to gastric protection therapy, as potential risks of therapy include stomach ulcers and gastrointestinal (GI) bleeding, as well as renal and cardiovascular toxicity. Colchicine is another mainstay therapy for pericarditis and is commonly used with NSAIDs to hasten the response to NSAIDs and reduce the risk of subsequent recurrences. However, its use may be associated with the risk of fatal overdosing, significant drug interactions, and neuromuscular toxicity. In addition, approximately 10% to 15% of patients experience significant GI side effects with colchicine, including GI intolerance or severe diarrhea, requiring treatment discontinuation (Imazio et al 2016).

Available ESC guidelines stipulate that CS should be prescribed for the management of pericarditis episodes only in cases of incomplete response, intolerance, or contraindications to NSAIDs and colchicine because of their unfavorable long-term benefit-risk profile. Corticosteroid use is associated with side effects, including weight gain, diabetes, osteoporosis, avascular bone necrosis, and increased risk for infections (Imazio et al 2008). For the management of pericarditis, CS are usually administered at low to moderate doses and can provide rapid control of symptoms. However, they often require many months of tapering after the normalization of CRP levels. In addition, there is a high rate of pericarditis relapse when CS use is tapered or stopped (Lotriionte et al 2010; Imazio et al 2005; Maisch et al 2004), particularly in the absence of concurrent colchicine treatment.

Patients with recurrent pericarditis who are refractory or intolerant to current therapeutic management options or who require long-term administration of CS to control their disease can be particularly challenging to manage. As a last resort, some refractory patients are being referred to the surgical procedure of pericardiectomy, with variable outcomes. Multiple immunosuppressive medications have been used without consistent benefit (Baskar et al 2016). [redacted]

1.2 Pathogenesis of Recurrent Pericarditis: Role of IL-1

Interleukin-1 is a key cytokine that drives the pathophysiology of many inflammatory processes, and it is implicated as a causative factor in various inflammatory diseases in humans.

The two distinct IL-1 genes, *IL1A* and *IL1B*, encode IL-1α and IL-1β, respectively. IL-1α and IL-1β bind to the universally-expressed cell surface receptor, IL-1 receptor type-1, triggering a cascade of inflammatory mediators. The precursor form of IL-1α is expressed in keratinocytes, mucous membrane epithelial cells, and organs such as the liver and vascular endothelium in healthy individuals. During pathological states, IL-1α moves to the cell surface or is released after cell death to activate IL-1 receptors in adjacent cells, thus beginning the cascade of sterile inflammation. IL-1β,

however, is not expressed in healthy individuals until a stimulus, such as microbial products or other chemokines, triggers its transcription in monocytes, tissue macrophages, and dendritic cells via the inflammasome. IL-1 drives the inflammatory cascade in classic autoinflammatory conditions, such as tumor necrosis factor (TNF)-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) and plays a significant role in systemic onset of juvenile idiopathic arthritis and in autoimmune diseases such as rheumatoid arthritis (Baskar et al 2016).

IL-1–blocking therapies are effective at controlling end-organ disease and damage in patients with various autoinflammatory disorders, and different strategies to block IL-1 have been used in clinical trials and demonstrated substantial success in controlling episodes of fever and elevations in acute-phase reactants (Cantarini et al 2015). [redacted]

This mechanistic plausibility of IL-1 antagonism in addressing pathophysiology related to the inflammasome extends to other conditions characterized by sterile acute inflammation, such as recurrent pericarditis. [redacted]

[redacted]

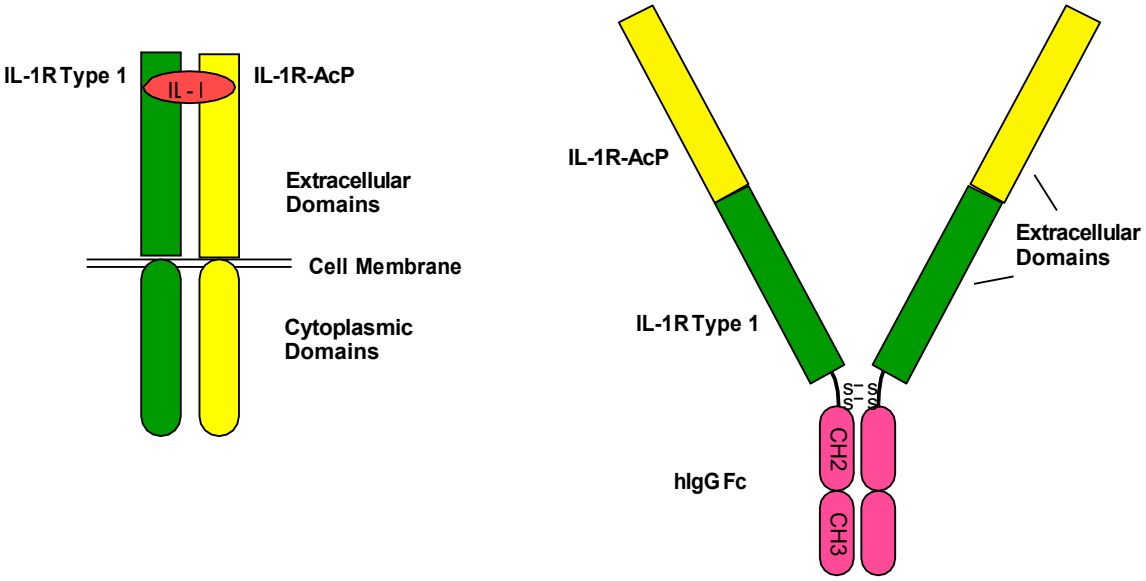
1.3 Rilonacept (KPL-914)

Rilonacept (designated in Kiniksa Pharmaceutical's development program as KPL-914) was developed by Regeneron Pharmaceuticals, Inc. (Regeneron) of Tarrytown, NY, and is approved with the trade name ARCALYST® in the US for the treatment of CAPS, including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children age 12 and older. Rilonacept is currently manufactured and marketed as ARCALYST® by Regeneron. Rilonacept received marketing authorization in the European Union for the treatment of CAPS with severe symptoms, including FCAS and MWS in adults and children aged 12 years and older, but based on a request from Regeneron, the marketing authorization was withdrawn. The withdrawal was a business decision and was not related to any concern with the safety or efficacy of rilonacept.

Rilonacept is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human IgG1. Rilonacept is a dimeric glycoprotein with a total molecular weight of approximately 250 kDa. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1 type I receptor (IL-1R1) and the IL-1 receptor accessory protein (IL-1R-AcP) (Figure 1).

Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells. Rilonacept blocks IL-1 by acting as a soluble decoy receptor that binds IL-1 and prevents its interaction with cell surface receptors.

Figure 1: Schematic of Rilonacept (KPL-914)



1.3.1 Safety of Rilonacept

For a detailed review of the available rilonacept safety data, please refer to the current Investigator Brochure and the ARCALYST® package insert (Section 13.1: ARCALYST® Prescribing Information). The available rilonacept safety data is summarized below.

Rilonacept has been evaluated in 23 studies, including 22 complete and 1 ongoing. In the completed studies, 2243 subjects (2152 patients and 91 healthy volunteers) were exposed to rilonacept. Thirty of these patients were pediatric (<18 years of age).

Doses up to 320 mg subcutaneously (SC) once weekly and 2000 mg intravenously (IV) monthly have been studied for different indications, including CAPS, gout, and other inflammatory disorders.

Injection Site Reactions

In clinical studies with rilonacept, the most common and consistently reported AE associated with rilonacept was injection site reaction (ISR). The ISRs included erythema, swelling, pruritus, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth, and hemorrhage. Most ISRs were mild to moderate. In the gout clinical studies, approximately 1% of subjects treated with rilonacept discontinued due to ISRs. Similar results have been seen in other patient populations.

Infections

Interleukin-1 blockade may interfere with immune response to infections. Serious life-threatening infections have been reported in clinical trials in subjects treated with rilonacept.

Changes in Laboratory Parameters

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Subjects treated with rilonacept in clinical trials experienced increases in their mean total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Antibodies directed against the receptor domains of rilonacept were detected using an enzyme-linked immunosorbent assay (ELISA). In clinical trials with rilonacept, approximately 30% to 35% of subjects tested positive for treatment-emergent antibodies to rilonacept on at least 1 occasion.

Systemic Hypersensitivity Reactions

Hypersensitivity reactions are a potential risk with protein therapeutics in general. In clinical studies with rilonacept, systemic hypersensitivity reactions have been rare.

Malignancies

The impact of treatment with rilonacept on the development of malignancies is not known. However, treatment with immunosuppressants, including rilonacept, may result in an increase in the risk for malignancies.

Fetal Defects

There are no adequate and well-controlled studies of rilonacept in pregnant women. Based on animal data, rilonacept may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15, or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human dose of 160 mg based on body surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100, or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

Nonteratogenic effects: A peri- and postnatal reproductive toxicology study was performed in which mice were administered a murine analog of rilonacept at doses of 20, 100, and 200 mg/kg SC 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F1 offspring during maturation at all doses tested.

1.3.2 KPL-914-C001 Study with Rilonacept (KPL-914) in Recurrent Pericarditis

KPL-914-C001 is an open-label, single active-arm Phase 2 proof-of-concept study in subjects age ≥6 to 75 years old with recurrent idiopathic or post-pericardiotomy syndrome (PPS) pericarditis. The study includes a 6-week Treatment Period in which all the subjects receive once-weekly rilonacept 160 mg SC (2.2 mg/kg for subjects ≥6 and <18 years old) following a loading dose of 320 mg SC in subjects ≥18 years old (4.4 mg/kg in subjects ≥6 and <18 years old) in addition to background pericarditis therapies (NSAIDS, colchicine, CS). After completing the 6-week Treatment Period and based on response status, the subjects have the option to enter the 18-week Extension Period during which they continue to receive rilonacept at the same dose, but during which investigators are encouraged to wean and stop background pericarditis medications.

The primary objectives of the study are to explore clinical and biochemical endpoints of recurrent pericarditis symptomatology, as well as to assess feasibility to wean from concomitant pericarditis medication in the Extension Period while continuing treatment with rilonacept. The study population includes the following 5 subject categories (Parts):

- Part 1 enrolls symptomatic subjects with recurrent idiopathic pericarditis with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 2 enrolls symptomatic subjects with recurrent idiopathic pericarditis with CRP level ≤1 mg/dL that, in the opinion of the investigator, can be attributed to concomitant medications (e.g., CS) and with pericardial inflammation present on cardiac MRI confirmed by the imaging core lab.
- Part 3 enrolls subjects with CS-dependent recurrent idiopathic pericarditis not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.
- Part 4 enrolls symptomatic subjects with recurrent PPS with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 5 enrolls subjects with CS-dependent recurrent PPS not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.

Preliminary data in this ongoing study suggest that subjects enrolled in Part 1 experience improvements in pain, CRP levels, and other pericarditis parameters compared to baseline.

Adverse events observed in the study are consistent with the overall rilonacept safety profile.

2 Study Objectives and Endpoints

2.1 Primary Objective

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

2.2 Secondary Objective

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

3 Investigational Plan

3.1 Study Design

This is a Phase 3, multi-center, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis. This study has 5 periods (Figure 2).

3.1.1 Screening Period (up to 4 weeks)

During the screening period, assessment of disease characteristics, baseline therapy, and thepre-treatment workup will be completed during a period of up to 4 weeks.

3.1.2 Single-blind Run-In (RI) Period (12 weeks)

During the single-blind RI period, treatment with blinded rilonacept is administered and subjects are weaned off background standard of care (SOC) therapy for their pericarditis disease. Subjects will be blinded regarding the time of transition from the single-blind to the double-blind period; i.e., they will not be aware of the duration of the RI period.

In the single-blind RI period, subjects ≥18 years old will receive blinded 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 blinded 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 the RI period.

The RI period includes:

- 1-week Stabilization period, during which blinded rilonacept is administered in addition to 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. The dosages of CS, NSAIDs, and colchicine will be tapered according to the weaning protocol in the Pharmacy Manual (for the purpose of the protocol, aspirin is considered an NSAID). In general, CS doses will be tapered off starting at RI Week 1 and will be withdrawn by RI Week 10 (over a total of 9 weeks). NSAID and colchicine doses will be tapered off starting at RI Week 4 and will be withdrawn by RI Week 10 (over a total of 6 weeks).
- 2-week Monotherapy period: Subjects who have been successfully weaned off background SOC pericarditis therapy will continue to receive blinded rilonacept.

Subjects who stopped background pericarditis medications and achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will proceed into the double-blind placebo-controlled Randomized-Withdrawal (RW) period of the study. For definition of Clinical Response, refer to Section 6.2.2.

Subjects who are unable to achieve Clinical Response on rilonacept m,onotherapy at RI Week 12/RW baseline are to be discontinued from study drug, transitioned to SOC pericarditis therapy at the investigator's discretion, and followed through the end of the RW period.

3.1.3 Double-blind Placebo-controlled RW Period (pericarditis recurrence event-driven duration with a minimum of 24 weeks)

During the RW period, subjects who were able to stop background pericarditis medications and who achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will be randomized 1:1 to double-blinded administration of study drug:

- Rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects ≥12 and <18 years old) SC injections once weekly OR
- Matching placebo SC injections once weekly

Pericarditis Recurrence in the RW Period

For the definition of pericarditis recurrence, refer to Section 6.2.3.

Upon pericarditis recurrence, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale [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 prior RW period treatment assignment. 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 Section 5.8.3 and detailed in the Pharmacy Manual.

Subjects with pericarditis recurrence who do not meet the protocol criteria for bailout rilonacept will continue blinded study drug until they meet the protocol criteria for bailout rilonacept 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 Section 5.8.3 and detailed in the 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.

The RW period will continue until the prespecified number of primary endpoint (CEC-confirmed pericarditis recurrence) events have occurred and approximately 50 randomized subjects have

achieved a minimum of 24 weeks of treatment in the RW period. Based on projected event accrual and subject randomization, Kiniksa Pharmaceutical will determine the end of the RW period and announce to sites so that subject End of Randomized Withdrawal (EORW) visits can occur. All subjects, including those who have transitioned to open-label rilonacept or who prematurely discontinued study drug, should complete an EORW visit.

3.1.4 Long Term Extension Treatment Period (LTE-TP) (24 weeks)

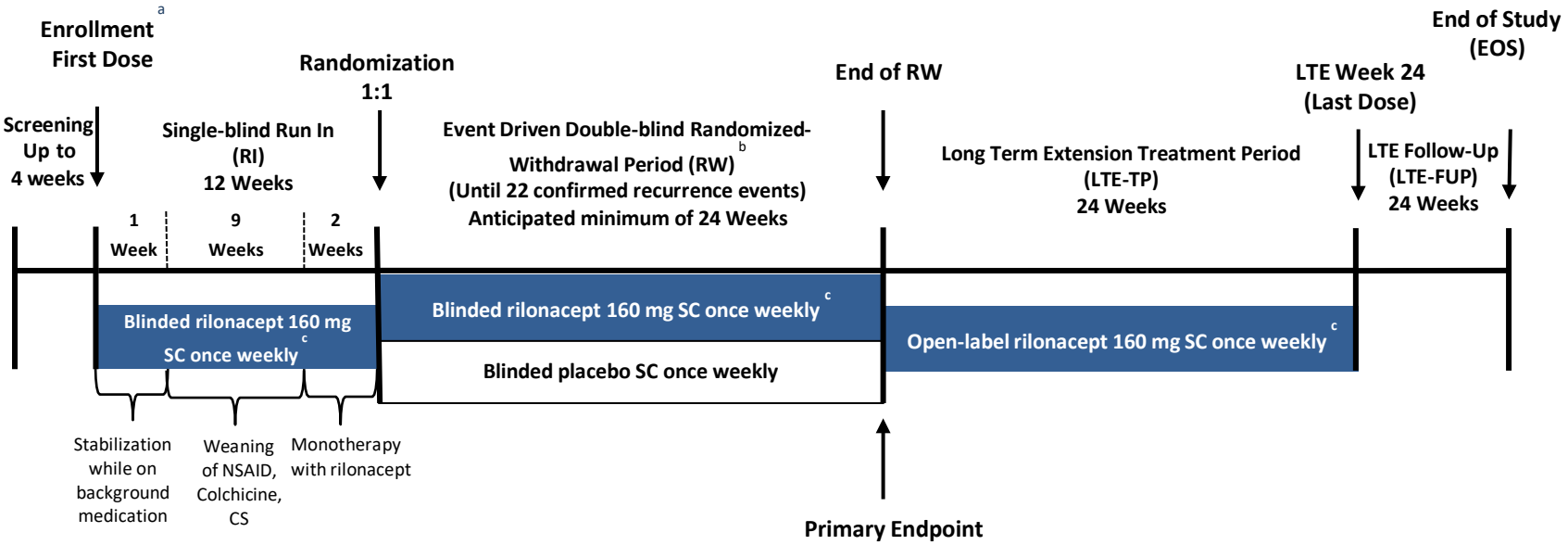
Upon completion of the RW period and the EORW visit (site and subject unblinding), all subjects completing the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) will have an option to receive up to 24 weeks of open-label rilonacept 160 mg (or 2.2 mg/kg for pediatric subjects) SC injections once weekly based on their clinical status and at the discretion of the investigator, after signing LTE informed consent. Any subject who, in the opinion of investigator, should not continue open-label rilonacept will be offered participation in the LTE off study drug after signing LTE informed consent.

3.1.5 Long Term Extension Follow-Up Period (LTE-FUP) (24 weeks)

All subjects in the LTE-TP will be followed in the LTE-FUP for an additional 24 weeks for safety and for potential pericarditis recurrence assessments.

The total duration of the study will be determined by the rate of enrollment, the rate of first recurrence of pericarditis events during the RW period, and the minimum duration of follow-up in the RW of 24 weeks. It is anticipated that study completers (including LTE-TP) will be dosed with rilonacept for approximately 1.2 years and up to 3 years based on enrollment assumptions and pericarditis recurrence events accrual time.

Figure 2: Overview of KPL-914-C002 Trial Design



Abbreviations: CS=corticosteroid; EOS=end of study, LTE=Long Term Extension; NSAID=nonsteroidal anti-inflammatory drug; RI=run in, RW=randomized withdrawal, SC=subcutaneously, TP=treatment period

a. The first dose given is a loading dose of rilonacept. In adult subjects ≥18 years old, 320 mg is given as 2 SC doses of 160 mg. In pediatric subjects ≥12 and <18 years old, 4.4 mg/kg is given as 2 SC doses of 2.2 mg/kg. After the loading dose, rilonacept will be administered as a 160 mg (adults) or 2.2 mg/kg (pediatric subjects) SC dose once weekly.

b. Subject's treatment duration will depend on when the subject is enrolled relative to the end of RW.

c. The adult dose is 160 mg SC once weekly. The pediatric dose is 2.2 mg/kg SC once weekly.

Note: This picture is not drawn to scale.

3.1.6 Rationale of Study Design

Subjects eligible for this KPL-914-C002 study will be subjects with recurrent pericarditis presenting with an acute pericarditis episode at screening.

The KPL-914-C002 study design ensures that during the RI period all subjects will receive rilonacept, a drug with evidence supporting clinical activity based on the preliminary clinical data with rilonacept from Part 1 of the ongoing Phase 2 proof-of-concept study (KPL-914-C001) obtained to date. During the RI period, pericarditis will be stabilized with symptoms controlled and background pericarditis medications (NSAIDs, colchicine, CS) will be tapered and withdrawn, while rilonacept treatment continues.

The design then allows half of the subjects to continue receiving active treatment after having achieved Clinical Response on that treatment, which maximizes subject exposure to a potentially beneficial therapy. The temporary withdrawal of rilonacept (by switching to placebo) in the half of the subjects who were randomly assigned to placebo is expected to result in an accelerated time to pericarditis recurrence and a higher recurrence rate compared to those who continue on active treatment, a finding that demonstrates that the underlying pericarditis etiology is still ongoing and will provide further support for the anticipated observation of the clinical effect of rilonacept during the RI period of the study. The period of exposure to an ineffective treatment is minimized in this design, as subjects will be removed from blinded treatment when the condition returns to a specified severity (i.e., for having met the criteria of pericarditis pain ≥4 on the 11-point NRS and CRP level ≥1 mg/dL) without unblinding them to prior treatment assignment, thus protecting the primary efficacy endpoint of the study. All subjects who meet the pain and CRP criteria described above will be treated with open-label bailout rilonacept using a loading dose, followed by once-weekly SC injections. In addition, sequential ORT such as NSAIDs and/or colchicine will be allowed upon recurrence at the investigator's discretion based on the subject's clinical status, as outlined in Section 5.8.3 and as stipulated in the Pharmacy Manual. Subjects with pericarditis recurrence not meeting criteria for bailout rilonacept, can be treated with sequential ORT based on investigator judgement and as described in protocol Section 5.8.3 and the Pharmacy Manual. If the subject requires the addition of CS treatment to control the pericarditis recurrence, the subject will be discontinued from study drug. All subjects will be followed for the duration of RW period.

In summary, the proposed RW trial with rilonacept allows all enrolled subjects an opportunity to receive the active drug during the acute episode of pericarditis yet provides pivotal-quality data on the efficacy of rilonacept in this enriched cohort by subsequently randomly assigning subjects to placebo versus active treatment after they achieve a predefined clinical response. Subjects with pericarditis recurrences after randomization will receive bailout rilonacept treatment and/or sequential ORT according to the protocol. This approach minimizes the exposure to placebo, which is important for a study that requires active disease upon enrollment and includes a pediatric population. The available regulatory guidance supports the use of an RW study design in the setting of recurrent pericarditis as

a means of establishing the long-term effectiveness of rilonacept, an approved product for the treatment of another rare autoinflammatory condition (CAPS).

3.1.7 Justification for Rilonacept Dose Selection

[redacted], i.e., 320 mg SC loading dose (4.4 mg/kg in subjects ≥12 and <18 years old), followed by once-weekly SC doses at 160 mg (2.2 mg/kg in subjects ≥12 and <18 years old).

In the rilonacept development program in CAPS, gout, rheumatoid arthritis, and other inflammatory conditions, over 2000 subjects were exposed to rilonacept, including 1650 subjects receiving a rilonacept dose of 160 mg or higher. A total of 103 and 169 subjects were exposed to any rilonacept dose for at least 1 year or 6 months, respectively. Most of the real-life experience with rilonacept comes from the CAPS population treated at this marketed dose. As of March 2018, approximately 365 CAPS patients have been exposed to rilonacept in the post-marketing setting since 2008. The safety data accumulated so far support the benefit/risk ratio for the rilonacept dose intended to be evaluated in subjects with recurrent pericarditis.

Based on the preliminary clinical data with rilonacept from Part 1 of the Phase 2 proof of concept study (KPL-914-C001) obtained to date, it is expected that rilonacept doses [redacted] (320 mg followed by 160 mg SC once weekly and corresponding pediatric doses), and evaluated in the KPL-914-C001 study, will consistently provide adequate suppression of clinical inflammatory response, including CRP levels, in patients with recurrent pericarditis.

Bailout Rilonacept Dose

Subjects who meet the protocol criteria for bailout rilonacept upon pericarditis recurrence in the RW period of the study (Sections 3.1 and 6.2.3), irrespective of treatment assignment at randomization, will receive open-label rilonacept (loading dose of 320 mg SC followed by once-weekly SC injections of 160 mg, or the corresponding pediatric doses). [redacted]

The rationale for bailout rilonacept treatment upon pericarditis recurrence for subjects who were randomly assigned to placebo is that rilonacept had controlled their disease activity during the RI period; therefore, re-initiation of rilonacept is justified to regain control of pericarditis signs and symptoms upon recurrence. Subjects who were randomly assigned to rilonacept and qualify for bailout rilonacept upon pericarditis recurrence in the RW period were initial responders to rilonacept treatment during the RI period; thus it could be assumed that the loss of response during the RW

period could be due to development of resistance to rilonacept due to different mechanisms, e.g., higher IL-1 levels or a change in rilonacept pharmacokinetics (PK)/ pharmacodynamics. Therefore, re-administration of a loading dose of rilonacept may help to restore Clinical Response.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 56 subjects will be enrolled (and not more than 75 subjects), which will allow at least 50 subjects to be randomized at approximately 50 sites globally. Subjects will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 pericarditis episodes (including the first episode and 1 recurrence) prior to screening. Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and CRP level ≥1 mg/dL within 7 days prior to the first study drug administration.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent form (ICF) or assent form (for pediatric subjects ≥12 and <18 years old), has provided signed and witnessed written informed consent or assent (as applicable), and agrees to comply with protocol requirements.
2. Is male or female 12 years of age or older with body weight of at least 23.6 kg (52 Lbs).
3. Has a diagnosis of recurrent pericarditis.
4. At least 1 of the pericarditis episodes experienced prior to screening has met at least 2 of the following 4 criteria, in the opinion of the investigator and based on the documented available data, according to the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al 2015):
    a. Pericarditic chest pain
    b. Pericardial rub
    c. New widespread ST-segment elevation or PR-segment depression according to ECG findings
    d. Pericardial effusion (new or worsening)
5. Presents with at least the third episode of pericarditis during screening (i.e., at least the second pericarditis recurrence following the first pericarditis episode), and within 7 days* prior to and including RI baseline (first administration of study drug) has:
    a. At least 1 day with pericarditis pain ≥4 on the 11-point NRS, **AND**
    b. CRP level ≥1.0 mg/dL (for details of CRP collection see Section 6.1.1)

    *Pericarditis pain ≥4 and CRP ≥1 mg/dL are not required to be present on the same day.
6. Has received NSAIDs and/or colchicine and/or CS (in any combination), if used, at stable dose levels (or at least not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs) are not anticipated, in the opinion of the investigator, to significantly alter assessments of baseline disease activity.
7. If using NSAIDs and/or colchicine and/or CS at the time of RI baseline (first administration of study drug), is willing and able, in the opinion of the investigator, to taper and discontinue those medications within the 9-week weaning time in the RI period of the study while continuing rilonacept treatment.

8. Female subjects must be:
    a. Postmenopausal, defined as at least 12 months after the cessation of menses (without an alternative medical cause) OR
    b. Incapable of pregnancy OR
    c. Permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation or having a male partner with vasectomy as affirmed by the subject OR
    d. If of childbearing potential, must agree to use a highly effective method of contraception during the study and for 3 months after the last study drug administration (i.e., hormonal contraceptives associated with inhibition of ovulation, intrauterine device [IUD], intrauterine hormone-releasing system [IUS], or sexual abstinence)
9. If male and sexually active, must have documented vasectomy or must practice birth control and not donate sperm during the study and for 3 months after the last study drug administration.
10. Must be up-to-date with all immunizations, in agreement with current local immunization guidelines for immunosuppressed subjects, before RI baseline (first administration of study drug).
11. Is able to adequately maintain a daily subject diary according to protocol.
12. Must be able to adhere to the study visit schedule and understand and comply with the other protocol requirements.
13. Agrees to refrain from making any new, major lifestyle changes that may affect pericarditis symptoms (e.g., changing exercise pattern) from the time of the ICF is signed through the end of the double-blind RW period.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Has a diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis; or systemic autoimmune diseases with exception of Still's disease.
2. Is pregnant, breastfeeding, or planning a pregnancy or fathering a child during the study or within 3 months after the last study drug administration.
3. Has a history of immunosuppression, including positive human immunodeficiency virus (HIV) test results.

4. Is currently receiving CS at a dose of >60 mg/day prednisone (or equivalent) for adult subjects, or >0.5 mg/kg/day (or >60 mg/day, whichever is lower) prednisone (or equivalent) in pediatric subjects (≥12 and <18 years old).
5. Has ever received cytotoxic drugs, including cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.
6. Has ever received agents that deplete B or T cells (e.g., rituximab, alemtuzumab).
7. Has received systemic immunomodulatory agents (with exception of CS) within the following time frames prior to RI baseline (first administration of study drug):
    a. Azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, or mercaptopurine within 24 weeks.
    b. TNF inhibitors, IL-6 inhibitors, or janus-activating kinase inhibitors within 12 weeks.
    c. Canakinumab within 12 weeks. Canakinumab could not have been discontinued due to safety unless it was discontinued due to local injection site reactions.
    d. Rilonacept within 6 weeks. Rilonacept could not have been discontinued due to lack of efficacy or due to safety.
    e. Methotrexate within 2 weeks.
    f. Anakinra within 5 days. Anakinra could not have been discontinued due to lack of efficacy or due to safety unless it was discontinued due to local injection site reactions.
8. Has a history of myeloproliferative disorder.
9. Has a history of demyelinating disease or symptoms suggestive of multiple sclerosis.
10. Meets the following TB criteria:
    a. History of active TB prior to screening OR
    b. History of latent TB that was not adequately treated prior to screening OR
    c. Signs or symptoms suggestive of active TB (e.g., new cough of >14 days in duration or a change in chronic cough, persistent fever, unintentional weight loss, or night sweats) upon review of medical history and/or physical examination at screening OR
    d. Recent close contact with a person with active TB OR
    e. Positive or indeterminate Interferon Gamma Release Assay (IGRA) test results or results from another positive TB test at screening based on acceptable clinical practice for the country in which the subject is enrolling.
11. Has chest x-ray (posterior-anterior view) at screening (or history of results within 12 weeks before receiving first administration of study drug), with evidence of malignancy or abnormality consistent with prior or active TB infection.

12. Has received immunization with a live (attenuated) vaccine within 12 weeks before screening or is expected to receive live (attenuated) vaccine during the study or within 12 weeks after the last study drug administration.
13. Has a history of positive or intermediate results for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening.
14. Has an estimated glomerular filtration rate (eGFR) <30 ml/min.
15. Has a history of malignancy of any organ system within the past 5 years before screening (other than a successfully treated non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
16. Has a known or suspected current active infection or a history of chronic or recurrent infectious disease, including, but not limited to, chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, or an open, draining infected skin wound.
17. Has had a serious infection, has been admitted to the hospital for an infection, has been treated with oral antibiotics within 2 weeks of RI baseline (first administration of study drug), or has been treated with IV antibiotics for an infection within 8 weeks of RI baseline.
18. Has had an organ transplant.
19. Has screening laboratory test results meeting any of the following criteria:
    a. Hemoglobin level <10.0 g/dL;
    b. WBC count $<3.0 \times 10^3/\mu L$
    c. Neutrophil count $<1.5 \times 10^3/\mu L$
    d. Platelet count $<100 \times 10^3/\mu L$
    e. Total bilirubin level >1.5 × the upper limit of normal (ULN) unless the test results are consistent with those for Gilbert's syndrome
    f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 × ULN
20. In the investigator's opinion, has a history of alcoholism or drug/chemical abuse within 2 years before screening.
21. Has a known hypersensitivity to ARCALYST® (rilonacept) or to any of its excipients.
22. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before screening or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
23. In the investigator's opinion, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations. This includes significant concomitant illnesses such as, but not limited to, cardiac, renal, neurological, endocrinological, metabolic, pulmonary, GI, or psychiatric diseases.

24. In the opinion of the investigator, is not likely to be compliant with the study protocol.
25. In the opinion of the investigator, should not participate in this study.

4.2 Subject Completion, Withdrawal from Study, and Study Drug Discontinuation

4.2.1 Completion

A subject will be considered to have completed the study if she/he has completed the RW period and has completed assessments at the EORW visit. At the EORW visit, subjects who were randomly assigned to rilonacept or subjects who transitioned to open-label rilonacept upon protocol-defined pericarditis recurrence (Section 6.2.3) in the RW period will be offered an opportunity to receive an additional 24 weeks of open-label rilonacept treatment based on their clinical status and at the discretion of the investigator, and after signing the LTE informed consent.

At the EORW visit, subjects who were randomly assigned to placebo and did not transition to bailout rilonacept will be offered an opportunity to receive an additional 24 weeks of open-label rilonacept treatment based on their clinical status and at the discretion of the investigator, after signing the LTE informed consent.

Any subject who in the opinion of investigator should not continue open-label rilonacept in LTE will be offered the opportunity to continue follow-up off study drug treatment in LTE, after signing the LTE informed consent.

Subjects who elect not to enter LTE will be followed for 6 weeks after receiving the last study drug administration.

4.2.2 Reasons for Discontinuation of Study Drug and Study Withdrawal

Subjects have the right to stop taking study drug before the end of the study or to withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject also may be asked to stop study drug at the investigator's discretion. In the event that a subject permanently discontinues study drug but does not withdraw the informed consent, the investigator should continue to follow up with the subject by telephone contact (TC) visits, in the clinic, or by other means through the EORW visit if the subject discontinues in RI or RW, or through the end of LTE-FUP if the subject discontinues in LTE-TP, unless consent is withdrawn.

The reasons for premature study drug discontinuation will be recorded in the electronic case report form (eCRF).

4.2.2.1 Discontinuation of Study Drug

The study drug dosing will be permanently stopped if any of the following occurs:

- The subject develops a serious or intolerable AE, TB, or malignancy, excluding non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma

- Initiation of protocol-prohibited medication (Section 5.8.6)
- Subject requires treatment with CS for pericarditis during RW or LTE-TP periods of the study
- Pregnancy or pregnancy planned during the study or within 3 months after the last study drug administration
- ALT or AST values ≥3 × ULN associated with total bilirubin ≥2 × ULN, with no underlying medical conditions to explain the elevated values
- Treatment with a live (attenuated) vaccine during the study
- Investigator or Sponsor's medical monitor or [redacted]-designated medical monitor decides that, for safety reasons, it is in the subject's best interest
- Termination of the study by Kiniksa Pharmaceuticals

Permanent or temporary study drug discontinuation should be strongly considered at the time if any of the following occurs:

- Subject develops an opportunistic infection.
- Subject develops moderate or severe infection
- Neutrophil count $<1.0 \times 10^3/\mu L$
- Isolated ALT or AST values >5 × ULN
- Surgical procedure

The Sponsor has the right to terminate the study at any time in case of safety concerns (e.g., suspected unexpected serious adverse reactions [SUSARs]) or if special circumstances concerning the study drug or the company itself occur. In this event, the investigator(s) will be informed of the reason for study termination.

4.2.2.2 Withdrawal from the Study

Subjects may withdraw from the study at any time and for any reason, without prejudice to their future medical care by the investigator or at the study site. However, prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow-up including options such as less frequent follow-up calls or visits, follow-up with a family member or friend, or follow-up through a local physician or medical records. Follow-up options will be summarized on a withdrawal of consent checklist source document that must be reviewed and signed by the investigator for any subject who withdraws consent for further participation in the study. The checklist must be completed for all enrolled subjects who have withdrawn consent. The reasons for a subject's withdrawal from the study are also required to be recorded in the eCRF.

A subject may be considered withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Documented withdrawal of informed consent
- Death

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and re-engage the subject in the study or determine the reason for withdrawal. The measures taken are to continue until study end and are required to be recorded in source documentation.

In subjects who are documented as having withdrawn consent from all study activities, no further study visits or study-related TCs can be conducted. All data collected prior to the date of the subject's confirmed withdrawal of consent will be included in the study, as specified in the subject's signed ICF.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

In the single-blind RI period, all subjects will receive blinded rilonacept at the same dose through Week 12; subjects will be blinded to the time of transitioning to RW. Subjects who stopped background SOC pericarditis therapy and who achieve Clinical Response on rilonacept at RI Week 12/RW baseline will be randomly assigned in a double-blind manner to continue to receive blinded rilonacept or matching placebo using a 1:1 allocation ratio. The definition of Clinical Response is provided in Section 6.2.2. An interactive web response system (IWRS) will be used to administer the randomization schedule. 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

5.2 Treatments Administered

Throughout this protocol, "study drug" refers to the investigational medicinal products: rilonacept and matching placebo. Both will be administered as applicable by SC injection.

Study drug administration will be performed once a week (every 7 ± 2 days). The interval between study drug administrations must be at least 5 days.

Study drug will be dosed as follows:

Adult Subjects (≥18 years old):

Rilonacept: Loading dose 320 mg administered as 2 SC injections, 160 mg each (2 ml) at RI baseline, followed by once-weekly SC injections of 160 mg (2ml).

Placebo: administered as once-weekly SC injections of 2 ml each in the RW period

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 320 mg administered as 2 SC injections, 160 mg each (2 ml) at the next scheduled study drug administration date, followed by once-weekly SC injections of 160 mg (2ml).

Pediatric Subjects (≥12 and <18 years old):

Rilonacept: Loading dose 4.4 mg/kg administered as 2 SC injections, 2.2 mg/kg each (maximum 160 mg each) at RI baseline, followed by once-weekly SC injections of 2.2 mg/kg (maximum 160 mg). The volume of injections will be based on the subject's weight (Table 5–1).

Placebo (in RW): once-weekly SC injections with volume based on the subject's weight (Table 5–1, maximum 2 ml).

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 4.4 mg/kg administered as 1 (maximum 2 ml) or 2 SC injections at the next scheduled study drug administration date, followed by once-weekly SC injections of 2.2 mg/kg (maximum 2 ml). The volume of injections will be based on the subject's weight (Table 5–1).

Study drug dose/volume will be calculated by the investigator or pharmacist during site clinic visits based on body weight (as specified in the Study Schedule of Activities) using a weight-based dosing chart in **kilograms** (Table 5–1).

Table 5–1: Study Drug Dose Volume (After Reconstitution) by Body Weight in Kilograms for Pediatric Subjects Aged ≥12 and <18 Years

Weight Range (kg)	Loading Dose Volume (ml)	Weekly Dose Volume (ml)
23.6 to 27.2	2 x 0.7	0.7
27.3 to 30.8	2 x 0.8	0.8
30.9 to 34.4	2 x 0.9	0.9
34.5 to 38.1	2 x 1.0	1.0
38.2 to 41.7	2 x 1.1	1.1
41.8 to 45.4	2 x 1.2	1.2
45.5 to 49.0	2 x 1.3	1.3
49.1 to 52.6	2 x 1.4	1.4
52.7 to 56.3	2 x 1.5	1.5
56.4 to 59.9	2 x 1.6	1.6
60.0 to 63.5	2 x 1.7	1.7
63.6 to 67.2	2 x 1.8	1.8
67.3 to 70.8	2 x 1.9	1.9
70.9 or greater	2 x 2.0	2.0

Study Drug Self-Administration

The first study drug dose on RI baseline will be administered at the study site. During this visit, the subject will be trained on study drug preparation and injection. In case the subject is unwilling or unable to prepare and self-inject the study drug, the subject's caregiver will be trained.

The first study drug administration for adult and pediatric subjects on RI baseline will consist of 2 SC injections, constituting a loading dose. The first injection will be prepared and administered by study site staff. The second injection will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration. If the subject or subject's caregiver is unable to prepare and inject the study dug, the subject may report for once-weekly injections to a study site, or injections can be administered by the visiting registered nurse (RN).

5.3 Identity of Investigational Medicinal Product

Rilonacept (KPL-914) is the drug being evaluated in the current study. Refer to Section 1.3 for a detailed description of rilonacept's mechanism of action.

Study drug (rilonacept or placebo) is supplied in a single-use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

Each placebo vial contains lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the placebo vial contains 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Product Packaging and Storage

Additional information regarding the preparation, dispensation, administration, and storage of rilonacept or placebo will be described in the Pharmacy Manual.

Study drug will be provided by Kiniksa Pharmaceuticals to the study sites in the lyophilized formulation in glass vials as described in Section 5.3. Each single-use vial will have a clinical label adhered to the vial. One labeled vial will be placed into a carton. Each carton will have a clinical label adhered to the outside of the carton. One tamper-evident seal will be placed on the top of the carton to securely close the lid.

Study drug is to be stored and shipped refrigerated at 2°C to 8°C (36°F to 46°F) inside the original carton to protect it from light.

5.4.2 Study Drug Accountability

The sites will receive study drug for on-site administration at study site visits. Upon receipt of study drug, the investigator (or delegate) will conduct an inventory of the supplies and verify that the supplies are received intact, at the appropriate temperature, and in the correct amounts prior to completing a supplies receipt. The investigator will confirm receipt of study drug in the IWRS and retain a copy of this receipt at the study site. The inventory of supplies at each study site will be reviewed by the study monitor.

Study drug will be dispensed to the study subjects for outpatient self-administration according to the supply chain described in the Pharmacy Manual.

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviating from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all used and unused study drug containers must be retained by the study site/clinic and subject for cataloguing and documentation of compliance. The full process for drug dispensing, documentation, and destruction will be described in the Pharmacy Manual.

A full drug accountability log will be maintained at the study site at all times.

5.4.3 Other Supplies

Rilonacept should be reconstituted with preservative-free WFI that will be provided by Kiniksa Pharmaceuticals or designee along with 27-gauge, ½-inch needles, 3-ml syringes, alcohol wipes, gauze pads, bandages, and a puncture resistant container for disposal of needles and syringes. Only the syringes and needles provided by the Sponsor or its designee should be used to prepare and inject the study drug. The Sponsor also will provide coolers and refrigerated gel packs to ensure that the subjects transport the study drug at the proper temperature. On occasion, sites may be asked to locally procure ancillary materials.

5.5 Study Drug Overdose

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose must be promptly reported to the [redacted] Pharmacovigilance (PVG) in the same way and using the same procedures as for a serious adverse event (SAE) (Section 6.4.6), regardless of whether any AEs are associated with the overdose.

If there are AEs associated with the overdose, these should be recorded on the relevant AE/SAE sections in the eCRF; however, overdoses without signs or symptoms do not need to be recorded as AEs in the eCRF.

5.5.1 Treatment of Study Drug Overdose

The maximum amount of rilonacept that can be safely administered has not been determined. Maximum once-weekly doses of rilonacept up to 320 mg have been administered SC for up to approximately 18 months in a small number of subjects with CAPS, and for up to 6 months in subjects in an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, rilonacept given IV at doses up to 2000 mg monthly for up to 6 months in another subject population was tolerated without dose-limiting toxicities (Rilonacept IB). In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of AEs and appropriate symptomatic treatment instituted immediately (Section 13.1, ARCALYST® Prescribing Information).

5.5.2 Other Study Drug Errors

To avoid study drug errors, it is important to note the following:

- In this study, rilonacept is designated for SC injections only. It should be taken only by the subjects participating in the study and as instructed by study site personnel.
- Guidelines regarding the management of temperature excursions during storage will be detailed in the Pharmacy Manual.
- Pediatric dosing is calculated based on body weight in **kilograms,** not pounds.

Any study drug error must be promptly reported to the [redacted] PVG, in the same way and using the same procedures as for an SAE (Section 6.4.6)

5.6 Transmission of Infectious Agents

The lyophilized study drug is to be stored refrigerated at 2°C to 8°C (36°F to 46°F) inside the original carton to protect it from light. Study drug should not be used beyond the date stamped on the label. After reconstitution, study drug may be kept at room temperature, should be protected from light, and should be used within 3 hours of reconstitution. Study drug does not contain preservatives; therefore, unused portions of study drug should be discarded.

5.7 Misuse for Illegal Purposes

Rilonacept does not have addicting potential, and the risk of misuse for illegal purposes is minimal.

5.8 Prior and Concomitant Medications

Use of all concomitant medications and any changes in concomitant medications will be recorded in the subject's eCRF. The minimum requirement is that drug name and dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF. The initiation of protocol prohibited medication (Section 5.8.6) requires discontinuation of study drug.

Guidelines regarding the use of concomitant medication will be detailed in the Pharmacy Manual and are summarized in the following sections.

5.8.1 Screening

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine, and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs), in the opinion of the investigator, are not anticipated to significantly alter assessments of baseline disease activity.

Analgesics can be used at the discretion of the investigator during screening activities prior to the first study drug dose, but only after the subject has documented a pericarditis pain level ≥4 on the 11-point NRS within 7 days prior to and including RI baseline (first administration of study drug).

Subjects can enter the study on prednisone (or equivalent dose) not exceeding 60 mg/day for adults and not exceeding 0.5 mg/kg/day (with a maximum dose of 60 mg/day) in pediatric subjects.

5.8.2 Single-blind RI Period

- 1-week Stabilization period, during which rilonacept is administered in addition to SOC pericarditis therapy and ongoing pericarditis episode is treated. All concomitant pericarditis medications including NSAIDs, analgesics, colchicine and CS will remain stable, unless the dosing must be decreased or stopped in the judgement of the investigator due to an AE.
- 9-week background medication Weaning period, during which subjects are weaned off background SOC pericarditis therapy, as applicable, while treatment with blinded rilonacept continues. The guidelines for background medication taper and discontinuation will be provided in the Pharmacy Manual.

  Corticosteroids

  Starting at Week 1 and through Week 10, CS will be tapered and discontinued at a rate dependent on the dose at study entry.

  Analgesics

  Starting at Week 1 and through Week 10, analgesics (non-opioid and opioid) will be tapered and discontinued. Opioid analgesics can continue beyond Week 10 at stable doses through the end of the RW period if it is not feasible to discontinue them without causing withdrawal symptoms.

  NSAIDs and Colchicine

  Starting at Week 4 and through Week 10, NSAIDs and colchicine will be tapered and discontinued.

- 2-week Monotherapy period during which rilonacept administration continues: Subjects are required to be off all background SOC pericarditis therapy, with the exception of opioid analgesics if their discontinuation is not feasible.

5.8.3 Double-blind Placebo-controlled RW Period

During the RW period, subjects should not be receiving any concomitant medications for pericarditis, with the exception of opioid analgesics in case their taper down and discontinuation was not feasible in the RI period.

5.8.3.1 Concomitant Medication Upon Pericarditis Recurrence

Subjects meeting protocol criteria for bailout rilonacept

Upon pericarditis recurrence and meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) and completing the diagnostic workup as confirmed by the [redacted] medical monitor, subjects will be transitioned to open-label rilonacept, as described in Section 3.1. Because open-label rilonacept can be administered only if at least 5 days have passed from the last blinded study drug administration, the investigators are allowed to use sequential ORT, i.e., analgesics, NSAIDs, and colchicine if necessary at their discretion. The use of those medications will be detailed in the Pharmacy Manual; it is briefly given as follows:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to open-label rilonacept based on the subject's clinical status and at the discretion of the investigator.
- If, after transition to open-label rilonacept, the investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from rilonacept and followed through the EORW visit.

Subjects not meeting protocol criteria for bailout rilonacept

If, based on the investigator's judgement, the subject is experiencing pericarditis recurrence that does not meet the protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) but does require additional treatment, the subject will continue blinded study drug, and the investigator should manage the pericarditis recurrence using sequential ORT for pericarditis, i.e., analgesics, NSAIDs, colchicine as described in the Pharmacy Manual and outlined briefly below:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to blinded study drug based on the subject's clinical status and at the discretion of the investigator.
- If, after the addition of NSAIDs and colchicine, the investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from blinded study drug and followed through the EORW visit.

5.8.4 Long Term Extension Treatment Period (LTE-TP)

Subjects who opt to continue open-label rilonacept in the LTE-TP will have their concomitant pericarditis medications managed at the discretion of the investigator and based on the subject's clinical status. If CS are required in addition to rilonacept to manage recurrent pericarditis, rilonacept should be discontinued.

5.8.5 Long Term Extension Follow-Up Period (LTE-FUP)

During LTE-FUP, pericarditis medication can be managed at the investigator's discretion.

5.8.6 Prohibited Concomitant Medicines During the Study

Prohibited medications during the study and throughout the end of LTE-TP include the following:

- Interleukin (IL) blockers other than rilonacept
- IL-6 blockers
- Janus-activating kinase inhibitors
- TNF inhibitors
- Potent immunosuppressants (azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, mercaptopurine, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents, agents that deplete B or T cells [e.g., rituximab, alemtuzumab])
- Live (attenuated) vaccines, which are prohibited during the study and within 12 weeks after the last study drug administration

5.9 Blinding

In the single-blind RI period, all subjects will receive rilonacept but will be blinded to the duration of the RI period and the timing of randomization.

The RW period is a double-blind period in which rilonacept and placebo are identical in appearance. Neither the subject nor any of the investigator/site staff, [redacted], or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Council for Harmonisation [ICH] E9).

In the event of a pericarditis recurrence that meets the criteria for bailout rilonacept (Sections 3.1 and 6.2.3), the subject will be transitioned to open-label rilonacept but will remain blinded to their prior RW treatment assignment.

At the end of the RW period, all sites and subjects will be unblinded. Subjects will be offered participation in the LTE-TP, in which once-weekly open-label rilonacept can be continued for an additional 24 weeks.

5.9.1 Breaking the Blind

A subject's treatment assignment will not be broken until the end of the RW period.

If the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the Sponsor must be notified immediately. If the investigator intends to unblind treatment allocation for a subject, then the Sponsor should be notified immediately. The investigator may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study drug is essential for the appropriate clinical management or welfare of the subject. In most cases, the management of a medical emergency would be the same, regardless of whether the subject received active drug. The treatment assignment will be unblinded through the IWRS. The investigator must notify Kiniksa Pharmaceuticals and [redacted] medical monitors as soon as possible but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the eCRF.

The [redacted] PVG staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the blinded report may be sent to clinical investigators in accordance with local regulations.

5.10 Treatment Compliance

Subjects will record the administration of all doses of study drug (whether as an outpatient or in the clinic) in a subject's diary. In addition, throughout all study periods, adherence to study drug administration will be assessed by the study site in collaboration with the visiting RN (Section 6).

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will provide informed consent or an assent, if applicable. Potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all questions answered for them. Subjects will undergo screening procedures specific to the study only after the ICF has been provided by the subject unless performed as part of SOC practice. The investigator or designee will also sign the ICF.

6.1 Study Visits

The schedule of assessments for the study site visits is summarized in the Study Schedule of Activities. Following screening assessments, qualifying subjects will be enrolled and enter the RI period. Subjects who stop background pericarditis medications and achieve Clinical Response at RI Week 12 (Section 6.2.2), will be randomized and enter the RW period. During both the RI and RW period, a combination of clinic and outpatient visits will occur. Outpatient visits may consist of telephone or virtual contacts as well as home visits conducted by a visiting nurse. For each scheduled visit of the study (including outpatient and clinic), assessments should occur prior to scheduled injections of study drug. Subjects can be brought to the clinic in place of a scheduled outpatient visit or for an unscheduled visit at the discretion of the investigator.

The visit schedule is derived from the day of the RI baseline visit. One week is equal to 7 calendar days. Although visits do not occur every week, subjects are required to record pericarditis pain NRS measurements on a daily basis in their study device and to administer study drug on a once-weekly basis and record it in their study electronic diary (eDiary). If a subject is unable to independently complete the daily eDiary, a caregiver may help enter the data.

Upon completion of the RI and RW periods, all subjects will have the opportunity to continue participating in the LTE. This will require each subject again providing informed consent prior to LTE participation. The LTE period will have a treatment period (LTE-TP) and an off treatment follow-up period (LTE-FUP).

Any subject who prematurely discontinues study drug will be followed for the duration of the trial as specified in Section 4.2.2. In addition, throughout all study periods, compliance with study drug administration will be assessed by the site in collaboration with the visiting RN.

6.1.1 Screening: Clinic and Remote as Needed

A study screening eCRF is required to be completed for every subject with a signed ICF. For each subject, the subject identification is obtained from the IWRS.

It is anticipated that some subjects may have a portion of the study screening procedures done as part of routine care outside the auspices of this study. As long as these procedures were done within the

allotted screening period timeframe, the results of these procedures may be used to support study screening and completion of the study screening eCRF. Any protocol-specified study qualification procedures/tests not already done as part of routine care will need to be conducted after the subject provides informed consent and before enrollment. It is possible that the screening and enrollment visit will occur on the same day.

The below procedures are required to be completed to screen a subject ≤28 days prior to enrollment. All assessments and procedures are not required to be completed on-site; however, the site is expected to obtain the medical records for subject source documentation.

- Obtain the ICF.
- Enter the subject into the IWRS.
- Review inclusion/exclusion criteria; ensure that the subject has a diagnosis of recurrent pericarditis based and is presenting with at least the **third** pericarditis episode.
- Record: demographic information, medical/surgical history, concomitant medications, all prior and current concomitant pericarditis medications, a detailed pericarditis history including all recurrent pericarditis events.
- Perform a full physical examination (may be performed by an investigator or other healthcare provider designated by the investigator).
- Perform/obtain:
  - 11-point pericarditis pain NRS assessment – required to be ≥4 within 7 days prior to and including the day of RI baseline. The qualifying NRS assessment and CRP are not required to occur on the same day.
  - CRP (mg/dL) – required within 7 days prior to and including the day of RI baseline. For study qualification purposes, the CRP may be assessed using 1 of 4 approaches:
    - Point of care (POC) device provided by Sponsor (preferred method)
    - Blood sample sent to the local laboratory
    - CRP measurement taken as part of the subject's routine care (e.g., not specifically obtained for this study)
    - Blood sample sent to the central laboratory
  - Local laboratory hematology, chemistry, IGRA, hepatitis serology, HIV
  - Chest x-ray (unless performed and available within the past 12 weeks)
  - Local or central laboratory urine pregnancy test for women of childbearing potential
  - AE collection

6.1.2 Single-blind Treatment: Run-In

6.1.2.1 Enrollment (RI Baseline): Clinic Visit

For subjects who meet study entry criteria, enrollment commences at the RI baseline visit. The following procedures occur:

- Review inclusion and exclusion criteria to confirm subject qualification.
- Review and record updates to recurrent pericarditis history since the screening visit.
- Revise IWRS status change to enrollment.
- Assess and record all concomitant medications as well as all prior and concomitant pericarditis medication.
- Perform an abbreviated physical examination, height and body weight.
- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; the ECHO is to be read locally prior to sending to the core lab.
- Perform cardiac MRI (for substudy participants only).
- Provide the subject with their study device and complete the following:
  - For subjects ≥18 years, have them complete the 36-Item Short Form Health Survey (SF-36), 5-level EuroQoL-5D (EQ-5D-5L), Insomnia Severity Index (ISI)
  - For all subjects, instruct how to complete the 11-point pericarditis pain NRS (as outlined in Section 6.2.1.2) and the medication diary.
  - Have all subjects complete the Patient Global Impression of Pericarditis Severity (PGIPS) score.
- The investigator is to complete the Physician Global Assessment of Pericarditis Activity (PGA-PA).
- Obtain the Pharmacogenomics ICF.
- Obtain a local or central laboratory urine pregnancy test for women of childbearing potential.
- Obtain central laboratory chemistry, hematology, lipid panel, CRP, anti-drug antibodies (ADAs), biomarkers, and urinalysis (laboratory tests should be drawn prior to the first study drug administration, but results of those tests are not required before enrollment).
- AE reporting.
- Additional discussion/assessment as needed.

Upon completion of the above study activities, study drug dispensing can commence. The following procedures occur:

- Complete the IWRS to dispense assigned study drug; record the amount (number of vials) dispensed.
- Explain the study drug, proper once-weekly dosing, proper study drug administration technique, study drug administration documentation, and confirm that the subject (and subject's caregiver as applicable) understands.
- For pediatric subjects, body weight (in kilograms) obtained at the RI baseline visit is to be used to determine appropriate study drug dosing in the RI period. Please refer to the pediatric study drug dosing Table 5–1 as well as the Study Schedule of Activities for subsequent visits with weight assessments for pediatric dosing.
- Prepare and administer the first injection of study drug and train the subject or caregiver to prepare and administer the second dose of study drug.
- Instruct the subject to bring to each clinic visit all medications the subject is taking, including used and unused study drug vials.
- Arrange upcoming study visits (as many visits as possible that can be arranged ahead of time is advised).

6.1.2.2 RI Day 2: Clinic Visit (24-hour PK Sub-study Participants Only)

The RI Day 2 visit includes a PK sample that is collected 24 hours after the loading dose of study drug and then sent to the central laboratory.

6.1.2.3 RI Day 4: TC/RN Visit

The timing of the site TC visit on the RI Day 4 visit can occur independently of the RN visit. During the site TC visit, the subject is contacted to assess for AEs in follow-up to the initial injections received, to review the daily input of the pericarditis pain NRS score, as well as to review all concomitant medications, including concomitant pericarditis medication. The site then dispenses study drug (along with ancillary supplies) through the IWRS and coordinates shipment as outlined in the Pharmacy Manual. During the visiting RN visit, a CRP sample is drawn and sent to the central lab.

6.1.2.4 RI Week 1: TC/RN Visit

It is preferred that the site TC occur prior to the RN visits. It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 1 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Provide instruction on the pericarditis concomitant medication oral corticosteroid tapering if applicable.
- Confirm and review upcoming visit arrangements.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

RN home visit:

- Obtain the central laboratory samples for CRP, PK, and biomarkers (these are collected prior to study drug administration).
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Ensure the subject records study drug administration in the medication diary.
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.5 RI Week 2: TC/RN Visit

It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 2 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the oral pericarditis corticosteroid tapering, if applicable.
- Review study drug administration and documentation compliance.
- Confirm and review upcoming visit arrangements.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

RN home visit:

- Record study drug dispensing to the subject.
- Obtain central laboratory samples for CRP, PK, and ADAs (these are drawn prior to study drug administration).
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.6 RI Week 4: TC/RN Visit

It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 4 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the oral corticosteroid tapering if applicable and provide instruction on NSAID and/or colchicine tapering if applicable.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm and review upcoming visit arrangements.
- Instruct the subject to bring used and unused study drug vials (those not yet obtained by the visiting RN) to the next clinic visit.

RN home visit:

- Obtain central laboratory samples for CRP, PK, and biomarkers (these are drawn prior to study drug administration).
- Obtain a pharmacogenomics sample for those subjects who have provided informed consent.
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.7 RI Week 6: Clinic Visit

The RI Week 6 visit in the clinic includes the following assessments and procedures:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the concomitant oral corticosteroid, NSAID and/or colchicine tapering if applicable.
- Obtain used and unused study drug vials for study drug compliance evaluation.
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for hematology, chemistry, CRP, and ADAs.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur:

- Have the subject administer the next scheduled injection of study drug (if within the study drug window) and have the subject record in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming visit arrangements.

6.1.2.8 RI Week 10: TC Visit

The following assessments and procedures are to be completed:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess concomitant oral corticosteroid, NSAID and/or colchicine tapering completion.
- Assess study drug administration documentation.
- Confirm the RI Week 12/RW baseline clinic visit arrangements.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).

6.1.2.9 Randomization (RI Week 12/RW Baseline): Clinic Visit

The following assessments and procedures are conducted at the RI Week 12 visit, **prior to randomization**:

- CRP assessment (local and central) (the POC device provided for the study is the preferred method for local laboratory CRP assessment).
- Obtain a pericarditis pain NRS average score for the prior 7 days, including the day of the visit (4 missing NRS values within this week may result in an inability to move forward with randomization).
- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; ECHO is read locally prior to submission to the core lab.
- Abbreviated physical examination, height and body weight.
- For subjects ≥18 years, complete on their device SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, PK, and ADAs.
- Evaluate concomitant medications including pericarditis concomitant medication.
- Assess for AEs.
- Obtain used and unused study drug vials for study drug compliance evaluation.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Assess for Clinical Response (refer to Section 6.2.2).

For subjects who have successfully completed the RI period and are assessed as achieving Clinical Response at the RI Week 12 visit, the RW baseline visit commences.

The following assessments and procedures are conducted at the RW baseline visit:

- Update the subject status in the IWRS by randomizing the subject in the IWRS.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1). Please refer to the pediatric study drug dosing Table 5–1 as well as the Study Schedule of Activities for subsequent visits with weight assessments for pediatric dosing during RW.
- Dispense study drug and record the amount (number of vials) dispensed.

- Have the subject administer the study drug and record in the diary (if within the study drug window).
- Instruct the subject to bring all medications including used and unused study drug to each clinic visit.
- Instruct the subjects on the process to follow for a pericarditis recurrence event.
- Arrange upcoming visits.

For subjects that do not qualify for randomization per the IWRS, the [redacted] medical monitor is to be immediately contacted to evaluate the reasons for non-qualification. Following medical monitor consultation, if the subject is deemed to not be a treatment responder, the RI Week 12 visit will be completed, study drug will be discontinued, and the subject will not proceed to randomization. The subject will be requested to perform a 6-week safety follow-up (SFU) visit after his/her last dose of study drug as well as continue with follow-up as agreed upon until the EORW period.

6.1.3 Randomized-Withdrawal (RW) Period

During the RW period, subjects will continue with once-weekly study drug administration as well as daily 11-point pericarditis pain NRS scoring. Visits will occur every 4 weeks, alternating TC/RN visits and clinic visits, with the first visit during the RW period (RW Week 4) being a TC/RN visit. Additional unscheduled visits may occur at any time for evaluation of suspected pericarditis recurrence (Section 6.1.6.1) or for other reasons as deemed necessary by the study investigator.

The following procedures are to occur during the TC/RN visits:

Site TC visits:

- Assess for AEs.
- Assess for suspected pericarditis recurrence events.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Additional discussion/assessment as needed.
- Confirm and review upcoming visit arrangements.
- Instruct the subject to bring used and unused study drug vials (those not yet obtained by visiting RN) to the next clinic visit.

RN home visits:

- Obtain central laboratory samples for CRP.
- Provide review of self-administration of the study drug as needed.

- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.

The following procedures are to occur during the clinic visits (except for Week 24; see below):

- Assess for AEs.
- Assess for suspected pericarditis recurrence events.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Record height and body weight.
- Obtain central laboratory samples for chemistry, hematology, and CRP.
- Obtain central laboratory sample for PK and biomarkers (Weeks 8 and 24 only).
- Obtain central laboratory sample for ADAs (Week 24 only).
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS entry).
- Obtain used and unused study drug vials for study drug compliance evaluation.

Upon completion of the above study activities, study drug dispensing can commence. The following procedures occur:

- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Monitor administration of the study drug dose (whenever possible) and have the subject record in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming visit arrangements.

6.1.3.1 RW WEEK 24: Clinic Visit

The Week 24 visit in the clinic includes the following assessments and procedures:

- Assess for AEs.
- Assess for suspected pericarditis recurrences.

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Perform a full physical examination, height and body weight.
- Acquire a 12-lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the ECHO is to be read locally before sending to the core lab.
- Obtain an MRI (for substudy participants only).
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, and biomarkers.
- Obtain used and unused study drug vials for study drug compliance evaluation.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur:

- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Have the subject administer the RW Week 24 study drug dose (if within the study drug window) and have the subject record it in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming study visits.

6.1.3.2 EORW (End of RW Period/LTE Baseline): Clinic Visit

The EORW visit will be same day as LTE-TP baseline visit.

All randomized subjects, including those that have had pericarditis recurrence or have permanently discontinued study drug will have an EORW visit at the end of the RW period. The EORW activities are listed below:

- Evaluate concomitant medications as well as pericarditis concomitant medications.

- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; the EHCO is to be read locally prior to submission to the core lab.
- Perform a full physical examination, height and body weight.
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrences.
- Obtain informed consent for participation in the LTE period.
- Additional discussion/assessment as needed.

Upon completion of the EORW visit procedures and obtaining subject informed consent to participate in the LTE period, the LTE baseline visit procedures are as follows:

- Change the subject's status in the IWRS and obtain unblinding information; proceed with subject unblinding.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Dispense study drug and record the amount (number of vials) dispensed.
- Have the subject administer the LTE-TP Day 1 study drug dose as applicable (if within the study drug window) and have the subject record it in the medication diary.
- Instruct subjects on continuing the 11-point pericarditis pain NRS score daily entry.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm the upcoming study visits.

6.1.4 Long Term Extension

6.1.4.1 LTE Weeks 8 and 16: Clinic Visit

The LTE Weeks 8 and 16 clinic visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, and CRP.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm upcoming visit arrangements.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Have the subject administer the regularly scheduled study drug dose as applicable (if within the study drug window) and have the subject record it in the medication diary.
- Confirm the upcoming study visits.

6.1.4.2 LTE Week 24 Clinic Visit

The LTE Week 24 visit is the final visit of the LTE-TP. However, if at any time throughout the course of the study a subject prematurely discontinues study drug, an End of Treatment (EOT) visit is to occur. The visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Acquire a 12-lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the EHCO is to be read locally prior to submission to the core lab.
- Obtain cardiac MRI (substudy participants only).
- Perform a full physical examination.
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.

- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, biomarkers, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Have the subject administer the regularly scheduled study drug as applicable (if within study drug window), and have the subject record it in the medication diary.
- Change the subject status in the IWRS.
- Arrange an LTE Week 30 visit.

6.1.5 LTE Follow-Up Period

Upon completion of the LTE Week 24 EOT visit, subjects continue long term follow-up until the end of the study (EOS). The LTE-FUP includes 2 visits.

6.1.5.1 LTE Week 30 Visit: Clinic

The LTE Week 30 visit is a clinic visit. Visit activities are as follows:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess for pericarditis recurrence events.
- Additional discussion/assessment as needed.
- Obtain central laboratory samples for CRP, ADAs, and urine pregnancy test.
- Any left-over ancillary supplies are to be returned to the site.

6.1.5.2 LTE Week 48 End of Study Visit: TC

The LTE Week 48 EOS TC visit procedures are as follows:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess pericarditis recurrence.

6.1.6 Supplemental Visits

6.1.6.1 Pericarditis Recurrence Assessment: Clinic Visit

If a subject experiences symptoms consistent with pericarditis recurrence, he/she should contact the study investigator immediately for evaluation. It is possible that a subject may have assessments performed remotely, however, assessments are also expected be performed at the study site as soon as possible. Required assessments include:

- Evaluate pericarditis pain on the 11-point NRS.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Obtain laboratory samples for CRP (local and central) (the POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment).
- Acquire a 12 lead ECG.
- Acquire a cardiac ECHO per core laboratory imaging parameters; this ECHO is read locally for the purpose of pericarditis recurrence assessment and is then submitted to the ECHO core laboratory for central review.
- Perform an abbreviated physical examination, height and body weight.
- For subjects >18 years, complete the SF 36, EQ-5D 5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA PA.
- Obtain central laboratory samples for PK, ADAs, and biomarkers.
- Other procedures deemed necessary per the investigator or delegated site personnel.

Upon having completed the evaluation, if the investigator makes a clinical diagnosis that the subject is having a pericarditis recurrence event, he/she should contact the [redacted] medical monitor to review and confirm that all assessments have been performed and collected. Upon [redacted] medical monitor confirmation of completion of the assessment, the investigator commences as described in Section 6.2.3.

Subjects treated for a pericarditis recurrence event will continue to follow the same visit schedule described for the RW period (Section 6.1.3).

Source documentation including the assessments and evaluations used to confirm a pericarditis recurrence event, are required to be sent to CEC.

6.1.6.2 End of Treatment Visit: Clinic

The EOT visit is to be conducted when a subject permanently discontinues study drug. For subjects who complete the RW period but do not consent to participate in the LTE period, the EORW and EOT visit can be combined. For those subjects who do consent to participate in the LTE period, the EOT visit can be combined with the LTE Week 24 visit. In the event that a subject prematurely discontinues study drug, it is expected that the subject will have an EOT visit as soon as possible and continue to be followed as described in Section 4.2.2.

The EOT visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Acquire a 12 lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the ECHO is to be read locally prior to submission to the core lab.
- Perform a cardiac MRI (for sub-study participants only) only if the previous MRI was done longer than 6 months ago.
- Perform a full physical examination.
- For subjects >18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, biomarkers, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Arrange SFU visit.

6.1.6.3 Safety Follow-Up Visit: Clinic or TC/RN

The SFU visit is to be conducted 6 weeks after the last dose of study drug. For those subjects who discontinue study drug at the LTE Week 24 visit, the SFU visit is to occur as a clinic visit. However, for those subjects who prematurely discontinue study drug during the study, the visit may be conducted in the clinic or as an outpatient (TC/RN visit) based on investigator discretion. The visit activities are as follows:

Site TC visit:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess for pericarditis recurrence events.
- Remind the subject to continue daily pericarditis pain NRS input if the SFU is occurring prior to the LTE Week 24 visit.
- Additional discussion/assessment as needed.

RN home visit:

- Obtain central laboratory samples for CRP, ADAs, and urine pregnancy test.
- Collect any leftover ancillary supplies and return to the site.

When the visit is conducted as a clinic visit, all of the RN visit activities are to be performed during the clinic visit.

6.2 Efficacy Assessments

Efficacy assessments to be performed at study visits are summarized in the Study Schedule of Activities and include: CRP, daily pericarditis pain assessment (11-point NRS), ECG, ECHO, Patient Global Impression of Pericarditis Severity (PGIPS), Physician Global Assessment of Pericarditis Activity (PGA-PA), and subject's quality of life assessments (SF-36, EQ-5D-5L) and insomnia questionnaire (ISI). In a substudy at selected sites in approximately 10 subjects, a cardiac MRI will be performed.

Note that in case the electronic versions of the PROs and assessments/questionnaires (PGIPS, PGA-PA, SF-36, EQ-5D-5L, and ISI) are not available, the paper forms must be completed until the electronic versions are available again.

6.2.1 Individual Efficacy Assessments

6.2.1.1 C-Reactive Protein

Central and local laboratory assessments of CRP will be performed at study visits as described in the Study Schedule of Activities. Centrally assayed CRP values will be used for statistical evaluations of changes from baseline. Locally assayed CRP will be used for screening, evaluation of treatment response prior to randomization, and assessment of suspected pericarditis recurrence in the RW period. The POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment.

6.2.1.2 11-Point Pericarditis Pain Numerical Rating Scale

Subjects will be asked to provide a daily assessment of pericarditis pain starting at RI baseline. A validated 11-point pericarditis NRS (Section 13.2) will be used to measure the subject's level of pain intensity on a daily basis throughout the study (Hawker et al 2011; Mannion et al 2007; Dworkin et al 2005).

It is recommended that daily pericarditis pain measurements using the 11-point NRS are performed by subjects at the same time of the day each day, and prior to study drug injection on days with study drug administration.

6.2.1.3 Electrocardiogram

Twelve-lead ECGs will be performed at study visits as described in the Study Schedule of Activities. Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-segment elevation or PR-segment depression.

6.2.1.4 Echocardiogram

Echocardiographic assessment of presence of pericardial effusion including new or worsening of pericardial effusion should be obtained at study visits as described in the Study Schedule of Activities. Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart, and pericarditis is one of the main causes of pericardial effusion. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening. Echocardiograms are to be acquired per the ECHO core imaging parameters. Upon local assessment and interpretation, the ECHO is then to be submitted to the designated central imaging laboratory.

6.2.1.5 Patient Global Impression of Pericarditis Severity

Patient Global Impression questionnaires have been developed for a variety of indications. The PGIPS is a single-item PRO measure that assesses the subject's impression of overall severity of pericarditis symptoms at the time the questionnaire is administered, using a 7-point rating scale ranging from absent (no recurrent pericarditis symptoms) to very severe (recurrent pericarditis symptoms cannot be ignored) (Guy 1976). The PGIPS can be completed in less than 30 seconds.

The subject will select the box that best describes the severity of pericarditis symptoms right now:

- ☐ Absent: no symptoms
- ☐ Minimal: can be easily ignored without effort
- ☐ Mild: can be ignored with effort
- ☐ Moderate: cannot be ignored but does not influence my daily activities
- ☐ Moderately severe: cannot be ignored and occasionally limits my daily activities

- ☐ Severe: cannot be ignored and often limits my concentration on daily activities
- ☐ Very severe: cannot be ignored and markedly limits my daily activities

The PGIPS will be collected as described in the Study Schedule of Activities.

6.2.1.6 Physician Global Assessment of Pericarditis Activity

Physician Global Assessment questionnaires have been developed for a variety of indications. The PGA-PA is a single-item clinician-reported outcome measure that investigators use to rate their impression of the patient's overall pericarditis disease activity at the time the assessment is completed, using a 7-point rating scale ranging from absent to very severe (Guy 1976). Like the PGIPS, the PGA-PA can be completed in less than 30 seconds.

The investigator will select the box that best describes subject's pericarditis activity right now.

- ☐ Absent
- ☐ Minimal
- ☐ Mild
- ☐ Moderate
- ☐ Moderately severe
- ☐ Severe
- ☐ Very severe

The PGA-PA will be collected as described in the Study Schedule of Activities.

6.2.1.7 36-Item Short Form Health Survey

The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. The SF-36 was developed at RAND Corporation as part of its Medical Outcomes Study. The SF-36 assesses 8 health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health.

SF-36 will be collected in subjects ≥18 years or older as described in the Study Schedule of Activities.

6.2.1.8 EQ-5D-5L

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The rating scale records the subject's self-rated health on a vertical VAS. This can be used as a quantitative

measure of health outcome that reflects the subject's own judgement. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles (https://euroqol.org/eq-5d-instruments).

The EQ-5D-5L will be collected in subjects ≥18 years or older as described in Study Schedule of Activities.

6.2.1.9 Insomnia Severity Index

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. The total score is interpreted as follows: no clinically significant insomnia (0–7); subthreshold insomnia (8–14); clinical (moderate) insomnia (15–21); and clinical (severe) insomnia (22–28) (Morin et al 2011).

The ISI will be collected in subjects ≥18 years or older as described in Study Schedule of Activities.

6.2.1.10 Cardiac MRI

Cardiac MRI will be performed as described in the Study Schedule of Activities at selected sites in approximately 10 subjects in the cardiac MRI substudy. Cardiac MRI will be performed to assess any changes in pericardial inflammation. Cardiac MRI readings will be performed by a central imaging laboratory. The study site/clinic reading of the MRI at the time of the examination may be used by the investigator for clinical decision-making.

6.2.2 Assessment of Clinical Response at the End of the Run-In Period Week 12/RW Baseline

At RI Week 12/RW baseline visit, all subjects receiving rilonacept who are able to discontinue background SOC pericarditis therapy during the RI period (Section 3.1) are assessed for Clinical Response. Only subjects who achieve Clinical Response at RI Week 12 and have discontinued background medications for pericarditis are eligible for randomization in the RW period.

Clinical Response at RI Week 12 is defined as follows:

- A weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS during the 7 days prior to and including the day of randomization, **AND**
- CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.

6.2.3 Management of Suspected Pericarditis Recurrence in the RW Period

Pericarditis Recurrence Definition: Pericarditis recurrence, for the purpose of the protocol, is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis.

At any time point during the RW period, subjects who experience suspected recurrence of their pericarditis will have been instructed to inform their site investigator as soon as possible. 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 (Section 6.1.6.1). The investigator will evaluate all assessments performed for a diagnostic workup, whether at the study site or at locations outside.

Upon completion of pericarditis workup, the investigator is required to contact the [redacted] medical monitor to confirm that the protocol required diagnostic workup is complete prior to implementing treatment for the event.

Following communication with the [redacted] medical monitor, if the event meets the criteria for bailout rilonacept (at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and one CRP value ≥1 mg/dL either on the same day or separated by no more than 7 days), and after the [redacted] medical monitor has confirmed with the investigator that the diagnostic workup is complete, the attainment of bailout criteria is confirmed in the IWRS, blinded study drug is discontinued, and open-label rilonacept treatment is dispensed. If needed, sequential ORT is allowed as outlined in Section 5.8.3. The subject will continue to be followed up according to the Study Schedule of Activities for the RW period.

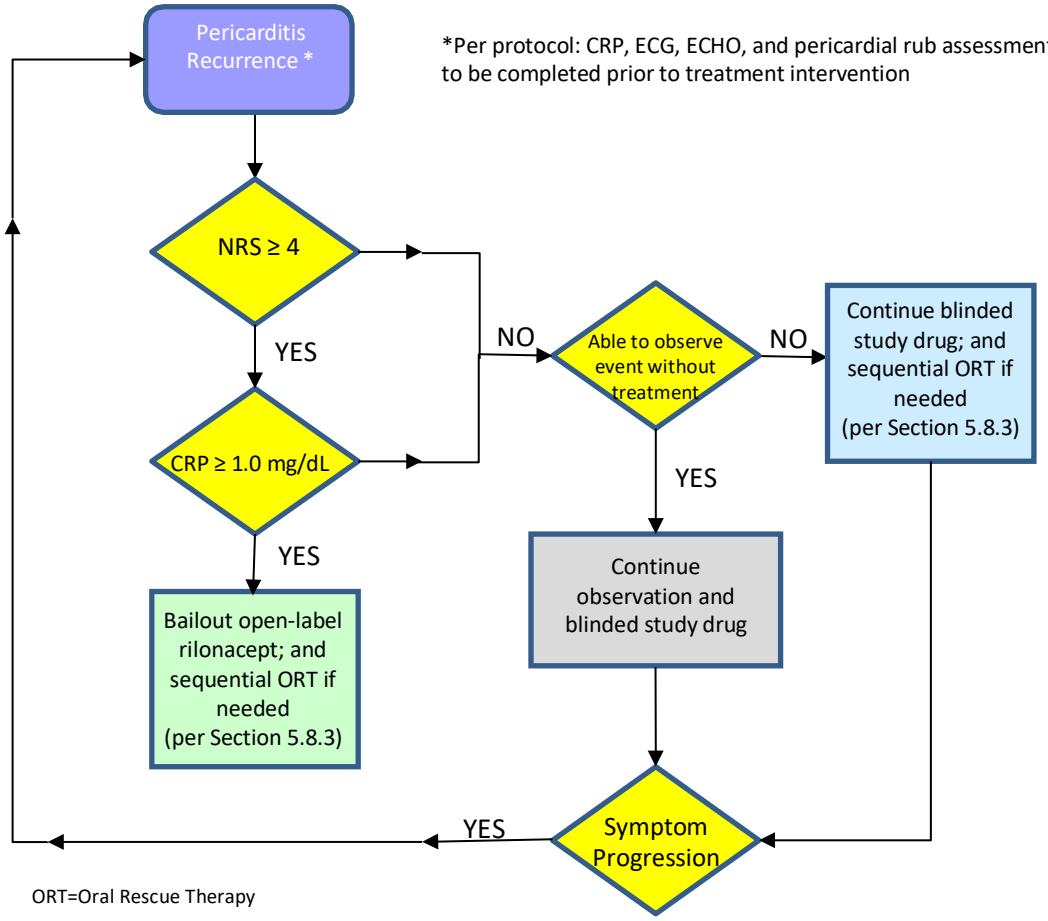
Following communication with the [redacted] medical monitor, if the event does not meet the protocol criteria for bailout rilonacept but in the judgement of investigator requires treatment, after the [redacted] medical monitor has confirmed with the investigator that the diagnostic workup is complete, the investigator is allowed to add sequential ORT to blinded study drug, and as outlined in Section 5.8.3. Blinded study drug treatment will continue until a pericarditis recurrence that meets criteria for bailout rilonacept, or until the end of the RW period.

For a summary of management of suspected pericarditis recurrence, refer to Figure 3.

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. The event package will include, but may not be limited to, data on the subject's pericarditis pain level, CRP value, ECG tracing, ECHO result, the presence or absence of pericardial rub, and any additional source documentation relevant to

the assessment of the suspected event. Details on endpoint package requirements will be described in the CEC charter. The CEC-confirmed pericarditis recurrences will be used for Primary Endpoint efficacy analysis. For more details on the CEC, refer to Section 6.7.2

Figure 3: Management of Suspected Pericarditis Recurrence in the Randomized-Withdrawal Period



6.3 Safety Assessments

Safety assessments to be performed at study visits are summarized in Study Schedule of Activities and include: assessment of AEs (Section 6.4), physical examinations (full and abbreviated) including vital signs measurements, chest x-ray, TB screening, and clinical laboratory tests (serology, hematology, chemistry, urinalysis) (Section 6.6). A pregnancy test (Section 6.6.6) will be conducted at screening and as needed during the study and must be performed 6 weeks after the last study drug administration.

6.3.1 Physical Examination

A full physical examination should include at minimum an evaluation of vital signs, head, eyes, ears, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. Body weight and height will be measured as per the Study Schedule of Activities and will be recorded in the eCRF. Any abnormality identified at baseline should be recorded on the medical history and physical examination eCRFs. At selected visits as specified in the Study Schedule of Activities, an abbreviated physical examination will be performed to evaluate vital signs, lung and heart sounds, including evaluation for pericardial rub.

At all visits at the study site, limited symptom-directed physical examinations may need to be performed in order to determine changes from baseline or abnormalities and should be recorded in the subject's trial notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

6.3.2 Vital Signs

Vital signs include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Blood pressure measurements should be obtained after the subject has been seated for at least 5 minutes.

6.3.3 Chest X-ray

Chest x-rays in accordance with local requirements will be obtained at screening (or an existing chest x-ray within 12 weeks of first study drug administration can be used) according to the Study Schedule of Activities. Chest x-rays should be reviewed by a qualified radiologist for clinically significant abnormalities and evidence of pulmonary disease that would exclude the potential subject.

6.3.4 Tuberculosis Screening

An IGRA test or another TB test based on acceptable clinical practice in each country will be performed in order to evaluate for the presence of active or latent TB infection at screening.

6.4 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

6.4.1 Definitions

6.4.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the reporting investigator to be clinically significant; and any untoward medical occurrence.

6.4.1.2 Treatment-emergent Adverse Event

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to the study drug or any event already present that worsens in either intensity or frequency after exposure to the study drug.

6.4.1.3 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence or effect that, at any dose:

- Results in *death*. Includes all deaths, even those that appear to be completely unrelated to the study drug (e.g., car accident where the subject is a passenger).
- Is *life-threatening*. In the view of the investigator, the subject was at immediate risk of death from the event at the time of the event (i.e., it does not include an AE that might have caused death if it had occurred in a more serious form).
- Requires *in-patient hospitalization* or prolongs an existing hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such pre-existing condition must be recorded on the medical history or physical examination page of the eCRF. Hospitalization is defined as an admission to the hospital ward, a short-stay type unit, or Emergency Room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay longer than originally anticipated for the event or development of a new AE as determined by the Investigator or treating physician.)
- Results in *persistent or significant disability/incapacity*. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.)
- Is a congenital anomaly/birth defect.
- Is an *important medical event*. Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above, i.e., any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the study drug.

All SAEs that occur after signing of study-related informed consent, whether or not the SAEs are related to the study drug or study procedures, must be reported.

6.4.1.4 Adverse Event of Special Interest

An adverse event of special interest (AESI) is defined as an AE of scientific and medical interest specific to the understanding of the study drug and requiring close monitoring and rapid communication by the investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of the study drug.

Treatments with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies. Therefore, malignancy is an AESI for rilonacept. Any AE of malignancy (excluding basal cell carcinoma of the skin) requires reporting to the [redacted] Pharmacovigilance (PHV) within 24 hours after the time the site personnel first learn about the event, following the process as described in Section 6.4.6.

6.4.1.5 Adverse Reaction

Any noxious and unintended response to the study drug (i.e., where a causal relationship between the study drug and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reaction.

6.4.1.6 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction that is "unexpected", i.e., it is not listed (or not listed at the severity that has been observed) in the designated Reference Safety Information of the Investigator's Brochure. Evaluation and reporting requirements for SUSARs are detailed in Section 6.4.8.

6.4.2 Assessing Adverse Events

6.4.2.1 Relationship to Study Drug

The investigator's assessment of an AE's relationship to the study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized by investigator using the following classification and criteria:

- **Not Related**: when the AE is definitely caused by the subject's clinical state or the study procedure/conditions
- **Unlikely Related**: when the temporal association between the AE and the study drug is such that the drug is not likely to have any reasonable association with the AE
- **Possibly Related**: when the AE follows a reasonable temporal sequence from the time of study drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- **Related**: when the AE follows a reasonable temporal sequence from administration of the study drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced

6.4.2.2 Intensity

The severity of an AE will be recorded as one of the following:

- **Mild**: easily tolerated, does not interfere with normal daily activities, does not require intervention
- **Moderate**: causes some interference with daily activities; minimal, local, or noninvasive intervention indicated
- **Severe**: as a consequence of the event, daily activities are limited or completely halted; hospitalization or prolongation of hospitalization indicated

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.3 Recording Adverse Events

Each subject should be monitored for the development of any AEs. This information should be collected by asking nonleading questions (such as "How are you feeling?") and from observations of and conversations with patients. AEs may also be collected by direct physical exam, diagnostic procedures, or any other appropriate source.

At every study visit (telephone or at the site), subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been admitted to the hospital, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

All AEs (serious and non-serious) will be documented in the subject's source documents and recorded in the eCRF. Any clinically relevant (as determined by the investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the subject's source documents and in the eCRF.

The AE term should be reported in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Information to be collected includes the following:

- Event term
- Date and time of onset
- Investigator-specified assessment of severity and relationship study drug
- Date of resolution of the event
- Seriousness
- Any required treatment or actions
- Outcome
- Whether or not it caused the subject to discontinue the study drug.
- Whether or not the AE is an Injection Site Reaction (ISR). ISR is defined as any AE that occurs at the study drug injection site. If an ISR is observed, the subject may be treated at the discretion of the investigator.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the condition deteriorates at any time during the study, it should be recorded as an AE.

6.4.3.1 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.3.2 Adverse Events Based on Examinations and Tests

If an abnormal laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical rather than the laboratory term (e.g., anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically significant findings on examinations and tests should be reported as AEs.

Any new or aggravated clinically significant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4.3.3 Pericarditis Disease Related Events

Signs, symptoms, and abnormal findings associated with pericarditis are to be captured as a pericarditis recurrence event rather than as an AE unless the event is more severe than expected for the subject. In any case, pericarditis recurrence is required to be captured in the eCRF (see Section 6.2.3) within 24 hours of learning of the event.

6.4.4 Time Period for Collection of Adverse Events

Adverse events will be assessed from the time the subjects signs the ICF and through the duration of the study, or at least through the SFU period (6 weeks after the last dose of study drug).

6.4.5 Follow-Up of Unresolved Adverse Events

Every reasonable effort will be made to follow subjects who have AEs.

Any AEs that are unresolved at the subject's SFU visit are to be followed up by the investigator until resolution or for as long as medically indicated. Additional information for any subject with an ongoing AE at the end of the SFU period may be requested by the [redacted] PHV, as needed.

6.4.6 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.4.1.3) must be reported to the [redacted] PHV using the EDC system, immediately (i.e., within 24 hours) after the time site personnel first learn about the event.

In the event the EDC entry is not possible (e.g., system failure or access problems), the study site should complete the paper SAE report form and fax the form to the [redacted] PHV within 24 hours of awareness. The EDC system should be updated as soon as it is available.

A full description of every SAE will need to be provided to the [redacted] PHV (this may be supported by source documentation such as discharge summary or laboratory report should these documents be requested by the [redacted] PHV). Additional follow-up information, if required or available, should be sent to the [redacted] PHV as soon as possible and placed with the original SAE information.

The following contact information is to be used for SAE reporting:

[redacted]

Information on non-serious AEs that become serious must also be reported to the [redacted] PHV as soon as it is available.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as applicable per institutional policy.

The Sponsor or designee will provide regulatory authorities, IRBs, IECs, and principal investigators with clinical safety updates/reports according to local requirements.

6.4.6.1 Other Reasons for Immediate Reporting

The following events require reporting to the [redacted] PHV within 24 hours after the time the site personnel first learn about the event:

- Pregnancy in subject or female partner of male subject
- Overdose of the study drug or concomitant medication, regardless of whether it is considered AE
- Other study drug errors
- Any AE of malignancy (excluding basal cell carcinoma of the skin)

6.4.7 Pregnancy

Pregnancy is regarded as an AE only if there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. Nonetheless, any pregnancy that occurs during study participation (including pregnancy in a female partner of a male subject) must be reported to the [redacted] PHV in the same way and using the same procedures as for an SAE (Section 6.4.6). The subject with pregnancy must not receive (additional) study drug. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriage must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study, and considered by the investigator as possibly related to the study drug, must be promptly reported to the [redacted] PHV.

In the event that a subject is found to be pregnant after having received at least 1 study drug dose, the study drug must be discontinued, and the pregnancy will be followed to term and the status of mother and child will be reported to the [redacted] PHV after delivery. Instances of perinatal death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of study drug, will be reported to the [redacted] PHV within 24 hours.

6.4.8 Evaluating and Reporting SUSARs

[redacted] Pharmacovigilance will promptly evaluate all SUSARs and nonserious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, [redacted] PHV staff in collaboration with Kiniksa Pharmaceuticals will assess the expectedness of these events using the Reference Safety Information (Section 6.2) of the rilonacept Investigator's Brochure.

[redacted] PHV will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by [redacted] PHV and Kiniksa Pharmaceuticals as needed.

All relevant information about suspected SUSARs that are fatal or life-threatening will be recorded and reported to the competent authorities in all the applicable countries, and IRBs/IECs in conjunction with Directive 2001/20/EC.

6.5 Other Assessments

6.5.1 Pharmacokinetic Sample

All subjects will have PK samples obtained according to the Study Schedule of Activities. For PK analyses, it is important that the exact time of the SC injection is recorded for each subject. When PK samples are to be collected on dosing days, serum will be collected pre-dose to measure rilonacept concentrations. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

A PK substudy will be conducted in a subset of subjects agreeing to provide a PK sample 24 hours after the first dose of study drug in the RI period. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

6.5.2 Anti-Drug Antibodies (ADAs) against Rilonacept (KPL-914)

Serum samples to measure the presence of ADAs against rilonacept will be collected according to the Study Schedule of Activities. Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the site.

6.5.3 Biomarkers

Serum and plasma will be collected according to the Study Schedule of Activities for biomarker analysis.

6.5.4 Pharmacogenomics

Whole blood will be collected for pharmacogenomics assessments after signing the separate Pharmacogenomics ICF.

6.6 Laboratory Analyses

Any abnormal laboratory test results (hematology, chemistry, or urinalysis) or other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

Laboratory assessments will be performed at study visits as summarized in Study Schedule of Activities. Unscheduled laboratory assessments for safety issues are permitted as deemed necessary by the investigator.

Whenever possible in pediatric subjects, local laboratory tests should be drawn using pediatric tubes.

6.6.1 Serology

Samples for local laboratory assessment of hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and HIV levels will be collected at screening. If clinically indicated, those tests may be also collected during the study.

6.6.2 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.

6.6.3 Chemistry

Blood chemistry tests performed in the central study laboratory include albumin, total protein, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, total bilirubin, bicarbonate, chloride, potassium, sodium, creatinine, glucose.

In addition, the following chemistry tests may be performed together with local CRP measurement when using POC device: chloride, creatine kinase, creatinine, glucose, potassium, sodium, total carbon dioxide, blood urea nitrogen.

6.6.4 Non-fasting Lipid Panel

Subjects treated with rilonacept may experience increases in their lipids, including total cholesterol, LDL, 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 Study Schedule of Activities.

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.

6.6.5 Urinalysis

Urinalysis performed by the central study laboratory includes specific gravity, pH, protein, urobilinogen, ketones, glucose, blood, bilirubin, nitrites, leukocyte esterase. It will be performed as described in the Study Schedule of Activities.

6.6.6 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. The purpose of pregnancy test is to prevent embryo/fetal exposure to study drug. Subjects with positive or indeterminate pregnancy test during the screening are not eligible for the study.

6.6.7 Sample Collection

The procedures for the collection, handling, and shipment of laboratory samples are specified in the Laboratory Manual supplied to sites by the central laboratory.

6.7 Committees

6.7.1 Independent Data Monitoring Committee (DMC)

A DMC will be utilized in this study to ensure external objective medical and/or statistical (if needed) review of safety data in order to protect the ethical and safety interests of subjects. The DMC will review unblinded aggregate (and, where necessary, individual) subject safety data at pre-defined intervals according to a DMC charter. The analysis plan for the DMC review will be described in the DMC charter, which will also contain details of the composition and the responsibilities of the DMC.

6.7.2 Clinical Endpoint Committee (CEC)

An independent CEC will review and adjudicate all suspected recurrent pericarditis events that occur during the RW period of the study. The procedures for adjudicating events will be described in the CEC Charter. This will be done independent of the investigators, and in a manner blinded to treatment assignment. The CEC will complete assessments on an ongoing basis.

7 Statistical and Analytical Plan

7.1 Primary Efficacy Endpoint

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.

A sensitivity analysis will be done based on the investigator's assessment of the event.

Pericarditis recurrence is defined in Section 6.2.3.

Subjects who do not have a pericarditis recurrence will be censored at the date of the last available assessment during the RW period before data cutoff. Detailed censoring rules will be specified in the Statistical Analysis Plan (SAP).

7.2 Secondary Efficacy Endpoints for the RW Period

This section defines secondary efficacy endpoints for the RW period. Endpoints for the RI period and for the LTE-TP are defined in Section 7.3.

7.2.1 Major Secondary Efficacy Endpoints

1. Proportion of subjects who maintained Clinical Response at Week 24 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.

2. Percentage of days with no or minimal pain in the first 24 weeks of the RW period. No or minimal pain is defined as non-missing NRS ≤1.
3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period.

7.2.2 Other Secondary Endpoints

All time-to-event endpoints start from the day of randomization. The following variables will be analyzed:

- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)
- Number (percentage) of subjects with absent or minimal pericarditis activity based onPGA- the PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in EQ-5D-5L. There are 6 questions in this instrument (Section 6.2.1.8). Each of the first 5 questions has 5 levels, from level 1 (best) to level 5 (worst). They are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The sixth question is the health on the day, from 0 (the worst) to 100 (the best) (van Reenen and Janssen 2015). The levels of the first 5 questions (EQ-5D-5L profile) will be converted to an index value. Change from baseline in each one of these 7 values will be an endpoint.
- Change over time in subject's sleep quality assessed with the ISI (Section 6.2.1.9). There are 7 items in the ISI. Change in ISI total score, which is the sum of the 7 items over time, will be the endpoint.
- Change over time in ISI categories. The ISI total scores are divided to 4 categories:
  - 0–7 = No clinically significant insomnia
  - 8–14 = Subthreshold insomnia

- 15–21 = Clinical insomnia (moderate severity)
- 22–28 = Clinical insomnia (severe)

- Number (percentage) of subjects who receive sequential ORT for pericarditis (analgesics, NSAIDs, and/or colchicine) in the RW period

7.3 Other Endpoints

These include efficacy endpoints in the RI period and the LTE-TP. Since there is no control arm in these 2 periods, only descriptive statistics will be provided. All time-to-event endpoints start from the day of receiving rilonacept in that period.

7.3.1 Efficacy Endpoints for the RI Period

The following efficacy endpoints are included in this period:

- Proportion of subjects who achieved Clinical Response at the RI Week 12/RW baseline visit. Clinical Response is defined as a weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS and CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.
- Time to CRP normalization (≤0.5 mg/dL)
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12
- Change from baseline in CRP level at RI Week 12
- Resolution of ECHO and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L (Section 7.2.2 contains details about calculation)
- Change over time in the subject's sleep quality assessed with the ISI (Section 7.2.2 contains details about calculation)
- Change over time in ISI categories
- Number (percentage) of subjects who were off background pericarditis medication at RI Week 12

7.3.2 Efficacy Endpoints for the LTE-TP

The efficacy endpoints below are included in this period. Each endpoint will be summarized through Week 24, by subjects who did and did not have an adjudicated pericarditis recurrence in the RW period, respectively, and overall:

- Number (percentage) of subjects with pericarditis recurrences
- Proportion of subjects with Clinical Response
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L (Section 7.2.2 contains details about calculation)
- Change over time in the subject's sleep quality assessed with the ISI (Section 7.2.2 contains details about calculation)
- Change over time in ISI categories
- Number (percentage) of subjects requiring addition of SOC pericarditis therapy

7.4 Sample Size Calculations

For the purpose of sample size estimation, 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) 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.

Patient 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 patients 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 patients may be enrolled and/or randomized at Kiniksa Pharmaceutical's discretion. However, at this time it is anticipated that no more than 75 subjects will be enrolled into this study. Since the data cutoff will be the event date of the 22nd adjudicated pericarditis recurrence AND all subjects still in the RW period have been treated for 24 weeks, the actual power could be higher if the assumed hazard ratio holds.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

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

Safety Analysis Set: 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.

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

Per-protocol Analysis Set: The per protocol (PP) analysis set is a subset of the ITT analysis set with the exclusion of subjects with major 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.

Pharmacokinetic Analysis Set: The PK analysis set includes subjects who receive at least 1 dose of study drug and have at least 1 PK sample. The PK analysis set will be used for all PK analyses.

7.6 Description of Subgroups to be Analyzed

Subgroup analyses for the primary endpoint will be performed by the stratification variable for randomization, as well as by important variables for baseline demographics and patient characteristics. These analyses are for the RW period only. Details will be provided in the SAP.

7.7 Statistical Analysis Methodology

This section outlines the overall methodologies. Details of the statistical analyses, methods, and data conventions will be described in the SAP.

7.7.1 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 25th, 50th, and 75th percentiles with 95% CI, if estimable. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

At each of RI and RW periods and in the LTE-TP, 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.

7.7.2 Stratified Analysis

There will be 2 stratification variables for randomization:

- Oral CS use at RI baseline: yes or no
- Diagnosis of recurrent idiopathic pericarditis at RI baseline: yes or no

When a stratified analysis is used in the analysis and a stratum has no event of interest or no responder, the stratum will be pooled with the other stratum in the same stratification variable.

7.7.3 Testing Hypotheses and Multiplicity Adjustment

All statistical tests for the treatment comparison of efficacy endpoints in the RW period will be based on the ITT analysis set with 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 7.2.1 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 24 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 7.2.1 will be tested with Hochberg's procedure at overall 1-sided α=00.52. 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.

7.7.4 Analysis of Primary Efficacy Endpoint

Primary analysis of this study will be done after 22nd CEC-confirmed pericarditis recurrence AND after all subjects in the RW period have been treated for 24 weeks. The log rank test will be the primary method for the analysis of time to recurrence, stratified by the stratification variables for randomization.

A sensitivity analysis will be performed based on the investigator's judgement of pericarditis recurrence. Additional sensitivity may be defined in the SAP.

7.7.5 Analysis of Secondary Efficacy Endpoints

7.7.5.1 Analysis of the Major Secondary Endpoints

1. Proportion of subjects who maintained Clinical Response at Week 24 of the RW period (defined as a weekly average of daily pericarditis pain ≤2.0 on the 11-point NRS and CRP ≤0.5 mg/dL at Week 24). The Cochran–Mantel–Haenszel (CMH) test will be used in this analysis, stratified by the stratification variables for randomization.
2. Percentage of days with minimal or no pain in the first 24 weeks post randomization. Minimal or no pain is defined as non-missing daily NRS ≤1. This endpoint will be analyzed with an analysis of covariance. In addition to treatment arm, the following covariates will be included in this analysis: the stratification variables for randomization, and baseline NRS weekly average in 2 categories: NRS ≤1 versus NRS >1.

3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period. The CMH test will be used in this analysis, stratified by the stratification variables for randomization.

7.7.5.2 Analyses of Other Secondary Endpoints in the RW Period

The following endpoints will be analyzed using the same method for the primary endpoint:

- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO

A mixed model with repeated measures (MMRM) will be used in the analysis of the endpoints below. 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, and the variables for stratification at randomization. The p-value for treatment comparison will be calculated at each scheduled assessment for at least 24 weeks as part of the summary statistics. This is done with the understanding that the comparison could be biased due to dropouts or subjects with pericarditis recurrence.

- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L: Health score and Index value, respectively
- Change over time in the subject's sleep quality: sum of the ISI scores.

The CMH test will be used in the analysis of the endpoints below, stratified by the stratification variables for randomization.

- Proportion of patients without pericarditis recurrence in the first 24 weeks of the RW period
- Number (percent) of subjects with absent or minimal pericarditis activity based on the investigator's assessment
- Number (percentage) of subjects who receive SOC pericarditis therapy in the RW period

The following endpoints will be analyzed using the Mantel-Haenszel test with 1 degree of freedom:

- Change in each 1 of the first 5 questions in the EQ-5D-5L, i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
- Change over time in ISI categories

[redacted]

7.7.6 Analyses of Other Endpoints

Endpoints listed in Section 7.3 for the RI period and the LTE-TP will be descriptive in nature since there is no control arm. Summary statistics will be generated following the methodologies stated in Section 7.7.

Other analyses include anti-rilonacept antibodies and biomarker analyses. These analyses will be described in the SAP.

7.7.7 Pharmacokinetic Analyses

For all subjects, serum samples will be collected at time points shown in the Study Schedule of Activities in order to quantify concentrations of rilonacept. Descriptive statistics will be calculated for the serum concentrations of rilonacept by visit. Individual listings of serum concentrations will be provided.

Pharmacokinetic data may be used in a subsequent population PK evaluation that will be conducted outside of this study and described in a separate report.

7.7.8 Safety Analyses

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 the most recent version of MedDRA. TEAEs will be analyzed for all subjects combined and by treatment group in the RW period. Further analyses by severity and relationship to study drug as well as analyses of serious TEAEs will be presented.

Descriptive statistics will be used to summarize safety endpoints by visit for all subjects combined in the RI period and by treatment group in the RW period. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for clinical laboratory analyses (including safety

laboratory measurements, ADAs, etc.), vital signs measurements, ECGs, and physical examination findings.

7.7.9 Interim Analyses

No interim analyses are planned for this study.

8 Data Quality Assurance

Assessment of subject compliance and adherence to study drug administration will be assessed by the site in collaboration with the visiting RN.

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management (ICH Q9).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

[redacted] will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant Standard Operating Procedures (SOPs) of [redacted]

Investigative site personnel will enter subject data into an EDC system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After the last study database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a Master DVD/CD-ROM copy of all of the site data from the study will be created and sent to Kiniksa for storage. [redacted] will maintain a duplicate Master DVD/CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to Kiniksa Pharmaceuticals.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Regulatory agencies and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, informed assent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by Kiniksa Pharmaceutical or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply Kiniksa Pharmaceutical or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Subject Information and Consent

A written informed consent in compliance approved by an IRB/IEC, as appropriate, at each center/country shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent for (or assent form, as applicable) template may be provided by Kiniksa Pharmaceutical or its designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by Kiniksa Pharmaceutical or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before screening, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the

subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

It should be emphasized to the subjects that they may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

For potential subjects under the age of 18, a parent or legal guardian is required to sign and date the ICF and the potential subject is also required to sign and date an informed assent form. The informed assent form explains the trial, it's purpose, procedures as well as risk and benefits in age-appropriate language. Both the ICF and informed assent form, as applicable, are required prior to participation in the trial. The investigator shall retain the signed original ICF(s)/assent form(s), as applicable, and give a copy of the signed original form to the subject or legal guardian.

For this study subjects will be required to sign and date the ICF (or assent form, if applicable) prior to entry to the study and prior to entry to LTE.

In addition, a separate ICF (assent, if applicable) will be needed for subjects participating in pharmacogenomic testing.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on local or country-specific industry and government standard operating procedures, working practice documents, or guidelines.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by Kiniksa Pharmaceuticals, its designee, the regulatory agencies/authorities, or the IRB/IEC.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Kiniksa Pharmaceuticals or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Kiniksa Pharmaceuticals or its designee to submit the complete and accurate certification or disclosure statements required under US Title 21 Code of Federal Regulations (CFR) Part 54. In addition, the investigator must provide to Kiniksa Pharmaceuticals a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 or local country-specific equivalent for outside the US
- Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572
- Financial disclosure information
- IRB/IEC-approved ICFs/assent forms, as applicable, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to [redacted] and/or IRB/IEC according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and Kiniksa Pharmaceuticals and regulatory authority(ies) with any reports required.

10.8 Records Retention

It is the responsibility of the investigator to ensure all essential trial documentation and source records (e.g., signed ICFs, study site/clinic files, subjects' hospital notes, copies of eCRFs) at their site are securely retained. The Sponsor will inform the investigator of the time periods for retaining study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations; otherwise, the retention period by default will be 15 years.

10.9 Publications

Kiniksa shall have the sole and exclusive right to publish information obtained from the study, including any data, results, and conclusions. Investigators are encouraged to participate in the study execution such that they may be invited to participate in the authorship of a potential publication in a manner commensurate with their participation in the study execution in accordance with International Committee of Medicinal Journal Editors standards. Any publication of the results will be subject to the terms and conditions provided in the study agreement.

11 Study Management

The administrative structure will include a Data Monitoring Committee (DMC) and a Clinical Endpoint Committee (CEC). Please refer to Section 6.7 for further details.

11.1 Monitoring

11.1.1 Monitoring of the Study

Data for each subject will be recorded in source records and in the eCRF. Data collection must be completed for each subject who signs an ICF.

For each subject enrolled, the investigator or designee will document in the source records of the subject that the subject is enrolled in this study along with all safety and efficacy information. The investigator is responsible for maintaining adequate case histories in the source records of each subject. Source data should be preserved for the maximum period of time permitted by the hospital/institution and made available by the investigator in the cases described above.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow Kiniksa Pharmaceuticals, representatives of Kiniksa Pharmaceuticals, or a regulatory agency(ies) access to all study records.

The investigator should promptly notify Kiniksa Pharmaceuticals and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Kiniksa Pharmaceuticals and [redacted]

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Sponsor initiated amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval and to the regulatory authorities, if required, before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is any change, divergence, or departure from the study design or procedures defined in the protocol. No waivers will be granted for exemptions to inclusion/exclusion criteria. The Investigator will conduct the study in compliance with the protocol agreed to with the Sponsor and, if required, the regulatory authorities, and which was given approval/favorable opinion by the IRB/IEC. In the event of a protocol deviation, the Sponsor or a designee must be notified.

The Investigator, or person designated by the Investigator, must document and explain any deviation from the approved protocol. The Investigator will notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

11.3 Study Termination

Although Kiniksa Pharmaceuticals has every intention of completing the study, Kiniksa Pharmaceuticals reserves the right to discontinue the study at any time in case of safety concerns (e.g., SUSARs) or if special circumstances concerning the study drug or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, Kiniksa Pharmaceutical will ensure that the clinical study report(s) are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified to approve the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, Kiniksa Pharmaceutical will provide the investigator(s) with the full summary of the study results. The investigator(s) are encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers, as applicable.

12 Reference List

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13 Appendices

13.1 Appendix: ARCALYST® Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARCALYST safely and effectively. See full prescribing information for ARCALYST.

ARCALYST® (rilonacept)
Injection for Subcutaneous Use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. (1)

DOSAGE AND ADMINISTRATION

- Adult patients 18 yrs and older: Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg on the same day at two different sites. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. Do not administer ARCALYST more often than once weekly. (2)
- Pediatric patients aged 12 to 17 years: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. Do not administer ARCALYST more often than once weekly. (2)

DOSAGE FORMS AND STRENGTHS

Sterile, single-use 20-mL, glass vial containing 220 mg of rilonacept as a lyophilized powder for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Interleukin-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking ARCALYST. Discontinue treatment with ARCALYST if a patient develops a serious infection. Do not initiate treatment with ARCALYST in patients with active or chronic infections. (5.1)
- Hypersensitivity reactions associated with ARCALYST administration have been rare. If a hypersensitivity reaction occurs, discontinue administration of ARCALYST and initiate appropriate therapy. (5.5)
- Live vaccines should not be given concurrently with ARCALYST. Prior to initiation of therapy with ARCALYST, patients should receive all recommended vaccinations. (5.3)

ADVERSE REACTIONS

The most common adverse reactions reported by patients with CAPS treated with ARCALYST are injection-site reactions and upper respiratory tract infections. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-REGN-777 (1-877-734-6777) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with ARCALYST. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy – No human data. Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2016

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARCALYST® (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Injection for Subcutaneous Use Only.

2.2 Dosing

Adult patients 18 years and older: Treatment should be initiated with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg each given on the same day at two different sites. Dosing should be continued with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. ARCALYST should not be given more often than once weekly. Dosage modification is not required based on advanced age or gender.

Pediatric patients aged 12 to 17 years: Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. ARCALYST should not be given more often than once weekly.

2.3 Preparation for Administration

Each single-use vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection (supplied separately) is required prior to subcutaneous administration of the drug.

2.4 Administration

Using aseptic technique, withdraw 2.3 mL of preservative-free Sterile Water for Injection through a 27-gauge, ½-inch needle attached to a 3-mL syringe and inject the preservative-free Sterile Water for Injection into the drug product vial for reconstitution. The needle and syringe used for reconstitution with preservative-free Sterile Water for Injection should then be discarded and should not be used for subcutaneous injections. After the addition of preservative-free Sterile Water for Injection, the vial contents should be reconstituted by shaking the vial for approximately one minute and then allowing it to sit for one minute. The resulting 80-mg/mL solution is sufficient to allow a withdrawal volume of up to 2 mL for subcutaneous administration. The reconstituted solution is viscous, clear, colorless to pale yellow,

and essentially free from particulates. Prior to injection, the reconstituted solution should be carefully inspected for any discoloration or particulate matter. If there is discoloration or particulate matter in the solution, the product in that vial should not be used.

Using aseptic technique, withdraw the recommended dose volume, up to 2 mL (160 mg), of the solution with a new 27-gauge, ½-inch needle attached to a new 3-mL syringe for subcutaneous injection. EACH VIAL SHOULD BE USED FOR A SINGLE DOSE ONLY. Discard the vial after withdrawal of drug.

Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard.

2.5 Stability and Storage

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be protected from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded.

3 DOSAGE FORMS AND STRENGTHS

ARCALYST is supplied in sterile, single-use, 20-mL, glass vials. Each vial contains 220 mg of rilonacept as a white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted ARCALYST is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Interleukin-1 (IL-1) blockade may interfere with the immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking ARCALYST [*see Clinical Studies (14)*]. There was a greater incidence of infections in patients on ARCALYST compared with placebo. In the controlled portion of the study, one infection was reported as severe, which was bronchitis in a patient on ARCALYST.

In an open-label extension study, one patient developed bacterial meningitis and died [*see Adverse Reactions (6.3)*]. ARCALYST should be discontinued if a patient develops a serious infection. Treatment with ARCALYST should not be initiated in patients with an active or chronic infection.

In clinical studies, ARCALYST has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of an IL-1 blocker in combination with TNF inhibitors. **Taking ARCALYST with TNF inhibitors is not recommended because this may increase the risk of serious infections.**

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as ARCALYST that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ARCALYST.

5.2 Immunosuppression

The impact of treatment with ARCALYST on active and/or chronic infections and the development of malignancies is not known [*see Adverse Reactions (6.3)*]. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.

5.3 Immunizations

Since no data are available on either the efficacy of live vaccines or on the risks of secondary transmission of infection by live vaccines in patients receiving ARCALYST, live vaccines should not be given concurrently with ARCALYST. In addition, because ARCALYST may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ARCALYST. No data are available on the effectiveness of vaccination with inactivated (killed) antigens in patients receiving ARCALYST.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ARCALYST adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current Recommended Immunizations schedules at the website of the Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/schedules/index.html).

5.4 Lipid Profile Changes

Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted [*see Adverse Reactions (6.7)*].

5.5 Hypersensitivity

Hypersensitivity reactions associated with ARCALYST administration in the clinical studies were rare. If a hypersensitivity reaction occurs, administration of ARCALYST should be discontinued and appropriate therapy initiated.

6 ADVERSE REACTIONS

Six serious adverse reactions were reported by four patients during the clinical program. These serious adverse reactions were *Mycobacterium intracellulare* infection; gastrointestinal bleeding and colitis; sinusitis and bronchitis; and *Streptococcus pneumoniae* meningitis [*see Adverse Reactions (6.3)*].

The most commonly reported adverse reaction associated with ARCALYST was injection-site reaction (ISR) [*see Adverse Reactions (6.2)*]. The next most commonly reported adverse reaction was upper respiratory infection [*see Adverse Reactions (6.3)*].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described herein reflect exposure to ARCALYST in 600 patients, including 85 exposed for at least 6 months and 65 exposed for at least one year. These included patients with CAPS, patients with other diseases, and healthy volunteers. Approximately 60 patients with CAPS have been treated weekly with 160 mg of ARCALYST. The pivotal trial population included 47 patients with CAPS. These patients were between the ages of 22 and 78 years (average 51 years). Thirty-one patients were female and 16 were male. All of the patients were White/Caucasian. Six pediatric patients (12-17 years) were enrolled directly into the open-label extension phase.

6.1 Clinical Trial Experience

Part A of the clinical trial was conducted in patients with CAPS who were naïve to treatment with ARCALYST. Part A of the study was a randomized, double-blind, placebo-controlled, six-week study comparing ARCALYST to placebo [*see Clinical Studies (14)*]. Table 1 reflects the frequency of adverse events reported by at least two patients during Part A.

Table 1: Most Frequent Adverse Reactions (Part A, Reported by at Least Two Patients)

Adverse Event	**ARCALYST 160 mg (n = 23)**	**Placebo (n= 24)**
Any AE	17 (74%)	13 (54%)
Injection-site reactions	11 (48%)	3 (13%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Nausea	1 (4%)	3 (13%)
Diarrhea	1 (4%)	3 (13%)
Sinusitis	2 (9%)	1 (4%)
Abdominal pain upper	0	2 (8%)
Cough	2 (9%)	0
Hypoesthesia	2 (9%)	0
Stomach discomfort	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)

6.2 Injection-Site Reactions

In patients with CAPS, the most common and consistently reported adverse event associated with ARCALYST was injection-site reaction (ISR). The ISRs included erythema, swelling, pruritus, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth and hemorrhage. Most injection-site reactions lasted for one to two days. No ISRs were assessed as severe, and no patient discontinued study participation due to an ISR.

6.3 Infections

During Part A, the incidence of patients reporting infections was greater with ARCALYST (48%) than with placebo (17%). In Part B, randomized withdrawal, the incidence of infections were similar in the ARCALYST (18%) and the placebo patients (22%). Part A of the trial was initiated in the winter months, while Part B was predominantly performed in the summer months.

In placebo-controlled studies across a variety of patient populations encompassing 360 patients treated with rilonacept and 179 treated with placebo, the incidence of infections was 34% and 27% (2.15 per patient-exposure year and 1.81 per patient-exposure year), respectively, for rilonacept and placebo.

Serious Infections: One patient receiving ARCALYST for an unapproved indication in another study developed an infection in his olecranon bursa with *Mycobacterium intracellulare*. The patient was on chronic glucocorticoid treatment. The infection occurred after an intraarticular glucocorticoid injection into the bursa with subsequent local exposure to a suspected source of mycobacteria. The patient recovered after the administration of the appropriate antimicrobial therapy. One patient treated for another unapproved indication developed bronchitis/sinusitis, which resulted in hospitalization. One patient died in an open-label study of CAPS from *Streptococcus pneumoniae* meningitis.

6.4 Malignancies

[*see Warnings and Precautions (5.2)*].

6.5 Hematologic Events

One patient in a study in an unapproved indication developed transient neutropenia (ANC < 1 x 10^9/L) after receiving a large dose (2000 mg intravenously) of ARCALYST. The patient did not experience any infection associated with the neutropenia.

6.6 Immunogenicity

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST. Nineteen of 55 patients (35%) who had received ARCALYST for at least 6 weeks tested positive for treatment-emergent binding antibodies on at least one occasion. Of the 19, seven tested positive at the last assessment (Week 18 or 24 of the open-label extension period), and five patients tested positive for neutralizing antibodies on at least one occasion. There was no correlation of antibody activity and either clinical effectiveness or safety.

The data reflect the percentage of patients whose test results were positive for antibodies to the rilonacept receptor domains in specific assays, and are highly dependent on the sensitivity and specificity of the assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is

highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to rilonacept with the incidence of antibodies to other products may be misleading.

6.7 Lipid Profiles

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with ARCALYST experienced increases in their mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were 19 mg/dL, 2 mg/dL, 10 mg/dL, and 57 mg/dL respectively after 6 weeks of open-label therapy. Physicians should monitor the lipid profiles of their patients (for example after 2-3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

7 DRUG INTERACTIONS

7.1 TNF-Blocking Agent and IL-1 Blocking Agent

Specific drug interaction studies have not been conducted with ARCALYST. Concomitant administration of another drug that blocks IL-1 with a TNF-blocking agent in another patient population has been associated with an increased risk of serious infections and an increased risk of neutropenia. The concomitant administration of ARCALYST with TNF-blocking agents may also result in similar toxicities and is not recommended [*see Warnings and Precautions (5.1)*]. The concomitant administration of ARCALYST with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of ARCALYST and other agents that block IL-1 or its receptors is not recommended.

7.2 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of ARCALYST, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of ARCALYST in pregnant women. Based on animal data, ARCALYST may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15 or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human doses of 160 mg based on body

surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100 or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). ARCALYST should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nonteratogenic effects. A peri- and post-natal reproductive toxicology study was performed in which mice were subcutaneously administered a murine analog of rilonacept at doses of 20, 100, 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F_1 offspring during maturation at all doses tested.

8.3 Nursing Mothers

It is not known whether rilonacept is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARCALYST is administered to a nursing woman.

8.4 Pediatric Use

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with ARCALYST at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24-weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g. Serum Amyloid A and C-Reactive Protein). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult patients.

The trough drug levels for four pediatric patients measured at the end of the weekly dose interval (mean 20 mcg/mL, range 3.6 to 33 mcg/mL) were similar to those observed in adult patients with CAPS (mean 24 mcg/mL, range 7 to 56 mcg/mL).

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

When administered to pregnant primates, rilonacept treatment may have contributed to alterations in bone ossification in the fetus. It is not known if ARCALYST will alter bone development in pediatric patients. Pediatric patients treated with ARCALYST should undergo appropriate monitoring for growth and development. [*see Use in Specific Populations (8.1)*]

8.5 Geriatric Use

In the placebo-controlled clinical studies in patients with CAPS and other indications, 70 patients randomized to treatment with ARCALYST were ≥ 65 years of age, and 6 were ≥ 75 years of age. In the CAPS clinical trial, efficacy, safety and tolerability were generally similar in elderly patients as compared to younger adults; however, only ten patients ≥ 65 years old participated in the trial. In an open-label extension study of CAPS, a 71 year old woman developed bacterial meningitis and died [*see Adverse*

Reactions (6.3)]. Age did not appear to have a significant effect on steady-state trough concentrations in the clinical study.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

There have been no reports of overdose with ARCALYST. Maximum weekly doses of up to 320 mg have been administered subcutaneously for up to approximately 18 months in a small number of patients with CAPS and up to 6 months in patients with an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, ARCALYST given intravenously at doses up to 2000 mg monthly in another patient population for up to six months were tolerated without dose-limiting toxicities. The maximum amount of ARCALYST that can be safely administered has not been determined.

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

ARCALYST is supplied in single-use, 20-mL glass vials containing a sterile, white to off-white, lyophilized powder. Each vial of ARCALYST is to be reconstituted with 2.3 mL of Sterile Water for Injection. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for subcutaneous administration only. The resulting solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Each vial contains 220 mg rilonacept. After reconstitution, each vial contains 80 mg/mL rilonacept, 46 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5 ± 0.3. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-

inflammatory Syndrome-1 [*CIAS1*]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

In most cases, inflammation in CAPS is associated with mutations in the NLRP-3 gene which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation.

Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1 receptor antagonist (IL-1ra) with reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.

12.2 Pharmacodynamics

C-Reactive Protein (CRP) and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Compared to placebo, treatment with ARCALYST resulted in sustained reductions from baseline in mean serum CRP and SAA to normal levels during the clinical trial. ARCALYST also normalized mean SAA from elevated levels.

12.3 Pharmacokinetics

The average trough levels of rilonacept were approximately 24 mcg/mL at steady-state following weekly subcutaneous doses of 160 mg for up to 48 weeks in patients with CAPS. The steady-state appeared to be reached by 6 weeks.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

No study was conducted to evaluate the effect of age, gender, or body weight on rilonacept exposure. Based on limited data obtained from the clinical study, steady state trough concentrations were similar between male and female patients. Age (26-78 years old) and body weight (50-120 kg) did not appear to have a significant effect on trough rilonacept concentrations. The effect of race could not be assessed because only Caucasian patients participated in the clinical study, reflecting the epidemiology of the disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of rilonacept. The mutagenic potential of rilonacept was not evaluated.

Male and female fertility was evaluated in a mouse surrogate model using a murine analog of rilonacept. Male mice were treated beginning 8 weeks prior to mating and continuing through female gestation day 15. Female mice were treated for 2 weeks prior to mating and on gestation days 0, 3, and 6. The murine analog of rilonacept did not alter either male or female fertility parameters at doses up to 200 mg/kg (this dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

14 CLINICAL STUDIES

The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS.

Part A was a 6-week, randomized, double-blind, parallel-group period comparing ARCALYST at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all patients received ARCALYST 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on ARCALYST 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with ARCALYST 160 mg weekly.

Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment.

The changes in mean symptom scores for the randomized parallel-group period (Part A) and the randomized withdrawal period (Part B) of the study are shown in Table 2. ARCALYST-treated patients had a larger reduction in the mean symptom score in Part A compared to placebo-treated patients. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on ARCALYST.

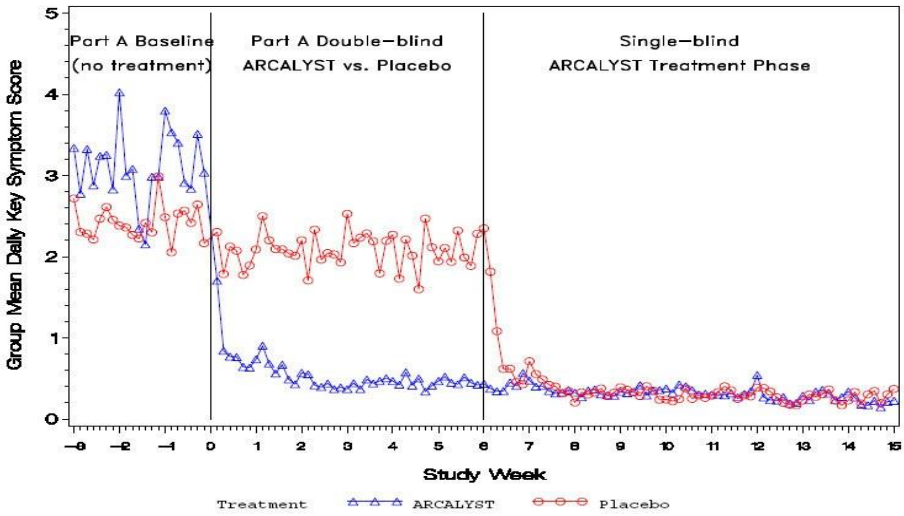
Table 2: Mean Symptom Scores

Part A	Placebo (n=24)	ARCALYST (n=23)	Part B	Placebo (n=23)	ARCALYST (n=22)
Pre-treatment Baseline Period (Weeks -3 to 0)	2.4	3.1	Active ARCALYST Baseline Period (Weeks 13 to 15)	0.2	0.3
Endpoint Period (Weeks 4 to 6)	2.1	0.5	Endpoint Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment groups	(-1.3, -0.4)**	

*Differences are adjusted using an analysis of covariance model with terms for treatment and Part A baseline.
**A confidence interval lying entirely below zero indicates a statistical difference favoring ARCALYST versus placebo.

Daily mean symptom scores over time for Part A are shown in Figure 1.

Figure 1: Group Mean Daily Symptom Scores by Treatment Group in Part A and Single-blind ARCALYST Treatment Phase from Week -3 to Week 15



Improvement in symptom scores was noted within several days of initiation of ARCALYST therapy in most patients.

In Part A, patients treated with ARCALYST experienced more improvement in each of the five components of the composite endpoint (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) than placebo-treated patients.

In Part A, a higher proportion of patients in the ARCALYST group experienced improvement from baseline in the composite score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%) and by at least 75% (70% vs. 0%) compared to the placebo group.

Serum Amyloid A (SAA) and C-Reactive Protein (CRP) levels are acute phase reactants that are typically elevated in patients with CAPS with active disease. During Part A, mean levels of CRP decreased versus baseline for the ARCALYST treated patients, while there was no change for those on placebo (Table 3). ARCALYST also led to a decrease in SAA versus baseline to levels within the normal range.

Table 3. Mean Serum Amyloid A and C-Reactive Protein Levels Over Time in Part A

Part A	ARCALYST	Placebo
SAA (normal range: 0.7 – 6.4 mg/L)	(n=22)	(n=24)
Pre-treatment Baseline	60	110
Week 6	4	110
CRP (normal range: 0.0 – 8.4 mg/L)	(n= 21)	(n=24)
Pre-treatment Baseline	22	30
Week 6	2	28

During the open-label extension, reductions in mean symptom scores, serum CRP, and serum SAA levels were maintained for up to one year.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each 20-mL glass vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. ARCALYST is supplied in a carton containing four vials (NDC 61755-001-01).

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be kept from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded. Discard the vial after a single withdrawal of drug.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

The first injection of ARCALYST should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer ARCALYST, he/she should be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously should be assessed to ensure proper administration of ARCALYST, including rotation of injection sites. (*See Patient Information Leaflet for ARCALYST®*). ARCALYST should be reconstituted with preservative-free Sterile Water for Injection to be provided by the pharmacy. A puncture-resistant container for disposal of vials, needles and syringes should be used. Patients or caregivers should be instructed in proper vial, syringe, and needle disposal, and should be cautioned against reuse of these items.

Injection-site Reactions: Physicians should explain to patients that almost half of the patients in the clinical trials experienced a reaction at the injection site. Injection-site reactions may include pain, erythema, swelling, pruritus, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Patients should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Infections: Patients should be cautioned that ARCALYST has been associated with serious, life-threatening infections, and not to initiate treatment with ARCALYST if they have a chronic or active infection. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ARCALYST. Treatment with ARCALYST should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ARCALYST, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ARCALYST with other IL-1 blocking agents, such as anakinra, is not recommended.

Vaccinations: Prior to initiation of therapy with ARCALYST physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ARCALYST.

REGENERON

Manufactured and distributed by:

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V 5.0

Patient Information

ARCALYST® (ARK-a-list)

(rilonacept)

Injection for Subcutaneous Use

Read the patient information that comes with ARCALYST before you start taking it and each time you refill your prescription. There may be new information. The information in this leaflet does not take the place of talking with your healthcare provider about your medical condition and your treatment.

What is the most important information I should know about ARCALYST?

ARCALYST can affect your immune system. ARCALYST can lower the ability of your immune system to fight infections. Serious infections, including life-threatening infections and death have happened in patients taking ARCALYST. **Taking ARCALYST can make you more likely to get infections, including life-threatening serious infections, or may make any infection that you have worse.**

You should not begin treatment with ARCALYST if you have an infection or have infections that keep coming back (chronic infection).

After starting ARCALYST, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have any open sores on your body, call your healthcare provider right away. **Treatment with ARCALYST should be stopped if you develop a serious infection.**

You should not take medicines that block Tumor Necrosis Factor (TNF), such as Enbrel® (etanercept), Humira® (adalimumab), or Remicade® (infliximab), while you are taking ARCALYST. You should also not take other medicines that block Interleukin-1 (IL-1), such as Kineret® (anakinra), while taking ARCALYST. Taking ARCALYST with any of these medicines may increase your risk of getting a serious infection.

Before starting treatment with ARCALYST, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as fever, cough, or flu-like symptoms
- have any open sores on your body
- have a history of infections that keep coming back
- have asthma. Patients with asthma may have an increased risk of infection.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis.
- have or have had HIV, Hepatitis B, or Hepatitis C
- take other medicines that affect your immune system

Before you begin treatment with ARCALYST, talk with your healthcare provider about your vaccination history. Ask your healthcare provider whether you should receive any vaccinations, including pneumonia vaccine and flu vaccine, before you begin treatment with ARCALYST.

What is ARCALYST?

ARCALYST is a prescription medicine called an interleukin-1 (IL-1) blocker. ARCALYST is used to treat adults and children 12 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle Wells Syndrome (MWS). ARCALYST can help lessen the signs and symptoms of CAPS, such as rash, joint pain, fever, and tiredness, but it can also lead to serious side effects because of the effects on your immune system.

What should I tell my healthcare provider before taking ARCALYST?

ARCALYST may not be right for you. **Before taking ARCALYST, tell your healthcare provider about all of your medical conditions, including if you:**

- are scheduled to receive any vaccines. You should not receive live vaccines if you take ARCALYST.
- are pregnant or planning to become pregnant. It is not known if ARCALYST will harm your unborn child. Tell your healthcare provider right away if you become pregnant while taking ARCALYST.
- are breast-feeding or planning to breast-feed. It is not known if ARCALYST passes into your breast milk.

See "What is the most important information I should know about ARCALYST?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take other medicines that affect your immune system, such as:

- other medicines that block IL-1, such as Kineret® (anakinra).
- medicines that block Tumor Necrosis Factor (TNF), such as Enbrel® (etanercept), Humira® (adalimumab), or Remicade® (infliximab).
- corticosteroids.

See "What is the most important information I should know about ARCALYST?"

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist every time you get a new prescription.

If you are not sure or have any questions about any of this information, ask your healthcare provider.

How should I take ARCALYST?

See the "Patient Instructions for Use" at the end of this leaflet.

- Take ARCALYST exactly as prescribed by your healthcare provider.
- ARCALYST is given by injection under the skin (subcutaneous injection) one time each week.
- Your healthcare provider will tell and show you or your caregiver:
    - how much ARCALYST to inject
    - how to prepare your dose
    - how to give the injection
- Do not try to give ARCALYST injections until you are sure that you or your caregiver understands how to prepare and inject your dose. Call your healthcare provider or pharmacist if you have any questions about preparing and injecting your dose, or if you or your caregiver would like more training.
- If you miss a dose of ARCALYST, inject it as soon as you remember, up to the day before your next scheduled dose. The next dose should be taken at the next regularly scheduled time. If you have any questions, contact your healthcare provider.
- If you accidentally take more ARCALYST than prescribed, call your healthcare provider.

What are the possible side effects of ARCALYST?

Serious side effects may occur while you are taking and after you finish taking ARCALYST including:

- **Serious Infections. See "What is the most important information I should know about taking ARCALYST?"** Treatment with ARCALYST should be discontinued if you develop a serious infection.
- **Allergic Reaction.** Call your healthcare provider or seek emergency care right away if you get any of the following symptoms of an allergic reaction while taking ARCALYST:
  - rash
  - swollen face
  - trouble breathing

Common side effects with ARCALYST include:

- **Injection-site reaction**. This includes: pain, redness, swelling, itching, bruising, lumps, inflammation, skin rash, blisters, warmth, and bleeding at the injection site.
- **Upper respiratory infection.**
- **Changes in your blood cholesterol and triglycerides (lipids).** Your healthcare provider will check you for this.

These are not all the possible side effects of ARCALYST. Tell your healthcare provider about any side effects that bother you or that do not go away. For more information ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ARCALYST?

- Keep ARCALYST in the carton it comes in.
- Store ARCALYST in a refrigerator between 36°F to 46°F (2°C to 8°C). Call your pharmacy if you have any questions.
- Always keep ARCALYST away from light.
- Refrigerated ARCALYST can be used until the expiration date printed on the vial and carton.
- ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing**.** Keep ARCALYST away from light.
- If you need to take ARCALYST with you when traveling, store the carton in a cool carrier with a cold pack and protect it from light.

Keep ARCALYST, injection supplies, and all other medicines out of reach of children.

What are the ingredients in ARCALYST?

Active ingredient: rilonacept.

Inactive ingredients: histidine, arginine, polyethylene glycol 3350, sucrose, and glycine.

General Information about ARCALYST

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use ARCALYST for a condition for which it was not prescribed. Do not give ARCALYST to other people even if they have the same condition. It may harm them.

This leaflet summarizes the most important information about ARCALYST. If you would like more information, speak with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ARCALYST that was written for healthcare professionals. For more information about ARCALYST, call 1-877-REGN-777 (1-877-734-6777), or visit www.ARCALYST.com.

Patient Instructions for Use

It is important for you to read, understand and follow the instructions below exactly. Following the instructions correctly will help to make sure that you use, prepare and inject the medicine the right way to prevent infection.

How do I prepare and give an injection of ARCALYST?

STEP 1: Setting up for an injection

1. Choose a table or other flat surface area to set up the supplies for your injection. Be sure that the area is clean or clean it with an antiseptic or soap and water first.
2. Wash your hands well with soap and water, and dry with a clean towel.
3. Put the following items on a table, or other flat surface, for each injection (see Figure 1):

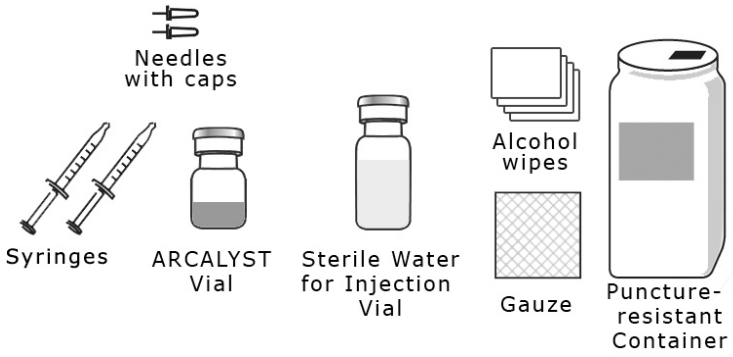

Figure 1

- 2 sterile, 3-milliliter (mL) disposable syringes with markings at each 0.1 mL (see Figure 2):
    - one needed for mixing (reconstitution) ARCALYST
    - one needed for injection

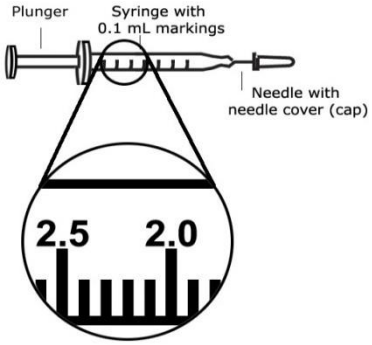

Figure 2

- 2 sterile disposable needles (27-gauge, ½-inch)
    - one needed for mixing
    - one needed for injection
- 4 alcohol wipes
- 1 2x2 gauze pad
- 1 vial of ARCALYST (powder in vial)
- 1 vial of preservative-free Sterile Water for Injection
- 1 puncture-resistant container for disposal of used needles, syringes, and vials

Note:

- Do not use Sterile Water for Injection, syringes or needles other than those provided by your pharmacy. Contact your pharmacy if you need replacement syringes or needles.
- Do not touch the needles or the rubber stoppers on the vials with your hands. If you do touch a stopper, clean it with a fresh alcohol wipe.
- If you touch a needle or the needle touches any surface, throw away the entire syringe into the puncture-resistant container and start over with a new syringe.
- **Do not reuse needles or syringes.**

- To protect yourself and others from possible needle sticks, it is very important to throw away every syringe, with the needle attached, in the puncture proof container right after use. ***Do not try to recap the needle.***

STEP 2: Preparing Vials

1. Check the expiration date on the carton of ARCALYST. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
2. Check the expiration date on the vial of Sterile Water for Injection. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
3. Remove the protective plastic cap from both vials.
4. Clean the top of each vial with an alcohol wipe. Use one wipe for each vial and wipe in one direction around the top of the vial (see Figure 3).

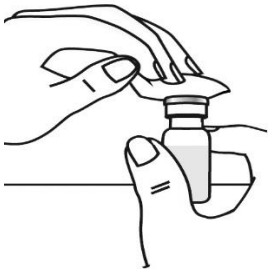

Figure 3

5. Open the wrapper that contains the 27-gauge needle by pulling apart the tabs and set it aside for later use. Do not remove the needle cover. This needle will be used to mix the water with powder. Open the wrapper that contains the syringe by pulling apart the tabs. Hold the barrel of the syringe with one hand and twist the 27-gauge needle onto the tip of the syringe until it fits snugly with the other hand (see Figure 4).

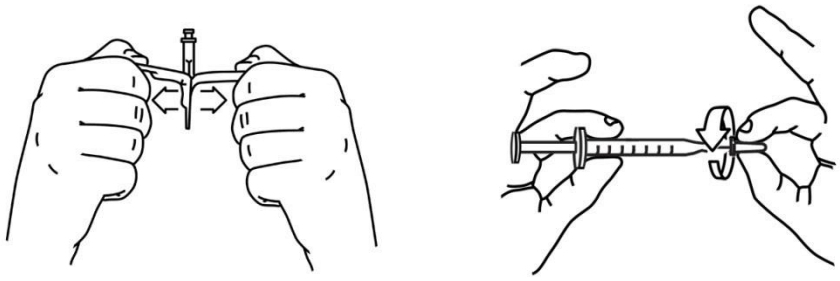

Figure 4

6. Hold the syringe at eye level. With the needle covered pull back the plunger to the 2.3 mL mark, filling the syringe with air (see Figure 5).

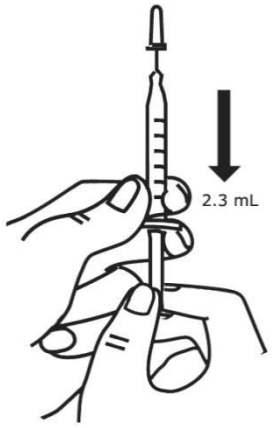

Figure 5

7. Hold the syringe in one hand, use the other hand to pull the needle cover straight off. Do not twist the needle as you pull off the cover. Place the needle cover aside. Hold the syringe in the hand that you will use to mix (reconstitute) your medicine. Hold the Sterile Water vial on a firm surface with your other hand. Slowly insert the needle straight through the rubber stopper. Do not bend the needle. Push the plunger in all the way to push the air into the vial (see Figure 6).

Figure 6

8. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up.
9. Make sure the tip of the needle is covered by the liquid and slowly pull back on the plunger to the 2.3 mL mark to withdraw the Sterile Water from the vial (see Figure 7).

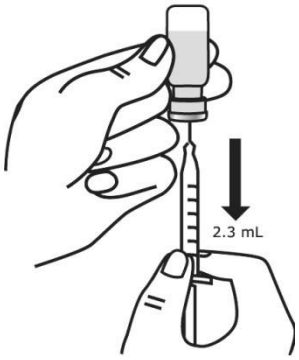

Figure 7

10. Keep the vial upside down and tap or flick the syringe with your fingers until any air bubbles rise to the top of the syringe.
11. To remove the air bubbles, gently push in the plunger so only the air is pushed out of the syringe and back into the bottle.
12. After removing the bubbles, check the syringe to be sure that the right amount of Sterile Water has been drawn into the syringe (see Figure 8).

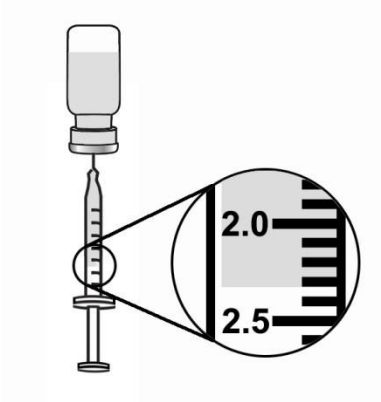

Figure 8

13. Carefully remove the syringe with needle from the Sterile Water vial. Do not touch the needle.

STEP 3: Mixing (Reconstituting) ARCALYST

1. With one hand, hold the ARCALYST vial on a firm surface.

2. With the other hand, take the syringe with the Sterile Water and the same needle, and slowly insert the needle straight down through the rubber stopper of the ARCALYST vial. Push the plunger in all the way to inject the Sterile Water into the vial.
3. Direct the water stream to gently go down the side of the vial into the powder (see Figure 9).

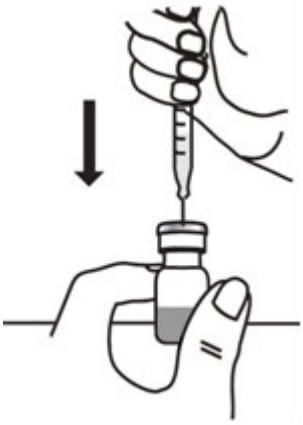

Figure 9

4. Remove the syringe and needle from the stopper and throw away the needle, syringe, and Sterile Water vial in the puncture-resistant container. Do not try to put the needle cover back on the needle.
5. Hold the vial containing the ARCALYST and sterile water for injection sideways (not upright) with your thumb and a finger at the top and bottom of the vial, and quickly shake the vial back and forth (side-to-side) for about 1 minute (see Figure 10).

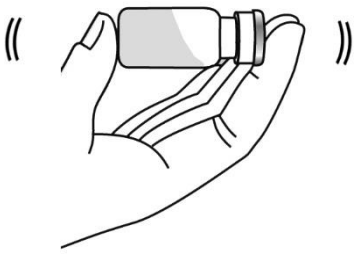

Figure 10

6. Put the vial back on the table and let the vial sit for about 1 minute.
7. Look at the vial for any particles or clumps of powder which have not dissolved.

8. If the powder has not completely dissolved, shake the vial quickly back and forth for 30 seconds more. Let the vial sit for about 1 minute.
9. Repeat Step 8 until the powder is completely dissolved and the solution is clear.
10. The mixed ARCALYST should be thick, clear, and colorless to pale yellow. Do not use the mixed liquid if it is discolored or cloudy, or if small particles are in it (see Figure 11).

    NOTE: Contact your pharmacy to report any mixed ARCALYST that is discolored or contains particles.

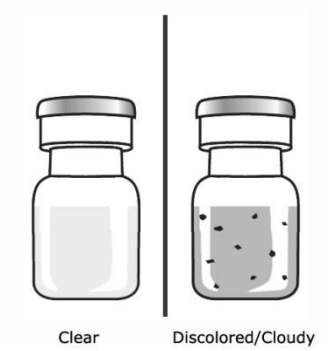

Figure 11

11. ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing. Keep ARCALYST away from light.

STEP 4: Preparing the injection

1. Hold the ARCALYST vial on a firm surface and wipe the top of the ARCALYST vial with a new alcohol wipe (see Figure 12).

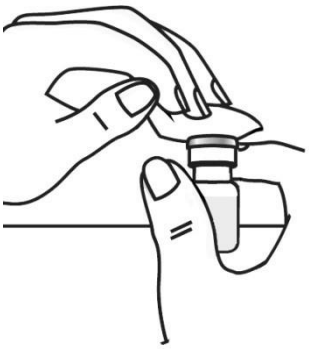

Figure 12

2. Take a new sterile, disposable needle and attach securely to a new syringe without removing the needle cover (see Figure 13).

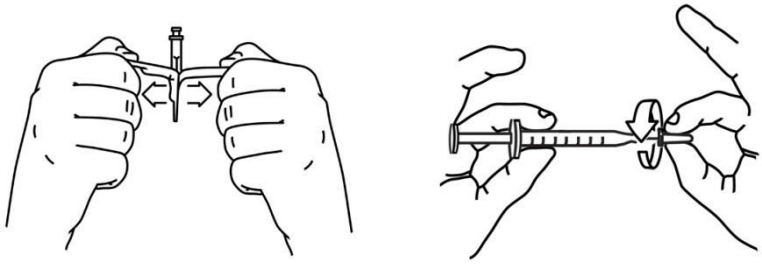

Figure 13

3. The amount of air you draw into the syringe should equal the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject.
4. To draw air into the syringe, hold the syringe at eye level. Do not remove the needle cover. Pull back the plunger on the syringe to the mark that is equal to the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject (see Figure 14).

Figure 14

5. Remove the needle cover and be careful not to touch the needle. Keep the ARCALYST vial on a flat surface and slowly insert the needle straight down through the stopper. Push the plunger down and inject all the air into the vial (see Figure 15).

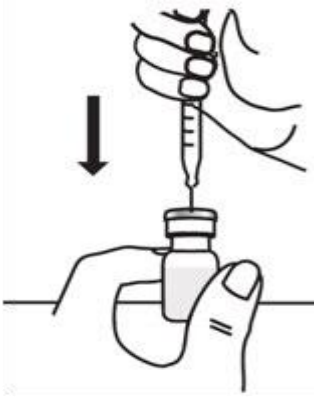

Figure 15

6. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up. Hold the vial at eye level.
7. Keep the tip of the needle in the liquid and slowly pull back on the plunger to the mark on the syringe that matches the amount of medicine prescribed by your healthcare provider (see Figure 16).

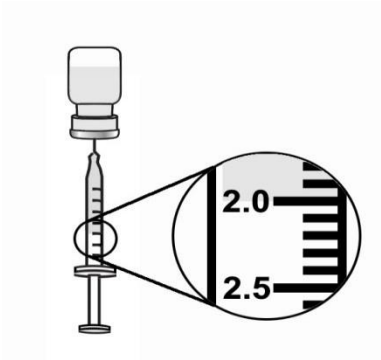

Figure 16

NOTE: The maximum adult dose of ARCALYST is 2 mL.

8. Keep the vial upside down with the needle straight up, and gently tap the syringe until any air bubbles rise to the top of the syringe (see Figure 17).

   It is important to remove air bubbles so that you withdraw up the right amount of medicine from the vial.

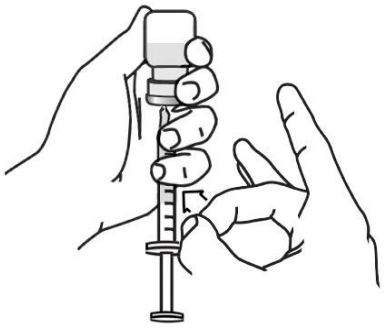

Figure 17

9. To remove the air bubbles, slowly and gently push in the plunger so only the air is pushed through the needle.
10. Check to make sure that you have the amount of medicine prescribed by your healthcare provider in the syringe.
11. Throw away the ARCALYST vial in the puncture-resistant container even if there is any medicine left in the vial (see Figure 18). Do not use any vial of ARCALYST more than one time.

Figure 18

STEP 5: Giving the Injection

1. ARCALYST is given by subcutaneous injection, an injection that is given into the tissue directly below the layers of skin. It is not meant to go into any muscle, vein, or artery.

   You should change (rotate) the sites and inject in a different place each time in order to keep your skin healthy.

Rotating injection sites helps to prevent irritation and allows the medicine to be completely absorbed. Ask your healthcare provider any questions that you have about rotating injection sites.

- Do not inject into skin that is tender, red, or hard. If an area is tender or feels hardened, choose another site for injection until the tenderness or "hardening" goes away.
- Tell your healthcare provider about any skin reactions including redness, swelling, or hardening of the skin.
- Areas where you may inject ARCALYST include the left and right sides of the abdomen, and left and right thighs. If someone else is giving the injection, the upper left and right arms may also be used for injection (see Figure 19):

  (Do not inject within a 2-inch area around the navel)

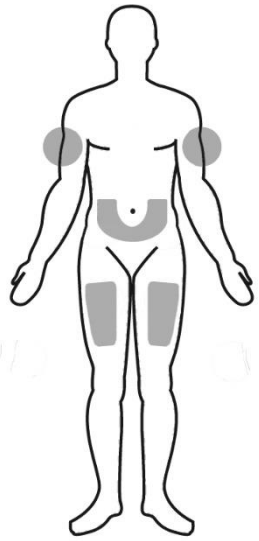

Figure 19

2. Choose the area for the injection. Clean the area in a circular motion with a new alcohol wipe. Begin at the center of the site and move outward. Let the alcohol air dry completely.
3. Take the cover off the needle and be careful not to touch the needle.
4. Hold the syringe in one hand like you would hold a pencil.
5. With the other hand gently pinch a fold of skin at the cleaned site for injection (see Figure 20).

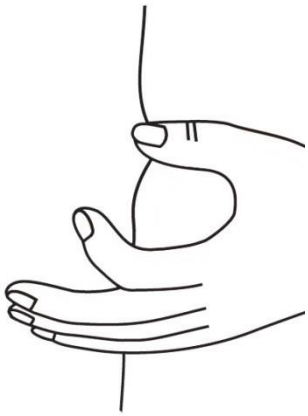

Figure 20

6. Use a quick "dart like" motion to insert the needle straight into the skin (90 degree angle) (see Figure 21). Do not push down on the plunger while inserting the needle into the skin.

   For small children or persons with little fat under the skin, you may need to hold the syringe and needle at a 45 degree angle (see Figure 21).

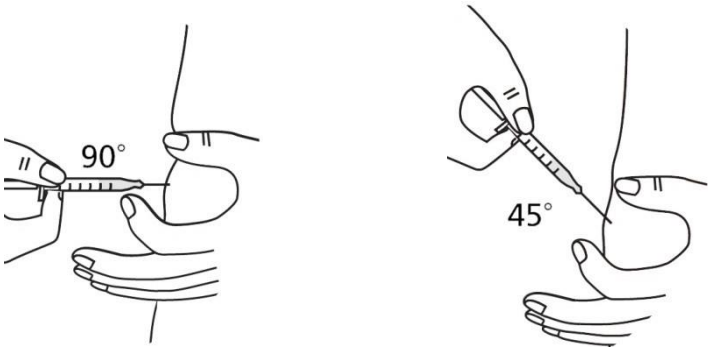

Figure 21

7. After the needle is completely in the skin, let go of the skin that you are pinching.
8. With your free hand hold the syringe near its base. Gently pull back the plunger. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle, discard the syringe and needle. Start over with "STEP 1: Setting up for an injection" using new supplies (syringes, needles, vials, alcohol swabs and gauze pad).
9. If no blood appears, inject all the medicine in the syringe at a slow, steady rate, pushing the plunger all the way down. It may take up to 30 seconds to inject the entire dose.
10. Pull the needle out of the skin, and hold a piece of sterile gauze over the injection site for several seconds (see Figure 22).

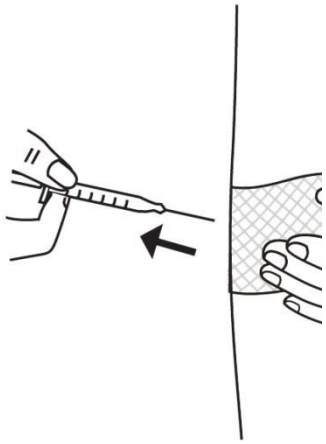

Figure 22

11. Do not replace the needle cover. Throw away the vials, used syringes and needles in the puncture-resistant container (see Figure 23). Do not recycle the container. DO NOT throw away vials, needles, or syringes in the household trash or recycle.

Figure 23

12. Keep the puncture-resistant container out of reach of children. When the container is about two-thirds full, dispose of it as instructed by your healthcare provider. Follow any special state or local laws about the right way to throw away needles and syringes.
13. Used alcohol wipes can be thrown away in the household trash.

Contact your healthcare provider right away with any questions or concerns about ARCALYST.

Notes: 1. Enbrel®, Humira®, Kineret®, and Remicade®, respectively, are trademarks of Immunex Corporation, AbbVie Biotechnology Ltd., Amgen Inc., and Janssen Biotech, Inc., respectively.

REGENERON

Manufactured and distributed by:

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NDC 61755-001-01

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V 4.0

13.2 Appendix: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Subjects will be asked to select the score that best describes their average level of pericarditis pain over the previous 24 hours using an 11-point NRS, where zero (0) indicates 'no pain' and ten (10) means indicates 'pain as bad as it could be'.

On this scale of 0-10, zero (0) indicates 'no pain' and ten (10) indicates 'pain as bad as it could be', please rate your pericarditis pain on average in the last 24 hours

NOTE TO FILE:

TO:	**KPL-914-C002**	**eTMF**
	IND#:	136.896
	EudraCT Number: 2018-002719-87	
FROM:	[redacted]	
DATE:		
SUBJECT:	**Justification for the administrative changes made to KPL-914-C002, Vl.0 dated 26 Sep 2018**	

To whom it may concern,

This note to file provides documentation to summarizing the changes made to the protocol KPL-9l4-C002, Vl.0 titled ·'PHASE 3, DOUBLE-BLIND. PLACEBO-CONTROLLED, RANDOMIZED WITHDRAW AL STUDY WITH OPEN-LABEL 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)"' finalized and signed on 26 Sep 2018. The PDF fiie containing the protocol KPL-914-C002. V1.0 document was transferred to Regulatory Affairs for publishing and filing to the applicable Regulatory Authorities. During the publishing process, minor administrative issues were noted by the publishing vendor, and as a result, the protocol document was updated as described in the table below.

KPL-914-C002, Vl.0 FROM:	KPL-914-C002, Vl.1 TO:
Global document change: Version 1.0, 26 September 2018	Version 1.1. 05 October 2018
Pg 12 vvas blank except for the header	Added ·This page was intentionally left blank."
In Section 12 Reference List. **Imazio M, Brucato A, Cumetti D, et al. Corticosteroids for recurrent pericarditis: high versus low doses: a nonrandomized observation. Circulation. 2008; 118(6):667-671.** was removed.	Two references were added to the Section 12 Reference List: **Imazio M, Brucato A, Trinchero R, et al. Corticosteroid therapy for pericarditis: a double-edged sword. Nature Clinical Practice Cardiovascular Medicine. 2008;5(3):188-119** and **Imazio M, Cecchi E, Demichelis B, et al. Myopericarditis versus viral or idiopathic acute pericarditis. Hea11. 2008;94:498-501**
Pg 91 **6.5.4 Pharmacogenomics** Whole blood for peripheral blood mononuclear cell (PBMC) isolation will be collected for pharmacogenomics assessments after signing the separate Pharmacogenomics ICF.	Pg 91 **6.5.4 Pharmacogenomics** Whole blood will be collected for pharmacogenomics assessments after signing the separate Pharmacogenomics ICF.

[redacted]

Kiniksa Pharmaceuticals, Ltd.

CLINICAL STUDY PROTOCOL

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPEN-LABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – **R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY** **(RHAPSODY)**

Amendment #1; Protocol Version 2.0
12 April 2019

IND: **136,896**
EudraCT: **2018-002719-87**

CONFIDENTIALITY STATEMENT
The information contained in this document, particularly unpublished data, is the property of Kiniksa Pharmaceuticals, Ltd., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, members of your staff who have a need to know the information, and an applicable Institutional Review Board or Independent Ethics Committee. You agree that the information contained herein shall be held in strict confidence and is only to be used by you and your staff as necessary to conduct the authorized clinical studies of the investigational drug described in the protocol. Documentation, data, and all other information generated during the study is the property of Kiniksa Pharmaceuticals, Ltd. and will be held in strict confidence by you and members of your staff. You further agree to not publish or otherwise disclose any of the information to others without written authorization from Kiniksa Pharmaceuticals, Ltd., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

KPL-914-C002

Sponsor:	Kiniksa Pharmaceuticals, Ltd.
Sponsor Study Contact:	
Sponsor Medical Contact	
Medical Monitor:	
Protocol Number:	KPL-914-C002-Amendment 1, Protocol Version 2.0
Protocol Date:	12 April 2019

Protocol Approval - Sponsor Signatory

Study Title	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis (RHAPSODY)
Protocol Numher	KPL-9I4-C002- Amendment 1, Protocol Version 2.0
Protocol Date	12 April 2019

Protocol accepted and approved by:

Chief Medical Officer

[redacted]

Protocol Approval - Lead Statistician

Study Title	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis (RHAPSODY)
Protocol Number	KPL-9 14-C002-Amendment 1, Protocol Version 2.0
Protocol Date	12 April 2019

Protocol accepted and approved by:

Lead Statistician

[redacted]

[redacted]

Declaration of Investigator

I have read and understood all Sections of the protocol entitled "Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis (RHAPSODY)" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 2.0, dated 12 April 2019, the International Council for Harmonisation tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Kiniksa Pharmaceuticals or implement protocol changes without Institutional Review Board Independent Ethics Committee approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Kiniksa Pharmaceuticals.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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PROTOCOL SYNOPSIS

Protocol Number:	KPL-914-C002-Amendment 1
Title:	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis
Study Acronym:	**R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY** **RHAPSODY**
Sponsor:	[redacted]
Study Phase:	3
Study Sites:	Multicenter, global
Indication:	Recurrent pericarditis

Study Rationale:

Recurrent pericarditis is a rare autoinflammatory condition with no approved therapies. Current treatments, utilizing nonspecific inhibitors of inflammation (nonsteroidal anti-inflammatory drugs [NSAIDs], colchicine, corticosteroids [CS]), result in significant morbidity with chronic use. Some patients develop CS dependency or require surgical pericardiectomy to treat the symptoms of their disease.

The interleukin-1 (IL-1) pathway plays a major role in the pathophysiology of recurrent pericarditis. Rilonacept (KPL-914) is a recombinant fusion protein that blocks IL-1 signaling. It is currently approved for treatment of another autoinflammatory condition, Cryopyrin-Associated Periodic Syndrome (CAPS). Based on its IL-1–antagonistic properties and pharmacokinetics (PK), which allow for once-weekly subcutaneous (SC) injections, it is reasonable to evaluate the efficacy and safety of rilonacept in subjects with recurrent pericarditis to address the unmet need in treatment of this disease.

Study Objectives:

Primary:	To assess the efficacy of rilonacept treatment in subjects with recurrent pericarditis.
Secondary:	To assess the safety of rilonacept treatment in subjects with recurrent pericarditis.

Study Population:

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 prior pericarditis episodes (including the first episode and 1 recurrence). Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present at screening with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale (NRS) and C-reactive protein (CRP) value ≥1 mg/dL (either on the same day or separated by no more than 7 days) within 7 days prior to first study drug administration.

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to first administration of study drug, and that changes in medications made within this time period (for instance, 1-time use of NSAIDs) are not anticipated by the investigator to significantly alter assessments of baseline disease activity.

Study Design:

This study has 5 periods:

(1) Screening period, during which assessment of disease characteristics, baseline therapy, and the pretreatment workup is completed (up to 4 weeks).

(2) Single-blind Run-In (RI) period (12 weeks), during which blinded rilonacept is administered SC once weekly in all subjects. 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 stopped background SOC pericarditis therapy and who achieve Clinical Response at RI Week 12, defined as the 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 Withdrawal (RW) baseline and a 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

Study Design Continued

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.

(3) Double-blind placebo-controlled RW period (pericarditis recurrence event-driven duration, with a minimum of 24 weeks), 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.

(4) Long Term Extension Treatment Period (LTE-TP) (24 weeks), during which all subjects completing the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) will have an option to receive up to 24 weeks 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. Any subject who, in the opinion of investigator, should not continue open-label rilonacept will be offered participation in the LTE off study drug and after signing LTE informed consent.

(5) Long Term Extension Follow-Up Period (LTE-FUP) (24 weeks), during which all subjects in the LTE-TP will be followed in the LTE-FUP for safety and potential pericarditis recurrences.

Estimated Study Duration:

Subjects completing LTE-TP are projected to be dosed with rilonacept for a minimum of approximately 1.2 years and up to 3 years based on enrollment assumptions and pericarditis recurrence events accrual time.

Study Efficacy Assessments:

- Daily pericarditis pain on the 11-point NRS in the subject's electronic diary
- CRP level
- Electrocardiogram (ECG)
- Echocardiography (ECHO)
- Patient Global Impression of Pericarditis Severity (PGIPS)
- Physician Global Assessment of Pericarditis Activity (PGA-PA)
- 36-Item Short Form Health Survey (SF-36)
- 5-Level EuroQoL-5D (EQ-5D-5L)
- Insomnia Severity Index (ISI)
- Cardiac magnetic resonance imaging (in a substudy)

Study Pharmacokinetic or Pharmacodynamic Assessments:

Pharmacokinetic or pharmacodynamic assessments will include:

- PK analysis
- Anti-rilonacept antibodies
- Biomarkers
- Pharmacogenomics (for subjects who sign the separate informed consent for pharmacogenomics assessments)

Study Safety Assessments:

Safety assessments during the study will include:

- Physical examination
- Vital signs measurements
- Adverse event (AE) monitoring
- Chest x-ray
- Tuberculosis screening
- Laboratory tests

Investigational Medicinal Product, Dosage, and Route of Administration:

Rilonacept (KPL-914) is a recombinant fusion protein consisting of the extracellular domains of human IL-1 cytokine receptor and the Fc portion of human immunoglobulin G1 (IgG1). It acts as a soluble decoy receptor binding IL-1α/IL-1β and prevents their interaction with the IL-1 cell-surface receptor.

Study drug (rilonacept or placebo) is supplied in a single use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml of placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

The first injection of rilonacept loading dose at the RI baseline visit will be administered at the study site by study site staff. The second injection of rilonacept loading dose at the RI baseline visit will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration.

Sample Size:

Approximately 56 subjects (not to exceed 75 subjects) with recurrent pericarditis will be enrolled, which will allow approximately 50 subjects to be randomly assigned to blinded treatment.

Statistical Methods:

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 efficacy analysis. A sensitivity analysis will be done based on the investigator's assessment of the pericarditis recurrence.

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 efficacy endpoints.

Major secondary efficacy endpoints for the RW period include:

- Proportion of subjects who maintained Clinical Response at Week 24 of the RW period
- Percentage of days with no or minimal pain (pain ≤1 on the 11-point NRS) in the first 24 weeks of the RW period
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point rating scale of PGIPS) at Week 24 of the RW period

Other secondary efficacy endpoints for the RW period include:

- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to pericarditis pain NRS ≥4

Statistical Methods Continued:

- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO
- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain (weekly average)
- Proportion of subjects with absent or minimal pericarditis activity based on Physician Global Assessment of Pericarditis Activity (PGA-PA)
- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who receive sequential ORT therapy for pericarditis recurrence (analgesics, NSAIDs, and/or colchicine) in the RW period

Efficacy endpoints for the RI period include:

- Proportion of subjects who achieved Clinical Response at the RI Week 12 visit
- Time to CRP normalization
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12
- Change from baseline in CRP level at RI Week 12
- Resolution of echocardiographic and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on the PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who were off background SOC pericarditis therapy at RI Week 12

Efficacy endpoints for the LTE-TP include:

- Number (percentage) of subjects with pericarditis recurrences
- Proportion of subjects with Clinical Response
- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on PGA-PA

Statistical Methods Continued:

- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects requiring addition of SOC pericarditis therapy

Primary analysis of this study will be done after the 22nd CEC-confirmed pericarditis recurrence and after all subjects in the RW period have been treated for 24 weeks. Subjects who have not had an adjudicated pericarditis recurrence will be censored on the day of the last available assessment before data cutoff.

Details of the analyses will be specified in the Statistical Analysis Plan.

Protocol Version and Date:	Version 2.0 12 April 2019

STUDY SCHEDULE OF ACTIVITIES

Table 1–1 Study Schedule of Activities – Screening and Run-In Period (Part 1 of 2)

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]
EQ-5D		X								X
SF-36		X								X
ISI		X								X
PGIPS		X						X		X
PGA-PA		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.

[m] All procedures are to be completed prior to study drug administration.

[q] The Randomization visit serves as both the RI Week 12 visit and the RW baseline visit.

Table 1–1 Study Schedule of Activities – Screening and Run-In Period (Part 2 of 2)

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
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, hepatitis serology, HIV (Local)	X									
Chest X-Ray	X									
Urine Pregnancy (Local or Central)[j]	X	X								
Urinalysis (Central)		X								
PK (Central)			X[i]		X	X	X			X
ADA (Central)		X				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
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.

[f] Both a documented CRP ≥ 1.0 mg/dL AND a pericarditis pain level of ≥ 4 is required 7 days prior to and including the Run-In Baseline visit. These are not required to occur on the same day.

[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.

Table 1–2 Study Schedule of Activities – Randomized Withdrawal (Part 1 of 2)

Trial Period	RANDOMIZATION WITHDRAWAL (minimum 24 weeks)[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

[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.

[m] All procedures are to be completed prior to study drug administration.

[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.

Table 1–2 Study Schedule of Activities – Randomized Withdrawal (Part 2 of 2)

Trial Period	RANDOMIZATION WITHDRAWAL (minimum 24 weeks)[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
Hematology, Chemistry Labs (Central)		X		X		X		X	X
Lipid Panel (Central)[h]						X			X
CRP (Local)									
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)									
Urinalysis (Central)									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]
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.

[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.

[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 1–3 Study Schedule of Activities – Long Term Extension (Part 1 of 2)

Trial Period	LONG TERM EXTENSION (48 WEEKS)				
	Long Term Extension Treatment (24 Weeks)[m]			Long Term Extension Follow Up (24 Weeks)	
Visit Name	LTE Week 8	LTE Week 16	LTE Week 24	LTE Week 30	EOS/ LTE Week 48
Visit Window[b] (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2
Visit Type	Clinic	Clinic	Clinic	Clinic	TC
Concomitant medications	X	X	X	X	X
Pericarditis Concomitant medications	X	X	X	X	X
Full Physical Examination[c]			X		
12-Lead ECG			X		
Echo[e]			X		
MRI (substudy only)			X		
Pericardial pain (11-point NRS)	DAILY				
EQ-5D			X		
SF-36			X		
ISI			X		
PGIPS	X	X	X		
PGA-PA	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.

[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.

[m] All procedures are to be completed prior to study drug administration.

Table 1–3 Study Schedule of Activities – Long Term Extension (Part 2 of 2)

Trial Period	LONG TERM EXTENSION (48 WEEKS)				
	Long Term Extension Treatment (24 Weeks)[m]			Long Term Extension Follow Up (24 Weeks)	
Visit Name	LTE Week 8	LTE Week 16	LTE Week 24	LTE Week 30	EOS/ LTE Week 48
Visit Window[b] (days)	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2
Visit Type	Clinic	Clinic	Clinic	Clinic	TC
Hematology, Chemistry Labs (Central)	X	X	X		
Lipid Panel (Central)[h]			X		
CRP (Central)	X	X	X		
PK (Central)			X	X	
ADA (Central)			X	X	
Biomarkers (Central)			X		
Urine Pregnancy[j] (Local or Central)				X	
Urinalysis			X		
IWRS Subject Status Update			X		
IWRS Weight Input (pediatric only)	X	X			
IWRS Drug Dispensing	X	X			
In Clinic Study Drug Administration[o]	X	X	X		
Outpatient Study Drug Administration[o]	WEEKLY				
Study Drug Compliance Review	X	X	X		
Assessment of Pericarditis Recurrence	X	X	X	X	X
Adverse Event Reporting[l]	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.

[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.

Table 1–4 Study Schedule of Activities – Supplemental Visits (Part 1 of 2)

Trial Period	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	

[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.

[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.

Table 1–4 Study Schedule of Activities – Supplemental Visits (Part 2 of 2)

Trial Period	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**
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
Biomarkers (Central)	X		
Urine Pregnancy[j] (Local or Central)			X
Urinalysis (Central)		X	
IWRS Subject Status Update	X[s]	X	
IWRS Weight Input (pediatric only)	X		
IWRS Drug Dispensing	X		
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] Upon investigator confirmation of pericarditis recurrence, the IWRS is to be updated.

[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.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAPS	Cryopyrin Associated Periodic Syndrome
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CMH	Cochran–Mantel–Haenszel
CRP	C-reactive protein
CS	corticosteroids
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiography; echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EORW	End of Randomized-Withdrawal(visit)
EOS	End of Study
EOT	End of Treatment (visit)
EQ-5D-5L	5-level EuroQoL-5D
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG1	human immunoglobulin G1
IGRA	Interferon Gamma Release Assay
IL-1	interleukin-1
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ISR	injection site reaction
ITT	intent to treat
IV	intravenous(ly)
IWRS	interactive web response system
KPL-914	rilonacept

LDL	low-density lipoprotein
LTE-FUP	Long Term Extension Follow-Up Period
LTE-TP	Long Term Extension Treatment Period
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MWS	Muckle-Wells Syndrome
NSAID	nonsteroidal anti-inflammatory drug
NRS	Numerical Rating Scale
ORT	Oral Rescue Therapy
PHV	Pharmacovigilance
PGA-PA	Physician Global Assessment of Pericarditis Activity
PGIPS	Patient Global Impression of Pericarditis Severity
PK	pharmacokinetic(s)
POC	point of care
PRO	patient-reported outcome
RI	Run-In (period)
RN	visiting registered nurse
RW	Randomized-Withdrawal (period)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SF-36	36-Item Short Form Health Survey
SFU	safety follow-up
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TC	site telephone visit (telephone contact)
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell
WFI	Water for Injection

1 Introduction

Pericarditis is inflammation of the pericardium, the double-walled sac surrounding the heart. Etiologies of pericarditis include infectious causes (viral, bacterial, fungal, and parasitic) and non-infectious causes (idiopathic, autoimmune, neoplastic, metabolic, traumatic, post-surgical, and drug-related)

(Adler et al 2015). In 80% of cases in developed countries, the cause of pericarditis is either post-viral or "idiopathic" in that it cannot be attributed to a specific condition (Imazio et al 2010; Zayas et al 1995).

The underlying pathogenesis of recurrent pericarditis remains unclear, although a growing body of evidence suggests that abnormal immune responses play a role in the pathogenic processes. While the adaptive immune system plays a role in autoimmune disorders that manifest with pericarditis as one of the many organ systems involved (such as in systemic lupus erythematosus or rheumatoid arthritis), the innate immune system, including interleukin 1 (IL-1) signaling, is often the major effector in autoinflammatory disorders, such as isolated pericarditis (Baskar et al 2016; Brucato et al 2016; Imazio et al 2016, Dinarello et al 2012).

Diagnosis of pericarditis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic changes, pericardial effusion, or elevated levels of inflammation markers (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Adler et al 2015). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define an acute pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rubs, new widespread ST-segment elevation or PR-segment depression based on electrocardiogram (ECG) findings, and pericardial effusion (new or worsening). Elevations of certain markers of inflammation (i.e., CRP, ESR, and WBC) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]) are used as supportive findings (Adler et al 2015).

Recurrent pericarditis is characterized by the recurrence of pericarditis signs and symptoms after a symptom-free period of at least 4 to 6 weeks (Adler et al 2015). Recurrent pericarditis affects 20% to 30% of patients with acute pericarditis (Imazio 2014) and can be debilitating for patients due to pain and limitations in physical function during pericarditis episodes. Pericarditis recurrences result in increased emergency room admissions and hospitalizations. In the United States, 5% of patients presenting to the emergency room with non-ischemic chest pain are diagnosed with pericarditis (Agarwal et al 2015).

The estimated prevalence of recurrent pericarditis in the US and Europe is 70,000 to 160,000 patients including approximately 8,000 to 21,000 patients who are refractory or intolerant to current therapies or who require long-term administration of corticosteroids (CS) to control their disease (Brucato et al 2016; Lazaros et al 2016; Imazio et al 2010; Khandaker et al 2010; Imazio et al 2008).

1.1 Current Therapeutic Management of Pericarditis

There are no approved therapies for the treatment of recurrent pericarditis. Current treatments include nonspecific inhibitors of inflammation, i.e., aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and CS (Lilly et al 2013).

Aspirin and other NSAIDs are the first-line approach. Because high doses of aspirin and NSAIDs are often required, consideration must be given to gastric protection therapy, as potential risks of therapy include stomach ulcers and gastrointestinal (GI) bleeding, as well as renal and cardiovascular toxicity.

Colchicine is another mainstay therapy for pericarditis and is commonly used with NSAIDs to hasten the response to NSAIDs and reduce the risk of subsequent recurrences. However, its use may be associated with the risk of fatal overdosing, significant drug interactions, and neuromuscular toxicity. In addition, approximately 10% to 15% of patients experience significant GI side effects with colchicine, including GI intolerance or severe diarrhea, requiring treatment discontinuation (Imazio et al 2016).

Available ESC guidelines stipulate that CS should be prescribed for the management of pericarditis episodes only in cases of incomplete response, intolerance, or contraindications to NSAIDs and colchicine because of their unfavorable long-term benefit-risk profile. Corticosteroid use is associated with side effects, including weight gain, diabetes, osteoporosis, avascular bone necrosis, and increased risk for infections (Imazio et al 2008). For the management of pericarditis, CS are usually administered at low to moderate doses and can provide rapid control of symptoms. However, they often require many months of tapering after the normalization of CRP levels. In addition, there is a high rate of pericarditis relapse when CS use is tapered or stopped (Lotriionte et al 2010; Imazio et al 2005; Maisch et al 2004), particularly in the absence of concurrent colchicine treatment.

Patients with recurrent pericarditis who are refractory or intolerant to current therapeutic management options or who require long-term administration of CS to control their disease can be particularly challenging to manage. As a last resort, some refractory patients are being referred to the surgical procedure of pericardiectomy, with variable outcomes. Multiple immunosuppressive medications have been used without consistent benefit (Baskar et al 2016). [redacted]

1.2 Pathogenesis of Recurrent Pericarditis: Role of IL-1

Interleukin-1 is a key cytokine that drives the pathophysiology of many inflammatory processes, and it is implicated as a causative factor in various inflammatory diseases in humans.

The two distinct IL-1 genes, *IL1A* and *IL1B*, encode IL-1α and IL-1β, respectively. IL-1α and IL-1β bind to the universally-expressed cell surface receptor, IL-1 receptor type-1, triggering a cascade of inflammatory mediators. The precursor form of IL-1α is expressed in keratinocytes, mucous membrane epithelial cells, and organs such as the liver and vascular endothelium in healthy individuals. During pathological states, IL-1α moves to the cell surface or is released after cell death to activate IL-1 receptors in adjacent cells, thus beginning the cascade of sterile inflammation. IL-1β, however, is not expressed in healthy individuals until a stimulus, such as microbial products or other chemokines, triggers its transcription in monocytes, tissue macrophages, and dendritic cells via the inflammasome. IL-1 drives the inflammatory cascade in classic autoinflammatory conditions, such as tumor necrosis factor (TNF)-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) and plays a significant role in systemic onset of juvenile idiopathic arthritis and in autoimmune diseases such as rheumatoid arthritis (Baskar et al 2016).

IL-1–blocking therapies are effective at controlling end-organ disease and damage in patients with various autoinflammatory disorders, and different strategies to block IL-1 have been used in clinical trials and demonstrated substantial success in controlling episodes of fever and elevations in acute-phase reactants (Cantarini et al 2015).

This mechanistic plausibility of IL-1 antagonism in addressing pathophysiology related to the inflammasome extends to other conditions characterized by sterile acute inflammation, such as recurrent pericarditis.

[redacted]

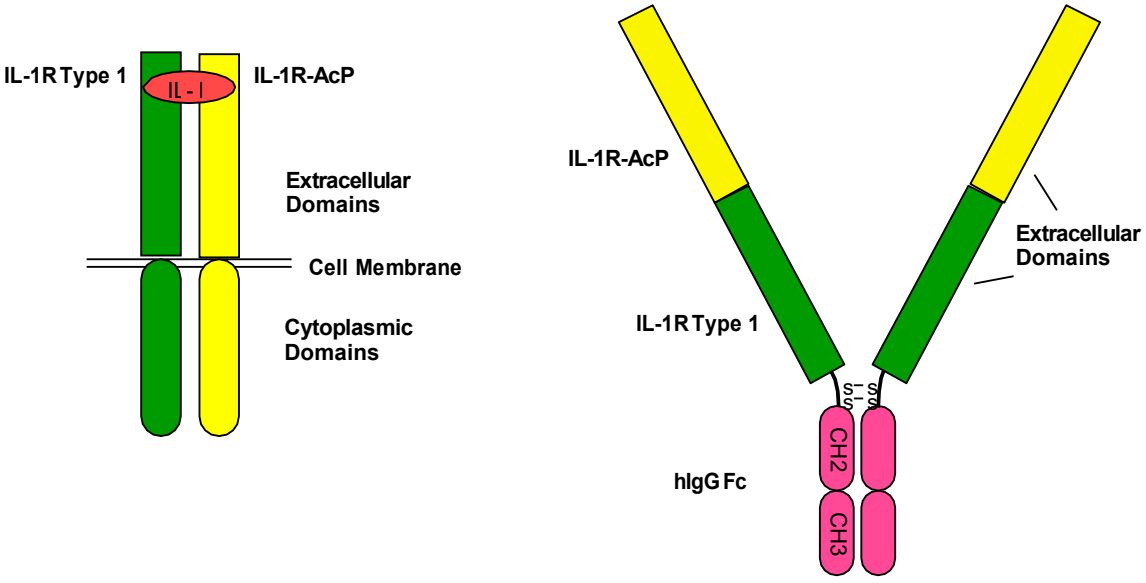
1.3 Rilonacept (KPL-914)

Rilonacept (designated in Kiniksa Pharmaceutical's development program as KPL-914) was developed by Regeneron Pharmaceuticals, Inc. (Regeneron) of Tarrytown, NY, and is approved with the trade name ARCALYST® in the US for the treatment of CAPS, including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children age 12 and older. Rilonacept is currently manufactured and marketed as ARCALYST® by Regeneron. Rilonacept received marketing authorization in the European Union for the treatment of CAPS with severe symptoms, including FCAS and MWS in adults and children aged 12 years and older, but based on a request from Regeneron, the marketing authorization was withdrawn. The withdrawal was a business decision and was not related to any concern with the safety or efficacy of rilonacept.

Rilonacept is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human IgG1. Rilonacept is a dimeric glycoprotein with a total molecular weight of approximately 250 kDa. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1 type I receptor (IL-1R1) and the IL-1 receptor accessory protein (IL-1R-AcP) (Figure 1).

Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells. Rilonacept blocks IL-1 by acting as a soluble decoy receptor that binds IL-1 and prevents its interaction with cell surface receptors.

Figure 1: Schematic of Rilonacept (KPL-914)



1.3.1 Safety of Rilonacept

For a detailed review of the available rilonacept safety data, please refer to the current Investigator Brochure and the ARCALYST® package insert (Section 13.1: ARCALYST® Prescribing Information). The available rilonacept safety data is summarized below.

Rilonacept has been evaluated in 23 studies, including 22 complete and 1 ongoing. In the completed studies, 2243 subjects (2152 patients and 91 healthy volunteers) were exposed to rilonacept. Thirty of these patients were pediatric (<18 years of age).

Doses up to 320 mg subcutaneously (SC) once weekly and 2000 mg intravenously (IV) monthly have been studied for different indications, including CAPS, gout, and other inflammatory disorders.

Injection Site Reactions

In clinical studies with rilonacept, the most common and consistently reported AE associated with rilonacept was injection site reaction (ISR). The ISRs included erythema, swelling, pruritus, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth, and hemorrhage. Most ISRs were mild to moderate. In the gout clinical studies, approximately 1% of subjects treated with rilonacept discontinued due to ISRs. Similar results have been seen in other patient populations.

Infections

Interleukin-1 blockade may interfere with immune response to infections. Serious life-threatening infections have been reported in clinical trials in subjects treated with rilonacept.

Changes in Laboratory Parameters

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Subjects treated with rilonacept in clinical trials experienced increases in their mean total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Antibodies directed against the receptor domains of rilonacept were detected using an enzyme-linked immunosorbent assay (ELISA). In clinical trials with rilonacept, approximately 30% to 35% of subjects tested positive for treatment-emergent antibodies to rilonacept on at least 1 occasion.

Systemic Hypersensitivity Reactions

Hypersensitivity reactions are a potential risk with protein therapeutics in general. In clinical studies with rilonacept, systemic hypersensitivity reactions have been rare.

Malignancies

Although malignancies have been reported in some subjects treated with rilonacept during clinical trials, the effect of rilonacept on the development of cancer is not known. Treatment with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies.

Fetal Defects

There are no adequate and well-controlled studies of rilonacept in pregnant women. Based on animal data, rilonacept may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15, or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human dose of 160 mg based on body surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100, or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

Nonteratogenic effects: A peri- and postnatal reproductive toxicology study was performed in which mice were administered a murine analog of rilonacept at doses of 20, 100, and 200 mg/kg SC 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F1 offspring during maturation at all doses tested.

1.3.2 KPL-914-C001 Study with Rilonacept (KPL-914) in Recurrent Pericarditis

KPL-914-C001 is an open-label, single active-arm Phase 2 proof-of-concept study in subjects age ≥6 to 75 years old with recurrent idiopathic or post-pericardiotomy syndrome (PPS) pericarditis. The study includes a 6-week Treatment Period in which all the subjects receive once-weekly rilonacept 160 mg SC (2.2 mg/kg for subjects ≥6 and <18 years old) following a loading dose of 320 mg SC in subjects ≥18 years old (4.4 mg/kg in subjects ≥6 and <18 years old) in addition to background pericarditis therapies (NSAIDS, colchicine, CS). After completing the 6-week Treatment Period and based on response status, the subjects have the option to enter the 18-week Extension Period during which they continue to receive rilonacept at the same dose, but during which investigators are encouraged to wean and stop background pericarditis medications.

The primary objectives of the study are to explore clinical and biochemical endpoints of recurrent pericarditis symptomatology, as well as to assess feasibility to wean from concomitant pericarditis medication in the Extension Period while continuing treatment with rilonacept. The study population includes the following 5 subject categories (Parts):

- Part 1 enrolls symptomatic subjects with recurrent idiopathic pericarditis with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 2 enrolls symptomatic subjects with recurrent idiopathic pericarditis with CRP level ≤1 mg/dL that, in the opinion of the investigator, can be attributed to concomitant medications (e.g., CS) and with pericardial inflammation present on cardiac MRI confirmed by the imaging core lab.
- Part 3 enrolls subjects with CS-dependent recurrent idiopathic pericarditis not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.
- Part 4 enrolls symptomatic subjects with recurrent PPS with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 5 enrolls subjects with CS-dependent recurrent PPS not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.

Preliminary data in this ongoing study suggest that subjects enrolled in Part 1 experience improvements in pain, CRP levels, and other pericarditis parameters compared to baseline.

Adverse events observed in the study are consistent with the overall rilonacept safety profile.

2 Study Objectives and Endpoints

2.1 Primary Objective

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

2.2 Secondary Objective

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

3 Investigational Plan

3.1 Study Design

This is a Phase 3, multi-center, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis. This study has 5 periods (Figure 2).

3.1.1 Screening Period (up to 4 weeks)

During the screening period, assessment of disease characteristics, baseline therapy, and thepre-treatment workup will be completed during a period of up to 4 weeks.

3.1.2 Single-blind Run-In (RI) Period (12 weeks)

During the single-blind RI period, treatment with blinded rilonacept is administered and subjects are weaned off background standard of care (SOC) therapy for their pericarditis disease. Subjects will be blinded regarding the time of transition from the single-blind to the double-blind period; i.e., they will not be aware of the duration of the RI period.

In the single-blind RI period, subjects ≥18 years old will receive blinded 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 blinded 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 the RI period.

The RI period includes:

- 1-week Stabilization period, during which blinded rilonacept is administered in addition to 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. The dosages of CS, NSAIDs, and colchicine will be tapered according to the weaning protocol in the Pharmacy Manual (for the purpose of the protocol, aspirin is considered an NSAID). In general, CS doses will be tapered off starting at RI Week 1 and will be withdrawn by RI Week 10 (over a total of 9 weeks). NSAID and colchicine doses will be tapered off starting at RI Week 4 and will be withdrawn by RI Week 10 (over a total of 6 weeks).
- 2-week Monotherapy period: Subjects who have been successfully weaned off background SOC pericarditis therapy will continue to receive blinded rilonacept.

Subjects who stopped background pericarditis medications and achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will proceed into the double-blind placebo-controlled Randomized-Withdrawal (RW) period of the study. For definition of Clinical Response, refer to Section 6.2.2.

Subjects who are unable to achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline are to be discontinued from study drug, transitioned to SOC pericarditis therapy at the investigator's discretion, and followed through the end of the RW period.

3.1.3 Double-blind Placebo-controlled RW Period (pericarditis recurrence event-driven duration with a minimum of 24 weeks)

During the RW period, subjects who were able to stop background pericarditis medications and who achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will be randomized 1:1 to double-blinded administration of study drug:

- Rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects ≥12 and <18 years old) SC injections once weekly OR
- Matching placebo SC injections once weekly

Pericarditis Recurrence in the RW Period

For the definition of pericarditis recurrence, refer to Section 6.2.3.

Upon pericarditis recurrence, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale [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 prior RW period treatment assignment. 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 Section 5.8.3 and detailed in the Pharmacy Manual.

Subjects with pericarditis recurrence who do not meet the protocol criteria for bailout rilonacept will continue blinded study drug until they meet the protocol criteria for bailout rilonacept 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 Section 5.8.3 and detailed in the 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.

The RW period will continue until the prespecified number of primary endpoint (CEC-confirmed pericarditis recurrence) events have occurred and approximately 50 randomized subjects have achieved a minimum of 24 weeks of treatment in the RW period. Based on projected event accrual and subject randomization, Kiniksa Pharmaceutical will determine the end of the RW period and announce to sites so that subject End of Randomized Withdrawal (EORW) visits can occur. All subjects, including those who have transitioned to open-label rilonacept or who prematurely discontinued study drug, should complete an EORW visit.

3.1.4 Long Term Extension Treatment Period (LTE-TP) (24 weeks)

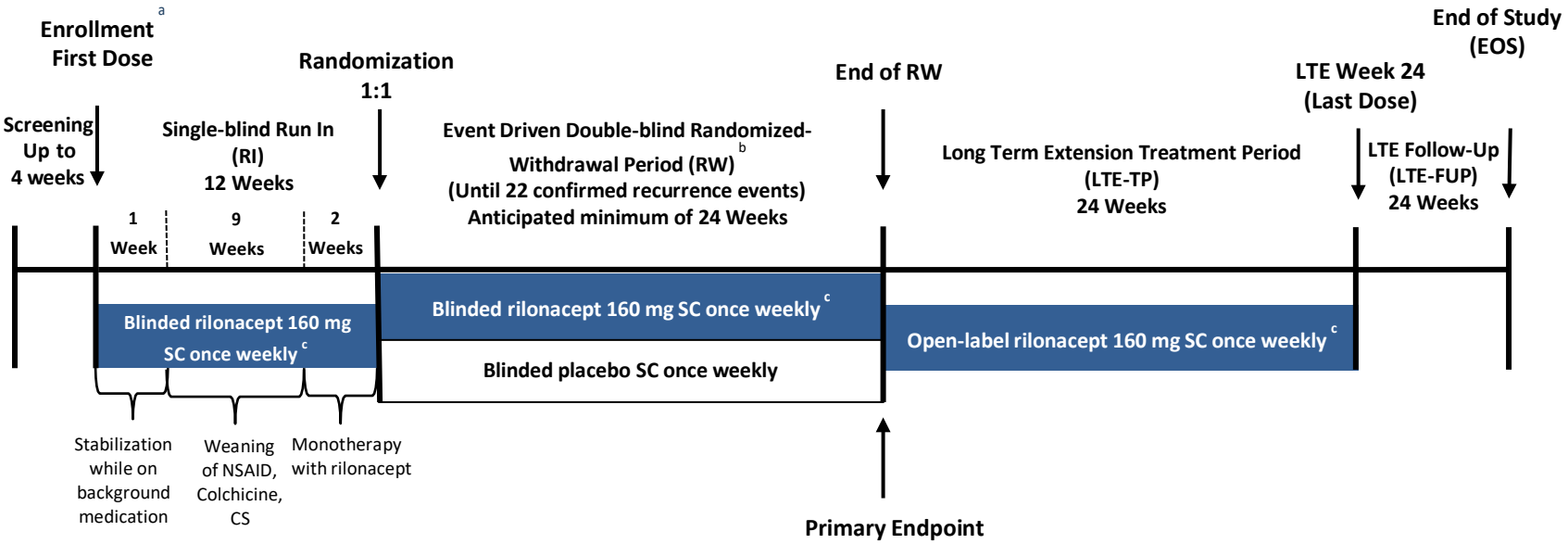
Upon completion of the RW period and the EORW visit (site and subject unblinding), all subjects completing the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) will have an option to receive up to 24 weeks of open-label rilonacept 160 mg (or 2.2 mg/kg for pediatric subjects) SC injections once weekly based on their clinical status and at the discretion of the investigator, after signing LTE informed consent. Any subject who, in the opinion of investigator, should not continue open-label rilonacept will be offered participation in the LTE off study drug after signing LTE informed consent.

3.1.5 Long Term Extension Follow-Up Period (LTE-FUP) (24 weeks)

All subjects in the LTE-TP will be followed in the LTE-FUP for an additional 24 weeks for safety and for potential pericarditis recurrence assessments.

The total duration of the study will be determined by the rate of enrollment, the rate of first recurrence of pericarditis events during the RW period, and the minimum duration of follow-up in the RW of 24 weeks. It is anticipated that study completers (including LTE-TP) will be dosed with rilonacept for approximately 1.2 years and up to 3 years based on enrollment assumptions and pericarditis recurrence events accrual time.

Figure 2: Overview of KPL-914-C002 Trial Design



Abbreviations: CS=corticosteroid; EOS=end of study, LTE=Long Term Extension; NSAID=nonsteroidal anti-inflammatory drug; RI=run in, RW=randomized withdrawal, SC=subcutaneously, TP=treatment period

a. The first dose given is a loading dose of rilonacept. In adult subjects ≥18 years old, 320 mg is given as 2 SC doses of 160 mg. In pediatric subjects ≥12 and <18 years old, 4.4 mg/kg is given as 2 SC doses of 2.2 mg/kg. After the loading dose, rilonacept will be administered as a 160 mg (adults) or 2.2 mg/kg (pediatric subjects) SC dose once weekly.

b. Subject's treatment duration will depend on when the subject is enrolled relative to the end of RW.

c. The adult dose is 160 mg SC once weekly. The pediatric dose is 2.2 mg/kg SC once weekly.

Note: This picture is not drawn to scale.

3.1.6 Rationale of Study Design

Subjects eligible for this KPL-914-C002 study will be subjects with recurrent pericarditis presenting with an acute pericarditis episode at screening.

The KPL-914-C002 study design ensures that during the RI period all subjects will receive rilonacept, a drug with evidence supporting clinical activity based on the preliminary clinical data with rilonacept from Part 1 of the ongoing Phase 2 proof-of-concept study (KPL-914-C001) obtained to date. During the RI period, pericarditis will be stabilized with symptoms controlled and background pericarditis medications (NSAIDs, colchicine, CS) will be tapered and withdrawn, while rilonacept treatment continues.

The design then allows half of the subjects to continue receiving active treatment after having achieved Clinical Response on that treatment, which maximizes subject exposure to a potentially beneficial therapy. The temporary withdrawal of rilonacept (by switching to placebo) in the half of the subjects who were randomly assigned to placebo is expected to result in an accelerated time to pericarditis recurrence and a higher recurrence rate compared to those who continue on active treatment, a finding that demonstrates that the underlying pericarditis etiology is still ongoing and will provide further support for the anticipated observation of the clinical effect of rilonacept during the RI period of the study. The period of exposure to an ineffective treatment is minimized in this design, as subjects will be removed from blinded treatment when the condition returns to a specified severity (i.e., for having met the criteria of pericarditis pain ≥4 on the 11-point NRS and CRP level ≥1 mg/dL) without unblinding them to prior treatment assignment, thus protecting the primary efficacy endpoint of the study. All subjects who meet the pain and CRP criteria described above will be treated with open-label bailout rilonacept using a loading dose, followed by once-weekly SC injections. In addition, sequential ORT such as NSAIDs and/or colchicine will be allowed upon recurrence at the investigator's discretion based on the subject's clinical status, as outlined in Section 5.8.3 and as stipulated in the Pharmacy Manual. Subjects with pericarditis recurrence not meeting criteria for bailout rilonacept, can be treated with sequential ORT based on investigator judgement and as described in protocol Section 5.8.3 and the Pharmacy Manual. If the subject requires the addition of CS treatment to control the pericarditis recurrence, the subject will be discontinued from study drug. All subjects will be followed for the duration of RW period.

In summary, the proposed RW trial with rilonacept allows all enrolled subjects an opportunity to receive the active drug during the acute episode of pericarditis yet provides pivotal-quality data on the efficacy of rilonacept in this enriched cohort by subsequently randomly assigning subjects to placebo versus active treatment after they achieve a predefined clinical response. Subjects with pericarditis recurrences after randomization will receive bailout rilonacept treatment and/or sequential ORT according to the protocol. This approach minimizes the exposure to placebo, which is important for a study that requires active disease upon enrollment and includes a pediatric population. The available regulatory guidance supports the use of an RW study design in the setting of recurrent pericarditis as a means of establishing the long-term effectiveness of rilonacept, an approved product for the treatment of another rare autoinflammatory condition (CAPS).

3.1.7 Justification for Rilonacept Dose Selection

[redacted], i.e., 320 mg SC loading dose (4.4 mg/kg in subjects ≥12 and <18 years old), followed by once-weekly SC doses at 160 mg (2.2 mg/kg in subjects ≥12 and <18 years old).

In the rilonacept development program in CAPS, gout, rheumatoid arthritis, and other inflammatory conditions, over 2000 subjects were exposed to rilonacept, including 1650 subjects receiving a rilonacept dose of 160 mg or higher. A total of 103 and 169 subjects were exposed to any rilonacept dose for at least 1 year or 6 months, respectively. Most of the real-life experience with rilonacept comes from the CAPS population treated at this marketed dose. As of March 2018, approximately 365 CAPS patients have been exposed to rilonacept in the post-marketing setting since 2008. The safety data accumulated so far support the benefit/risk ratio for the rilonacept dose intended to be evaluated in subjects with recurrent pericarditis.

Based on the preliminary clinical data with rilonacept from Part 1 of the Phase 2 proof of concept study (KPL-914-C001) obtained to date, it is expected that rilonacept doses [redacted] (320 mg followed by 160 mg SC once weekly and corresponding pediatric doses), and evaluated in the KPL-914-C001 study, will consistently provide adequate suppression of clinical inflammatory response, including CRP levels, in patients with recurrent pericarditis.

Bailout Rilonacept Dose

Subjects who meet the protocol criteria for bailout rilonacept upon pericarditis recurrence in the RW period of the study (Sections 3.1 and 6.2.3), irrespective of treatment assignment at randomization, will receive open-label rilonacept (loading dose of 320 mg SC followed by once-weekly SC injections of 160 mg, or the corresponding pediatric doses). [redacted]

The rationale for bailout rilonacept treatment upon pericarditis recurrence for subjects who were randomly assigned to placebo is that rilonacept had controlled their disease activity during the RI period; therefore, re-initiation of rilonacept is justified to regain control of pericarditis signs and symptoms upon recurrence. Subjects who were randomly assigned to rilonacept and qualify for bailout rilonacept upon pericarditis recurrence in the RW period were initial responders to rilonacept treatment during the RI period; thus it could be assumed that the loss of response during the RW period could be due to development of resistance to rilonacept due to different mechanisms, e.g., higher IL-1 levels or a change in rilonacept pharmacokinetics (PK)/ pharmacodynamics. Therefore, re-administration of a loading dose of rilonacept may help to restore Clinical Response.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 56 subjects will be enrolled (and not more than 75 subjects), which will allow at least 50 subjects to be randomized at approximately 50 sites globally. Subjects will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 pericarditis episodes (including the first episode and 1 recurrence) prior to screening. Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and CRP level ≥1 mg/dL within 7 days prior to the first study drug administration.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent form (ICF) or assent form (for pediatric subjects ≥12 and <18 years old), has provided signed and witnessed written informed consent or assent (as applicable), and agrees to comply with protocol requirements.
2. Is male or female 12 years of age or older with body weight of at least 23.6 kg (52 Lbs).
3. Has a diagnosis of recurrent pericarditis.
4. At least 1 of the pericarditis episodes experienced prior to screening has met at least 2 of the following 4 criteria, in the opinion of the investigator and based on the documented available data, according to the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al 2015):
    a. Pericarditic chest pain
    b. Pericardial rub
    c. New widespread ST-segment elevation or PR-segment depression according to ECG findings
    d. Pericardial effusion (new or worsening)
5. Presents with at least the third episode of pericarditis during screening (i.e., at least the second pericarditis recurrence following the first pericarditis episode), and within 7 days* prior to and including RI baseline (first administration of study drug) has:
    a. At least 1 day with pericarditis pain ≥4 on the 11-point NRS, **AND**
    b. CRP level ≥1.0 mg/dL (for details of CRP collection see Section 6.1.1)

    *Pericarditis pain ≥4 and CRP ≥1 mg/dL are not required to be present on the same day.
6. Has received NSAIDs and/or colchicine and/or CS (in any combination), if used, at stable dose levels (or at least not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs) are not anticipated, in the opinion of the investigator, to significantly alter assessments of baseline disease activity.
7. If using NSAIDs and/or colchicine and/or CS at the time of RI baseline (first administration of study drug), is willing and able, in the opinion of the investigator, to taper and discontinue those medications within the 9-week weaning time in the RI period of the study while continuing rilonacept treatment.
8. Female subjects must be:
    a. Postmenopausal, defined as at least 12 months after the cessation of menses (without an alternative medical cause) OR
    b. Incapable of pregnancy OR

c. Permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation or having a male partner with vasectomy as affirmed by the subject OR

d. If of childbearing potential, must agree to use a highly effective method of contraception during the study and for 3 months after the last study drug administration (i.e., hormonal contraceptives associated with inhibition of ovulation, intrauterine device [IUD], intrauterine hormone-releasing system [IUS], or sexual abstinence)

9. If male and sexually active, must have documented vasectomy or must practice birth control and not donate sperm during the study and for 3 months after the last study drug administration.
10. Must be up-to-date with all immunizations, in agreement with current local immunization guidelines for immunosuppressed subjects, before RI baseline (first administration of study drug).
11. Is able to adequately maintain a daily subject diary according to protocol.
12. Must be able to adhere to the study visit schedule and understand and comply with the other protocol requirements.
13. Agrees to refrain from making any new, major lifestyle changes that may affect pericarditis symptoms (e.g., changing exercise pattern) from the time of the ICF is signed through the end of the double-blind RW period.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Has a diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis; or systemic autoimmune diseases with exception of Still's disease.
2. Is pregnant, breastfeeding, or planning a pregnancy or fathering a child during the study or within 3 months after the last study drug administration.
3. Has a history of immunosuppression, including positive human immunodeficiency virus (HIV) test results.
4. Is currently receiving CS at a dose of >60 mg/day prednisone (or equivalent) for adult subjects, or >0.5 mg/kg/day (or >60 mg/day, whichever is lower) prednisone (or equivalent) in pediatric subjects (≥12 and <18 years old).
5. Has ever received cytotoxic drugs, including cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.
6. Has ever received agents that deplete B or T cells (e.g., rituximab, alemtuzumab).

7. Has received systemic immunomodulatory agents (with exception of CS) within the following time frames prior to RI baseline (first administration of study drug):
    a. Azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, or mercaptopurine within 24 weeks.
    b. TNF inhibitors, IL-6 inhibitors, or janus-activating kinase inhibitors within 12 weeks.
    c. Canakinumab within 12 weeks. Canakinumab could not have been discontinued due to safety unless it was discontinued due to local injection site reactions.
    d. Rilonacept within 6 weeks. Rilonacept could not have been discontinued due to lack of efficacy or due to safety.
    e. Methotrexate within 2 weeks.
    f. Anakinra within 5 days. Anakinra could not have been discontinued due to lack of efficacy or due to safety unless it was discontinued due to local injection site reactions.
8. Has a history of myeloproliferative disorder.
9. Has a history of demyelinating disease or symptoms suggestive of multiple sclerosis.
10. Meets the following TB criteria:
    a. History of active TB prior to screening OR
    b. History of latent TB that was not adequately treated prior to screening OR
    c. Signs or symptoms suggestive of active TB (e.g., new cough of >14 days in duration or a change in chronic cough, persistent fever, unintentional weight loss, or night sweats) upon review of medical history and/or physical examination at screening OR
    d. Recent close contact with a person with active TB OR
    e. Positive or indeterminate Interferon Gamma Release Assay (IGRA) test results or results from another positive TB test at screening based on acceptable clinical practice for the country in which the subject is enrolling.
11. Has chest x-ray (posterior-anterior view) at screening (or history of results within 12 weeks before receiving first administration of study drug), with evidence of malignancy or abnormality consistent with prior or active TB infection.
12. Has received immunization with a live (attenuated) vaccine within 12 weeks before screening or is expected to receive live (attenuated) vaccine during the study or within 12 weeks after the last study drug administration.
13. Has a history of positive or intermediate results for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening.
14. Has an estimated glomerular filtration rate (eGFR) <30 ml/min.
15. Has a history of malignancy of any organ system within the past 5 years before screening (other than a successfully treated non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma and/or localized carcinoma in situ of the cervix).

16. Has a known or suspected current active infection or a history of chronic or recurrent infectious disease, including, but not limited to, chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, or an open, draining infected skin wound.
17. Has had a serious infection, has been admitted to the hospital for an infection, has been treated with oral antibiotics within 2 weeks of RI baseline (first administration of study drug), or has been treated with IV antibiotics for an infection within 8 weeks of RI baseline.
18. Has had an organ transplant.
19. Has screening laboratory test results meeting any of the following criteria:
    a. Hemoglobin level <10.0 g/dL;
    b. WBC count $<3.0 \times 10^3/\mu L$
    c. Neutrophil count $<1.5 \times 10^3/\mu L$
    d. Platelet count $<100 \times 10^3/\mu L$
    e. Total bilirubin level >1.5 × the upper limit of normal (ULN) unless the test results are consistent with those for Gilbert's syndrome
    f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 × ULN
20. In the investigator's opinion, has a history of alcoholism or drug/chemical abuse within 2 years before screening.
21. Has a known hypersensitivity to ARCALYST® (rilonacept) or to any of its excipients.
22. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before screening or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
23. In the investigator's opinion, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations. This includes significant concomitant illnesses such as, but not limited to, cardiac, renal, neurological, endocrinological, metabolic, pulmonary, GI, or psychiatric diseases.
24. In the opinion of the investigator, is not likely to be compliant with the study protocol.
25. In the opinion of the investigator, should not participate in this study.

4.2 Subject Completion, Withdrawal from Study, and Study Drug Discontinuation

4.2.1 Completion

A subject will be considered to have completed the study if she/he has completed the RW period and has completed assessments at the EORW visit. At the EORW visit, subjects who were randomly

assigned to rilonacept or subjects who transitioned to open-label rilonacept upon protocol-defined pericarditis recurrence (Section 6.2.3) in the RW period will be offered an opportunity to receive an additional 24 weeks of open-label rilonacept treatment based on their clinical status and at the discretion of the investigator, and after signing the LTE informed consent.

At the EORW visit, subjects who were randomly assigned to placebo and did not transition to bailout rilonacept will be offered an opportunity to receive an additional 24 weeks of open-label rilonacept treatment based on their clinical status and at the discretion of the investigator, after signing the LTE informed consent.

Any subject who in the opinion of investigator should not continue open-label rilonacept in LTE will be offered the opportunity to continue follow-up off study drug treatment in LTE, after signing the LTE informed consent.

Subjects who elect not to enter LTE will be followed for 6 weeks after receiving the last study drug administration.

4.2.2 Reasons for Discontinuation of Study Drug and Study Withdrawal

Subjects have the right to stop taking study drug before the end of the study or to withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject also may be asked to stop study drug at the investigator's discretion. In the event that a subject permanently discontinues study drug but does not withdraw the informed consent, the investigator should continue to follow up with the subject by telephone contact (TC) visits, in the clinic, or by other means through the EORW visit if the subject discontinues in RI or RW, or through the end of LTE-FUP if the subject discontinues in LTE-TP, unless consent is withdrawn.

The reasons for premature study drug discontinuation will be recorded in the electronic case report form (eCRF).

4.2.2.1 Discontinuation of Study Drug

The study drug dosing will be permanently stopped if any of the following occurs:

- The subject develops TB or malignancy, excluding non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma
- Initiation of protocol-prohibited medication (Section 5.8.6)
- Subject requires treatment with CS for pericarditis during RW or LTE-TP periods of the study
- Pregnancy or pregnancy planned during the study or within 3 months after the last study drug administration
- ALT or AST values ≥3 × ULN associated with total bilirubin ≥2 × ULN, with no underlying medical conditions to explain the elevated values

- Treatment with a live (attenuated) vaccine during the study
- Investigator or Sponsor's medical monitor or [redacted] medical monitor decides that, for safety reasons, it is in the subject's best interest
- Termination of the study by Kiniksa Pharmaceuticals

Permanent or temporary study drug discontinuation should be strongly considered at the time if any of the following occurs:

- Subject develops an opportunistic infection.
- Subject develops moderate or severe infection
- Neutrophil count $<1.0 \times 10^3/\mu L$
- Isolated ALT or AST values $>5 \times$ ULN
- Surgical procedure

The Sponsor has the right to terminate the study at any time in case of safety concerns (e.g., suspected unexpected serious adverse reactions [SUSARs]) or if special circumstances concerning the study drug or the company itself occur. In this event, the investigator(s) will be informed of the reason for study termination.

4.2.2.2 Withdrawal from the Study

Subjects may withdraw from the study at any time and for any reason, without prejudice to their future medical care by the investigator or at the study site. However, prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow-up including options such as less frequent follow-up calls or visits, follow-up with a family member or friend, or follow-up through a local physician or medical records. Follow-up options will be summarized on a withdrawal of consent checklist source document that must be reviewed and signed by the investigator for any subject who withdraws consent for further participation in the study. The checklist must be completed for all enrolled subjects who have withdrawn consent. The reasons for a subject's withdrawal from the study are also required to be recorded in the eCRF.

A subject may be considered withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Documented withdrawal of informed consent
- Death

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and re-engage the subject in the study or determine the reason for withdrawal. The measures taken are to continue until study end and are required to be recorded in source documentation.

In subjects who are documented as having withdrawn consent from all study activities, no further study visits or study-related TCs can be conducted. All data collected prior to the date of the subject's confirmed withdrawal of consent will be included in the study, as specified in the subject's signed ICF.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

In the single-blind RI period, all subjects will receive blinded rilonacept at the same dose through Week 12; subjects will be blinded to the time of transitioning to RW. Subjects who stopped background SOC pericarditis therapy and who achieve Clinical Response on rilonacept at RI Week 12/RW baseline will be randomly assigned in a double-blind manner to continue to receive blinded rilonacept or matching placebo using a 1:1 allocation ratio. The definition of Clinical Response is provided in Section 6.2.2. An interactive web response system (IWRS) will be used to administer the randomization schedule. 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

5.2 Treatments Administered

Throughout this protocol, "study drug" refers to the investigational medicinal products: rilonacept and matching placebo. Both will be administered as applicable by SC injection.

Study drug administration will be performed once a week (every 7 ± 2 days). The interval between study drug administrations must be at least 5 days.

Study drug will be dosed as follows:

Adult Subjects (≥18 years old):

Rilonacept: Loading dose 320 mg administered as 2 SC injections, 160 mg each (2 ml) at RI baseline, followed by once-weekly SC injections of 160 mg (2ml).

Placebo: administered as once-weekly SC injections of 2 ml each in the RW period

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 320 mg administered as 2 SC injections, 160 mg each (2 ml) at the next scheduled study drug administration date, followed by once-weekly SC injections of 160 mg (2ml).

Pediatric Subjects (≥12 and <18 years old):

Rilonacept: Loading dose 4.4 mg/kg administered as 2 SC injections, 2.2 mg/kg each (maximum 160 mg each) at RI baseline, followed by once-weekly SC injections of 2.2 mg/kg (maximum 160 mg). The volume of injections will be based on the subject's weight (Table 5–1).

Placebo (in RW): once-weekly SC injections with volume based on the subject's weight (Table 5–1, maximum 2 ml).

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 4.4 mg/kg administered as 1 (maximum 2 ml) or 2 SC injections at the next scheduled study drug administration date, followed by once-weekly SC injections of 2.2 mg/kg (maximum 2 ml). The volume of injections will be based on the subject's weight (Table 5–1).

Study drug dose/volume will be calculated by the investigator or pharmacist during site clinic visits based on body weight (as specified in the Study Schedule of Activities) using a weight-based dosing chart in **kilograms** (Table 5–1).

Table 5–1: Study Drug Dose Volume (After Reconstitution) by Body Weight in Kilograms for Pediatric Subjects Aged ≥12 and <18 Years

Weight Range (kg)	Loading Dose Volume (ml)	Weekly Dose Volume (ml)
23.6 to 27.2	2 x 0.7	0.7
27.3 to 30.8	2 x 0.8	0.8
30.9 to 34.4	2 x 0.9	0.9
34.5 to 38.1	2 x 1.0	1.0
38.2 to 41.7	2 x 1.1	1.1
41.8 to 45.4	2 x 1.2	1.2
45.5 to 49.0	2 x 1.3	1.3
49.1 to 52.6	2 x 1.4	1.4
52.7 to 56.3	2 x 1.5	1.5
56.4 to 59.9	2 x 1.6	1.6
60.0 to 63.5	2 x 1.7	1.7
63.6 to 67.2	2 x 1.8	1.8
67.3 to 70.8	2 x 1.9	1.9
70.9 or greater	2 x 2.0	2.0

Study Drug Self-Administration

The first study drug dose on RI baseline will be administered at the study site. During this visit, the subject will be trained on study drug preparation and injection. In case the subject is unwilling or unable to prepare and self-inject the study drug, the subject's caregiver will be trained.

The first study drug administration for adult and pediatric subjects on RI baseline will consist of 2 SC injections, constituting a loading dose. The first injection will be prepared and administered by study site staff. The second injection will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration. If the subject or subject's caregiver is unable to prepare and inject the study dug, the subject may report for once-weekly injections to a study site, or injections can be administered by the visiting registered nurse (RN).

5.3 Identity of Investigational Medicinal Product

Rilonacept (KPL-914) is the drug being evaluated in the current study. Refer to Section 1.3 for a detailed description of rilonacept's mechanism of action.

Study drug (rilonacept or placebo) is supplied in a single-use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

Each placebo vial contains lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the placebo vial contains 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Product Packaging and Storage

Additional information regarding the preparation, dispensation, administration, and storage of rilonacept or placebo will be described in the Pharmacy Manual.

Study drug will be provided by Kiniksa Pharmaceuticals to the study sites in the lyophilized formulation in glass vials as described in Section 5.3. Each single-use vial will have a clinical label adhered to the vial. One labeled vial will be placed into a carton. Each carton will have a clinical label adhered to the

outside of the carton. One tamper-evident seal will be placed on the top of the carton to securely close the lid.

Study drug is to be stored and shipped refrigerated at 2°C to 8°C (36°F to 46°F) inside the original carton to protect it from light.

5.4.2 Study Drug Accountability

The sites will receive study drug for on-site administration at study site visits. Upon receipt of study drug, the investigator (or delegate) will conduct an inventory of the supplies and verify that the supplies are received intact, at the appropriate temperature, and in the correct amounts prior to completing a supplies receipt. The investigator will confirm receipt of study drug in the IWRS and retain a copy of this receipt at the study site. The inventory of supplies at each study site will be reviewed by the study monitor.

Study drug will be dispensed to the study subjects for outpatient self-administration according to the supply chain described in the Pharmacy Manual.

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviating from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all used and unused study drug containers must be retained by the study site/clinic and subject for cataloguing and documentation of compliance. The full process for drug dispensing, documentation, and destruction will be described in the Pharmacy Manual.

A full drug accountability log will be maintained at the study site at all times.

5.4.3 Other Supplies

Rilonacept should be reconstituted with preservative-free WFI that will be provided by Kiniksa Pharmaceuticals or designee along with 27-gauge, ½-inch needles, 3-ml syringes, alcohol wipes, gauze pads, bandages, and a puncture resistant container for disposal of needles and syringes. Only the syringes and needles provided by the Sponsor or its designee should be used to prepare and inject the study drug. The Sponsor also will provide coolers and refrigerated gel packs to ensure that the subjects transport the study drug at the proper temperature. On occasion, sites may be asked to locally procure ancillary materials.

5.5 Study Drug Overdose

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose must be promptly reported to the [redacted] Pharmacovigilance (PHV) in the same way and using the same procedures as for a serious adverse event (SAE) (Section 6.4.6), regardless of whether any AEs are associated with the overdose.

If there are AEs associated with the overdose, these should be recorded on the relevant AE/SAE Sections in the eCRF; however, overdoses without signs or symptoms do not need to be recorded as AEs in the eCRF.

5.5.1 Treatment of Study Drug Overdose

The maximum amount of rilonacept that can be safely administered has not been determined. Maximum once-weekly doses of rilonacept up to 320 mg have been administered SC for up to approximately 18 months in a small number of subjects with CAPS, and for up to 6 months in subjects in an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, rilonacept given IV at doses up to 2000 mg monthly for up to 6 months in another subject population was tolerated without dose-limiting toxicities (Rilonacept IB). In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of AEs and appropriate symptomatic treatment instituted immediately (Section 13.1, ARCALYST® Prescribing Information).

5.5.2 Other Study Drug Errors

To avoid study drug errors, it is important to note the following:

- In this study, rilonacept is designated for SC injections only. It should be taken only by the subjects participating in the study and as instructed by study site personnel.
- Guidelines regarding the management of temperature excursions during storage will be detailed in the Pharmacy Manual.
- Pediatric dosing is calculated based on body weight in **kilograms,** not pounds.

Any study drug error must be promptly reported to the [redacted] PHV, in the same way and using the same procedures as for an SAE (Section 6.4.6)

5.6 Transmission of Infectious Agents

The lyophilized study drug is to be stored refrigerated at 2°C to 8°C (36°F to 46°F) inside the original carton to protect it from light. Study drug should not be used beyond the date stamped on the label. After reconstitution, study drug may be kept at room temperature, should be protected from light, and should be used within 3 hours of reconstitution. Study drug does not contain preservatives; therefore, unused portions of study drug should be discarded.

5.7 Misuse for Illegal Purposes

Rilonacept does not have addicting potential, and the risk of misuse for illegal purposes is minimal.

5.8 Prior and Concomitant Medications

Use of all concomitant medications and any changes in concomitant medications will be recorded in the subject's eCRF. The minimum requirement is that drug name and dates of administration are to be

recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF. The initiation of protocol prohibited medication (Section 5.8.6) requires discontinuation of study drug.

Guidelines regarding the use of concomitant medication will be detailed in the Pharmacy Manual and are summarized in the following Sections.

5.8.1 Screening

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine, and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs), in the opinion of the investigator, are not anticipated to significantly alter assessments of baseline disease activity.

Analgesics can be used at the discretion of the investigator during screening activities prior to the first study drug dose, but only after the subject has documented a pericarditis pain level ≥4 on the 11-point NRS within 7 days prior to and including RI baseline (first administration of study drug).

Subjects can enter the study on prednisone (or equivalent dose) not exceeding 60 mg/day for adults and not exceeding 0.5 mg/kg/day (with a maximum dose of 60 mg/day) in pediatric subjects.

5.8.2 Single-blind RI Period

- 1-week Stabilization period, during which rilonacept is administered in addition to SOC pericarditis therapy and ongoing pericarditis episode is treated. All concomitant pericarditis medications including NSAIDs, analgesics, colchicine and CS will remain stable, unless the dosing must be decreased or stopped in the judgement of the investigator due to an AE.
- 9-week background medication Weaning period, during which subjects are weaned off background SOC pericarditis therapy, as applicable, while treatment with blinded rilonacept continues. The guidelines for background medication taper and discontinuation will be provided in the Pharmacy Manual.

  Corticosteroids

  Starting at Week 1 and through Week 10, CS will be tapered and discontinued at a rate dependent on the dose at study entry.

  Analgesics

Starting at Week 1 and through Week 10, analgesics (non-opioid and opioid) will be tapered and discontinued. Opioid analgesics can continue beyond Week 10 at stable doses through the end of the RW period if it is not feasible to discontinue them without causing withdrawal symptoms.

NSAIDs and Colchicine

Starting at Week 4 and through Week 10, NSAIDs and colchicine will be tapered and discontinued.

- 2-week Monotherapy period during which rilonacept administration continues: Subjects are required to be off all background SOC pericarditis therapy, with the exception of opioid analgesics if their discontinuation is not feasible.

5.8.3 Double-blind Placebo-controlled RW Period

During the RW period, subjects should not be receiving any concomitant medications for pericarditis, with the exception of opioid analgesics in case their taper down and discontinuation was not feasible in the RI period.

5.8.3.1 Concomitant Medication Upon Pericarditis Recurrence

Subjects meeting protocol criteria for bailout rilonacept

Upon pericarditis recurrence and meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) and completing the diagnostic workup as confirmed by the [redacted] medical monitor, subjects will be transitioned to open-label rilonacept, as described in Section 3.1. Because open-label rilonacept can be administered only if at least 5 days have passed from the last blinded study drug administration, the investigators are allowed to use sequential ORT, i.e., analgesics, NSAIDs, and colchicine if necessary at their discretion. The use of those medications will be detailed in the Pharmacy Manual; it is briefly given as follows:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to open-label rilonacept based on the subject's clinical status and at the discretion of the investigator.
- If, after transition to open-label rilonacept, the investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from rilonacept and followed through the EORW visit.

Subjects not meeting protocol criteria for bailout rilonacept

If, based on the investigator's judgement, the subject is experiencing pericarditis recurrence that does

not meet the protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) but does require additional treatment, the subject will continue blinded study drug, and the investigator should manage the pericarditis recurrence using sequential ORT for pericarditis, i.e., analgesics, NSAIDs, colchicine as described in the Pharmacy Manual and outlined briefly below:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to blinded study drug based on the subject's clinical status and at the discretion of the investigator.
- If, after the addition of NSAIDs and colchicine, the investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from blinded study drug and followed through the EORW visit.

5.8.4 Long Term Extension Treatment Period (LTE-TP)

Subjects who opt to continue open-label rilonacept in the LTE-TP will have their concomitant pericarditis medications managed at the discretion of the investigator and based on the subject's clinical status. If CS are required in addition to rilonacept to manage recurrent pericarditis, rilonacept should be discontinued.

5.8.5 Long Term Extension Follow-Up Period (LTE-FUP)

During LTE-FUP, pericarditis medication can be managed at the investigator's discretion.

5.8.6 Prohibited Concomitant Medicines During the Study

Prohibited medications during the study and throughout the end of LTE-TP include the following:

- Interleukin (IL) blockers other than rilonacept
- IL-6 blockers
- Janus-activating kinase inhibitors
- TNF inhibitors
- Potent immunosuppressants (azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, mercaptopurine, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents, agents that deplete B or T cells [e.g., rituximab, alemtuzumab])
- Live (attenuated) vaccines, which are prohibited during the study and within 12 weeks after the last study drug administration

5.9 Blinding

In the single-blind RI period, all subjects will receive rilonacept but will be blinded to the duration of the RI period and the timing of randomization.

The RW period is a double-blind period in which rilonacept and placebo are identical in appearance. Neither the subject nor any of the investigator/site staff, [redacted], or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Council for Harmonisation [ICH] E9).

In the event of a pericarditis recurrence that meets the criteria for bailout rilonacept (Sections 3.1 and 6.2.3), the subject will be transitioned to open-label rilonacept but will remain blinded to their prior RW treatment assignment.

At the end of the RW period, all sites and subjects will be unblinded. Subjects will be offered participation in the LTE-TP, in which once-weekly open-label rilonacept can be continued for an additional 24 weeks.

5.9.1 Breaking the Blind

A subject's treatment assignment will not be broken until the end of the RW period.

If the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the Sponsor must be notified immediately. If the investigator intends to unblind treatment allocation for a subject, then the Sponsor should be notified immediately. The investigator may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study drug is essential for the appropriate clinical management or welfare of the subject. In most cases, the management of a medical emergency would be the same, regardless of whether the subject received active drug. The treatment assignment will be unblinded through the IWRS. The investigator must notify Kiniksa Pharmaceuticals and [redacted] medical monitors as soon as possible but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the eCRF.

The [redacted] PHV staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the blinded report may be sent to clinical investigators in accordance with local regulations.

5.10 Treatment Compliance

Subjects will record the administration of all doses of study drug (whether as an outpatient or in the clinic) in a subject's diary. In addition, throughout all study periods, adherence to study drug administration will be assessed by the study site in collaboration with the visiting RN (Section 6).

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will provide informed consent or an assent, if applicable. Potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all questions answered for them. Subjects will undergo screening procedures specific to the study only after the ICF has been provided by the subject unless performed as part of SOC practice. The investigator or designee will also sign the ICF.

6.1 Study Visits

The schedule of assessments for the study site visits is summarized in the Study Schedule of Activities. Following screening assessments, qualifying subjects will be enrolled and enter the RI period. Subjects who stop background pericarditis medications and achieve Clinical Response at RI Week 12 (Section 6.2.2), will be randomized and enter the RW period. During both the RI and RW period, a combination of clinic and outpatient visits will occur. Outpatient visits may consist of telephone or virtual contacts as well as home visits conducted by a visiting nurse. For each scheduled visit of the study (including outpatient and clinic), assessments should occur prior to scheduled injections of study drug. Subjects can be brought to the clinic in place of a scheduled outpatient visit, for an unscheduled visit at the discretion of the investigator, or if arranging a visiting nurse for an at home visit is logistically not feasible.

The visit schedule is derived from the day of the RI baseline visit. One week is equal to 7 calendar days. Although visits do not occur every week, subjects are required to record pericarditis pain NRS measurements on a daily basis in their study device and to administer study drug on a once-weekly basis and record it in their study electronic diary (eDiary). If a subject is unable to independently complete the daily eDiary, a caregiver may help enter the data.

Upon completion of the RI and RW periods, all subjects will have the opportunity to continue participating in the LTE. This will require each subject again providing informed consent prior to LTE participation. The LTE period will have a treatment period (LTE-TP) and an off treatment follow-up period (LTE-FUP).

Any subject who prematurely discontinues study drug will be followed for the duration of the trial as specified in Section 4.2.2. In addition, throughout all study periods, compliance with study drug administration will be assessed by the site in collaboration with the visiting RN.

6.1.1 Screening: Clinic and Remote as Needed

A study screening eCRF is required to be completed for every subject with a signed ICF. For each subject, the subject identification is obtained from the IWRS.

It is anticipated that some subjects may have a portion of the study screening procedures done as part of routine care outside the auspices of this study. As long as these procedures were done within the allotted screening period timeframe, the results of these procedures may be used to support study screening and completion of the study screening eCRF. Any protocol-specified study qualification

procedures/tests not already done as part of routine care will need to be conducted after the subject provides informed consent and before enrollment. It is possible that the screening and enrollment visit will occur on the same day.

The below procedures are required to be completed to screen a subject ≤28 days prior to enrollment. All assessments and procedures are not required to be completed on-site; however, the site is expected to obtain the medical records for subject source documentation.

- Obtain the ICF.
- Enter the subject into the IWRS.
- Review inclusion/exclusion criteria; ensure that the subject has a diagnosis of recurrent pericarditis based and is presenting with at least the **third** pericarditis episode.
- Record: demographic information, medical/surgical history, concomitant medications, all prior and current concomitant pericarditis medications, a detailed pericarditis history including all recurrent pericarditis events.
- Perform a full physical examination (may be performed by an investigator or other healthcare provider designated by the investigator).
- Perform/obtain:
  - 11-point pericarditis pain NRS assessment – required to be ≥4 within 7 days prior to and including the day of RI baseline. The qualifying NRS assessment and CRP are not required to occur on the same day.
  - CRP (mg/dL) – required within 7 days prior to and including the day of RI baseline. For study qualification purposes, the CRP may be assessed using 1 of 4 approaches:
    - Point of care (POC) device provided by Sponsor (preferred method)
    - Blood sample sent to the local laboratory
    - CRP measurement taken as part of the subject's routine care (e.g., not specifically obtained for this study)
    - Blood sample sent to the central laboratory
  - Local laboratory hematology, chemistry, IGRA, hepatitis serology, HIV test
  - Chest x-ray (unless performed and available within the past 12 weeks)
  - Local or central laboratory urine pregnancy test for women of childbearing potential
  - AE collection

6.1.2 Single-blind Treatment: Run-In

6.1.2.1 Enrollment (RI Baseline): Clinic Visit

For subjects who meet study entry criteria, enrollment commences at the RI baseline visit. The following procedures occur:

- Review inclusion and exclusion criteria to confirm subject qualification.
- Review and record updates to recurrent pericarditis history since the screening visit.
- Revise IWRS status change to enrollment.
- Assess and record all concomitant medications as well as all prior and concomitant pericarditis medication.
- Perform an abbreviated physical examination, height and body weight.
- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; the ECHO is to be read locally prior to sending to the core lab.
- Perform cardiac MRI (for substudy participants only).
- Provide the subject with their study device and complete the following:
  - For subjects ≥18 years, have them complete the 36-Item Short Form Health Survey (SF-36), 5-level EuroQoL-5D (EQ-5D-5L), Insomnia Severity Index (ISI)
  - For all subjects, instruct how to complete the 11-point pericarditis pain NRS (as outlined in Section 6.2.1.2) and the medication diary.
  - Have all subjects complete the Patient Global Impression of Pericarditis Severity (PGIPS) score.
- The investigator is to complete the Physician Global Assessment of Pericarditis Activity (PGA-PA).
- Obtain the Pharmacogenomics ICF.
- Obtain a local or central laboratory urine pregnancy test for women of childbearing potential.
- Obtain central laboratory chemistry, hematology, lipid panel, CRP, anti-drug antibodies (ADAs [ADA sample will be also used for PK measurement]), biomarkers, and urinalysis (laboratory tests should be drawn prior to the first study drug administration, but results of those tests are not required before enrollment).
- AE reporting.
- Additional discussion/assessment as needed.

Upon completion of the above study activities, study drug dispensing can commence. The following procedures occur:

- Complete the IWRS to dispense assigned study drug; record the amount (number of vials) dispensed.
- Explain the study drug, proper once-weekly dosing, proper study drug administration technique, study drug administration documentation, and confirm that the subject (and subject's caregiver as applicable) understands.
- For pediatric subjects, body weight (in kilograms) obtained at the RI baseline visit is to be used to determine appropriate study drug dosing in the RI period. Please refer to the pediatric study drug dosing Table 5–1 as well as the Study Schedule of Activities for subsequent visits with weight assessments for pediatric dosing.
- Prepare and administer the first injection of study drug and train the subject or caregiver to prepare and administer the second dose of study drug.
- Instruct the subject to bring to each clinic visit all medications the subject is taking, including used and unused study drug vials.
- Arrange upcoming study visits (as many visits as possible that can be arranged ahead of time is advised).

6.1.2.2 RI Day 2: Clinic Visit (24-hour PK Sub-study Participants Only)

The RI Day 2 visit includes a PK sample that is collected 24 hours after the loading dose of study drug and then sent to the central laboratory.

6.1.2.3 RI Day 4: TC/RN Visit

The timing of the site TC visit on the RI Day 4 visit can occur independently of the RN visit. During the site TC visit, the subject is contacted to assess for AEs in follow-up to the initial injections received, to review the daily input of the pericarditis pain NRS score, as well as to review all concomitant medications, including concomitant pericarditis medication. The site then dispenses study drug (along with ancillary supplies) through the IWRS and coordinates shipment as outlined in the Pharmacy Manual. During the visiting RN visit, a CRP sample is drawn and sent to the central lab.

6.1.2.4 RI Week 1: TC/RN Visit

It is preferred that the site TC occur prior to the RN visits. It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 1 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.

- Provide instruction on the pericarditis concomitant medication oral corticosteroid tapering if applicable.
- Confirm and review upcoming visit arrangements.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

RN home visit:

- Obtain the central laboratory samples for CRP, PK, and biomarkers (these are collected prior to study drug administration).
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Ensure the subject records study drug administration in the medication diary.
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.5 RI Week 2: TC/RN Visit

It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 2 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the oral pericarditis corticosteroid tapering, if applicable.
- Review study drug administration and documentation compliance.
- Confirm and review upcoming visit arrangements.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

RN home visit:

- Record study drug dispensing to the subject.
- Obtain central laboratory samples for CRP, PK, and ADAs (these are drawn prior to study drug administration).
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).

- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.6 RI Week 4: TC/RN Visit

It is required that visit assessments occur prior to scheduled study drug dosing. The RI Week 4 visit is as follows:

Site TC visit:

- Assess for AEs.
- Evaluate all concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the oral corticosteroid tapering if applicable and provide instruction on NSAID and/or colchicine tapering if applicable.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm and review upcoming visit arrangements.
- Instruct the subject to bring used and unused study drug vials (those not yet obtained by the visiting RN) to the next clinic visit.

RN home visit:

- Obtain central laboratory samples for CRP, PK, and biomarkers (these are drawn prior to study drug administration).
- Obtain a pharmacogenomics sample for those subjects who have provided informed consent.
- Provide review of self-administration of the study drug.
- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.
- Confirm upcoming visit arrangements.

6.1.2.7 RI Week 6: Clinic Visit

The RI Week 6 visit in the clinic includes the following assessments and procedures:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess subject progress on the concomitant oral corticosteroid, NSAID and/or colchicine tapering if applicable.

- Obtain used and unused study drug vials for study drug compliance evaluation.
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for hematology, chemistry, CRP, and ADAs.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur:

- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Have the subject administer the next scheduled injection of study drug (if within the study drug window) and have the subject record in the medication diary.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming visit arrangements.

6.1.2.8 RI Week 10: TC Visit

The following assessments and procedures are to be completed:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess concomitant oral corticosteroid, NSAID and/or colchicine tapering completion.
- Assess study drug administration documentation.
- Confirm the RI Week 12/RW baseline clinic visit arrangements.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).

6.1.2.9 Randomization (RI Week 12/RW Baseline): Clinic Visit

The following assessments and procedures are conducted at the RI Week 12 visit, **prior to randomization**:

- CRP assessment (local and central) (the POC device provided for the study is the preferred method for local laboratory CRP assessment).
- Obtain a pericarditis pain NRS average score for the prior 7 days, including the day of the visit (4 missing NRS values within this week may result in an inability to move forward with randomization).

- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; ECHO is read locally prior to submission to the core lab.
- Abbreviated physical examination, height and body weight.
- For subjects ≥18 years, complete on their device SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, PK, and ADAs.
- Evaluate concomitant medications including pericarditis concomitant medication.
- Assess for AEs.
- Obtain used and unused study drug vials for study drug compliance evaluation.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Assess for Clinical Response (refer to Section 6.2.2).

For subjects who have successfully completed the RI period and are assessed as achieving Clinical Response at the RI Week 12 visit, the RW baseline visit commences.

The following assessments and procedures are conducted at the RW baseline visit:

- Update the subject status in the IWRS by randomizing the subject in the IWRS.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1). Please refer to the pediatric study drug dosing Table 5–1 as well as the Study Schedule of Activities for subsequent visits with weight assessments for pediatric dosing during RW.
- Dispense study drug and record the amount (number of vials) dispensed.
- Have the subject administer the study drug and record in the diary (if within the study drug window).
- Instruct the subject to bring all medications including used and unused study drug to each clinic visit.
- Instruct the subjects on the process to follow for a pericarditis recurrence event.
- Arrange upcoming visits.

For subjects that do not qualify for randomization per the IWRS, the [redacted] medical monitor is to be immediately contacted to evaluate the reasons for non-qualification. Following medical monitor consultation, if the subject is deemed to not be a treatment responder, the RI Week 12 visit will be completed, study drug will be discontinued, and the subject will not proceed to randomization. The

subject will be requested to perform a 6-week safety follow-up (SFU) visit after his/her last dose of study drug as well as continue with follow-up as agreed upon until the EORW period.

6.1.3 Randomized-Withdrawal (RW) Period

During the RW period, subjects will continue with once-weekly study drug administration as well as daily 11-point pericarditis pain NRS scoring. Visits will occur every 4 weeks, alternating TC/RN visits and clinic visits, with the first visit during the RW period (RW Week 4) being a TC/RN visit. Additional unscheduled visits may occur at any time for evaluation of suspected pericarditis recurrence (Section 6.1.6.1) or for other reasons as deemed necessary by the study investigator.

The following procedures are to occur during the TC/RN visits:

Site TC visits:

- Assess for AEs.
- Assess for suspected pericarditis recurrence events.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Additional discussion/assessment as needed.
- Confirm and review upcoming visit arrangements.
- Instruct the subject to bring used and unused study drug vials (those not yet obtained by visiting RN) to the next clinic visit.

RN home visits:

- Obtain central laboratory samples for CRP.
- Provide review of self-administration of the study drug as needed.
- Monitor administration of the study drug (whenever possible).
- Obtain used study drug vials and materials.

The following procedures are to occur during the clinic visits (except for Week 24; see below):

- Assess for AEs.
- Assess for suspected pericarditis recurrence events.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Record height and body weight.
- Obtain central laboratory samples for chemistry, hematology, and CRP.
- Obtain central laboratory sample for PK and biomarkers (Weeks 8 and 24 only).

- Obtain central laboratory sample for ADAs (Week 24 only).
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS entry).
- Obtain used and unused study drug vials for study drug compliance evaluation.

Upon completion of the above study activities, study drug dispensing can commence. The following procedures occur:

- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Monitor administration of the study drug dose (whenever possible) and have the subject record in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming visit arrangements.

6.1.3.1 RW WEEK 24: Clinic Visit

The Week 24 visit in the clinic includes the following assessments and procedures:

- Assess for AEs.
- Assess for suspected pericarditis recurrences.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Perform a full physical examination, height and body weight.
- Acquire a 12-lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the ECHO is to be read locally before sending to the core lab.
- Obtain an MRI (for substudy participants only).
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, and biomarkers.
- Obtain used and unused study drug vials for study drug compliance evaluation.

- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).

Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur:

- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Have the subject administer the RW Week 24 study drug dose (if within the study drug window) and have the subject record it in the medication diary.
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Confirm upcoming study visits.

6.1.3.2 EORW (End of RW Period/LTE Baseline): Clinic Visit

The EORW visit will be same day as LTE-TP baseline visit.

All randomized subjects, including those that have had pericarditis recurrence or have permanently discontinued study drug will have an EORW visit at the end of the RW period. The EORW activities are listed below:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Acquire a 12-lead ECG.
- Acquire and submit a cardiac ECHO to the core laboratory per the core laboratory imaging guidelines; the EHCO is to be read locally prior to submission to the core lab.
- Perform a full physical examination, height and body weight.
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrences.
- Obtain informed consent for participation in the LTE period.
- Additional discussion/assessment as needed.

Upon completion of the EORW visit procedures and obtaining subject informed consent to participate in the LTE period, the LTE baseline visit procedures are as follows:

- Change the subject's status in the IWRS and obtain unblinding information; proceed with subject unblinding.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Dispense study drug and record the amount (number of vials) dispensed.
- Have the subject administer the LTE-TP Day 1 study drug dose as applicable (if within the study drug window) and have the subject record it in the medication diary.
- Instruct subjects on continuing the 11-point pericarditis pain NRS score daily entry.
- Review the study drug dosing schedule, administration techniques, and documentation.
- Additional discussion/assessments as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm the upcoming study visits.

6.1.4 Long Term Extension

6.1.4.1 LTE Weeks 8 and 16: Clinic Visit

The LTE Weeks 8 and 16 clinic visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Have all subjects complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, and CRP.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Additional discussion/assessment as needed (i.e., remind the subject about daily pericarditis pain NRS input).
- Confirm upcoming visit arrangements.
- Obtain weight for pediatric drug dispensing and dosing (Table 5–1).
- Dispense study drug through the IWRS and record the amount (number of vials) dispensed.
- Review the study drug dosing schedule, administration techniques, and documentation.

- Have the subject administer the regularly scheduled study drug dose as applicable (if within the study drug window) and have the subject record it in the medication diary.
- Confirm the upcoming study visits.

6.1.4.2 LTE Week 24 Clinic Visit

The LTE Week 24 visit is the final visit of the LTE-TP. However, if at any time throughout the course of the study a subject prematurely discontinues study drug, an End of Treatment (EOT) visit is to occur. The visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Acquire a 12-lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the EHCO is to be read locally prior to submission to the core lab.
- Obtain cardiac MRI (substudy participants only).
- Perform a full physical examination.
- For subjects ≥18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA-PA.
- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, biomarkers, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Have the subject administer the regularly scheduled study drug as applicable (if within study drug window), and have the subject record it in the medication diary.
- Change the subject status in the IWRS.
- Arrange an LTE Week 30 visit.

6.1.5 LTE Follow-Up Period

Upon completion of the LTE Week 24 EOT visit, subjects continue long term follow-up until the end of the study (EOS). The LTE-FUP includes 2 visits.

6.1.5.1 LTE Week 30 Visit: Clinic

The LTE Week 30 visit is a clinic visit. Visit activities are as follows:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess for pericarditis recurrence events.
- Additional discussion/assessment as needed.
- Obtain central laboratory samples for CRP, ADAs, and urine pregnancy test.
- Any left-over ancillary supplies are to be returned to the site.

6.1.5.2 LTE Week 48 End of Study Visit: TC

The LTE Week 48 EOS TC visit procedures are as follows:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess pericarditis recurrence.

6.1.6 Supplemental Visits

6.1.6.1 Pericarditis Recurrence Assessment: Clinic Visit

If a subject experiences symptoms consistent with pericarditis recurrence, he/she should contact the study investigator immediately for evaluation. It is possible that a subject may have assessments performed remotely, however, assessments are also expected be performed at the study site as soon as possible. Required assessments include:

- Evaluate pericarditis pain on the 11-point NRS.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Obtain laboratory samples for CRP (local and central) (the POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment).
- Acquire a 12 lead ECG.
- Acquire a cardiac ECHO per core laboratory imaging parameters; this ECHO is read locally for the purpose of pericarditis recurrence assessment and is then submitted to the ECHO core laboratory for central review.
- Perform an abbreviated physical examination, height and body weight.
- For subjects >18 years, complete the SF 36, EQ-5D 5L, ISI.

- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA PA.
- Obtain central laboratory samples for PK, ADAs, and biomarkers.
- Other procedures deemed necessary per the investigator or delegated site personnel.

Upon having completed the evaluation, if the investigator makes a clinical diagnosis that the subject is having a pericarditis recurrence event, he/she should contact the [redacted] medical monitor to review and confirm that all assessments have been performed and collected. Upon [redacted] medical monitor confirmation of completion of the assessment, the investigator commences as described in Section 6.2.3.

Subjects treated for a pericarditis recurrence event will continue to follow the same visit schedule described for the RW period (Section 6.1.3).

Source documentation including the assessments and evaluations used to confirm a pericarditis recurrence event, are required to be sent to CEC.

6.1.6.2 End of Treatment Visit: Clinic

The EOT visit is to be conducted when a subject permanently discontinues study drug. For subjects who complete the RW period but do not consent to participate in the LTE period, the EORW and EOT visit can be combined. For those subjects who do consent to participate in the LTE period, the EOT visit can be combined with the LTE Week 24 visit. In the event that a subject prematurely discontinues study drug, it is expected that the subject will have an EOT visit as soon as possible and continue to be followed as described in Section 4.2.2.

The EOT visit procedures are as follows:

- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Acquire a 12 lead ECG.
- Acquire a cardiac ECHO for core laboratory central review; the ECHO is to be read locally prior to submission to the core lab.
- Perform a cardiac MRI (for sub-study participants only) only if the previous MRI was done longer than 6 months ago.
- Perform a full physical examination.
- For subjects >18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The investigator is to complete the PGA PA.

- Obtain central laboratory samples for chemistry, hematology, lipid panel, CRP, PK, ADAs, biomarkers, and urinalysis.
- Assess for AEs.
- Assess for pericarditis recurrence events.
- Arrange SFU visit.

6.1.6.3 Safety Follow-Up Visit: Clinic or TC/RN

The SFU visit is to be conducted 6 weeks after the last dose of study drug. For those subjects who discontinue study drug at the LTE Week 24 visit, the SFU visit is to occur as a clinic visit. However, for those subjects who prematurely discontinue study drug during the study, the visit may be conducted in the clinic or as an outpatient (TC/RN visit) based on investigator discretion. The visit activities are as follows:

Site TC visit:

- Assess for AEs.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Assess for pericarditis recurrence events.
- Remind the subject to continue daily pericarditis pain NRS input if the SFU is occurring prior to the LTE Week 24 visit.
- Additional discussion/assessment as needed.

RN home visit:

- Obtain central laboratory samples for CRP, ADAs, and urine pregnancy test.
- Collect any leftover ancillary supplies and return to the site.

When the visit is conducted as a clinic visit, all of the RN visit activities are to be performed during the clinic visit.

6.2 Efficacy Assessments

Efficacy assessments to be performed at study visits are summarized in the Study Schedule of Activities and include: CRP, daily pericarditis pain assessment (11-point NRS), ECG, ECHO, Patient Global Impression of Pericarditis Severity (PGIPS), Physician Global Assessment of Pericarditis Activity (PGA-PA), and subject's quality of life assessments (SF-36, EQ-5D-5L) and insomnia questionnaire (ISI). In a substudy at selected sites, a cardiac MRI will be performed.

Note that in case the electronic versions of the PROs and assessments/questionnaires (PGIPS, PGA-PA, SF-36, EQ-5D-5L, and ISI) are not available, the paper forms must be completed until the electronic versions are available again.

6.2.1 Individual Efficacy Assessments

6.2.1.1 C-Reactive Protein

Central and local laboratory assessments of CRP will be performed at study visits as described in the Study Schedule of Activities. Centrally assayed CRP values will be used for statistical evaluations of changes from baseline. Locally assayed CRP will be used for screening, evaluation of treatment response prior to randomization, and assessment of suspected pericarditis recurrence in the RW period. The POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment.

6.2.1.2 11-Point Pericarditis Pain Numerical Rating Scale

Subjects will be asked to provide a daily assessment of pericarditis pain starting at RI baseline. A validated 11-point pericarditis NRS (Section 13.2) will be used to measure the subject's level of pain intensity on a daily basis throughout the study (Hawker et al 2011; Mannion et al 2007; Dworkin et al 2005).

It is recommended that daily pericarditis pain measurements using the 11-point NRS are performed by subjects at the same time of the day each day, and prior to study drug injection on days with study drug administration.

6.2.1.3 Electrocardiogram

Twelve-lead ECGs will be performed at study visits as described in the Study Schedule of Activities. Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-segment elevation or PR-segment depression.

6.2.1.4 Echocardiogram

Echocardiographic assessment of presence of pericardial effusion including new or worsening of pericardial effusion should be obtained at study visits as described in the Study Schedule of Activities. Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart, and pericarditis is one of the main causes of pericardial effusion. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening. Echocardiograms are to be acquired per the ECHO core imaging parameters. Upon local assessment and interpretation, the ECHO is then to be submitted to the designated central imaging laboratory.

6.2.1.5 Patient Global Impression of Pericarditis Severity

Patient Global Impression questionnaires have been developed for a variety of indications. The PGIPS is a single-item PRO measure that assesses the subject's impression of overall severity of pericarditis symptoms at the time the questionnaire is administered, using a 7-point rating scale ranging from absent

(no recurrent pericarditis symptoms) to very severe (recurrent pericarditis symptoms cannot be ignored) (Guy 1976). The PGIPS can be completed in less than 30 seconds.

The subject will select the box that best describes the severity of pericarditis symptoms right now:

- Absent: no symptoms
- Minimal: can be easily ignored without effort
- Mild: can be ignored with effort
- Moderate: cannot be ignored but does not influence my daily activities
- Moderately severe: cannot be ignored and occasionally limits my daily activities
- Severe: cannot be ignored and often limits my concentration on daily activities
- Very severe: cannot be ignored and markedly limits my daily activities

The PGIPS will be collected as described in the Study Schedule of Activities.

6.2.1.6 Physician Global Assessment of Pericarditis Activity

Physician Global Assessment questionnaires have been developed for a variety of indications. The PGA-PA is a single-item clinician-reported outcome measure that investigators use to rate their impression of the patient's overall pericarditis disease activity at the time the assessment is completed, using a 7-point rating scale ranging from absent to very severe (Guy 1976). Like the PGIPS, the PGA-PA can be completed in less than 30 seconds.

The investigator will select the box that best describes subject's pericarditis activity right now.

- Absent
- Minimal
- Mild
- Moderate
- Moderately severe
- Severe
- Very severe

The PGA-PA will be collected as described in the Study Schedule of Activities.

6.2.1.7 36-Item Short Form Health Survey

The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. The SF-36 was developed at RAND Corporation as part of its Medical Outcomes Study. The SF-36 assesses 8 health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health.

SF-36 will be collected in subjects ≥18 years or older as described in the Study Schedule of Activities.

6.2.1.8 EQ-5D-5L

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The rating scale records the subject's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgement. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles (https://euroqol.org/eq-5d-instruments).

The EQ-5D-5L will be collected in subjects ≥18 years or older as described in Study Schedule of Activities.

6.2.1.9 Insomnia Severity Index

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. The total score is interpreted as follows: no clinically significant insomnia (0–7); subthreshold insomnia (8–14); clinical (moderate) insomnia (15–21); and clinical (severe) insomnia (22–28) (Morin et al 2011).

The ISI will be collected in subjects ≥18 years or older as described in Study Schedule of Activities.

6.2.1.10 Cardiac MRI

Cardiac MRI will be performed as described in the Study Schedule of Activities in subjects at selected sites in the cardiac MRI substudy. Cardiac MRI will be performed to assess any changes in pericardial inflammation. Cardiac MRI readings will be performed by a central imaging laboratory. The study site/clinic reading of the MRI at the time of the examination may be used by the investigator for clinical decision-making.

6.2.2 Assessment of Clinical Response at the End of the Run-In Period Week 12/RW Baseline

At RI Week 12/RW baseline visit, all subjects receiving rilonacept who are able to discontinue background SOC pericarditis therapy during the RI period (Section 3.1) are assessed for Clinical Response. Only subjects who achieve Clinical Response at RI Week 12 and have discontinued background medications for pericarditis are eligible for randomization in the RW period.

Clinical Response at RI Week 12 is defined as follows:

- A weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS during the 7 days prior to and including the day of randomization, **AND**
- CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.

6.2.3 Management of Suspected Pericarditis Recurrence in the RW Period

Pericarditis Recurrence Definition: Pericarditis recurrence, for the purpose of the protocol, is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis.

At any time point during the RW period, subjects who experience suspected recurrence of their pericarditis will have been instructed to inform their site investigator as soon as possible. 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 (Section 6.1.6.1). The investigator will evaluate all assessments performed for a diagnostic workup, whether at the study site or at locations outside.

Upon completion of pericarditis workup, the investigator is required to contact the [redacted] medical monitor to confirm that the protocol required diagnostic workup is complete prior to implementing treatment for the event.

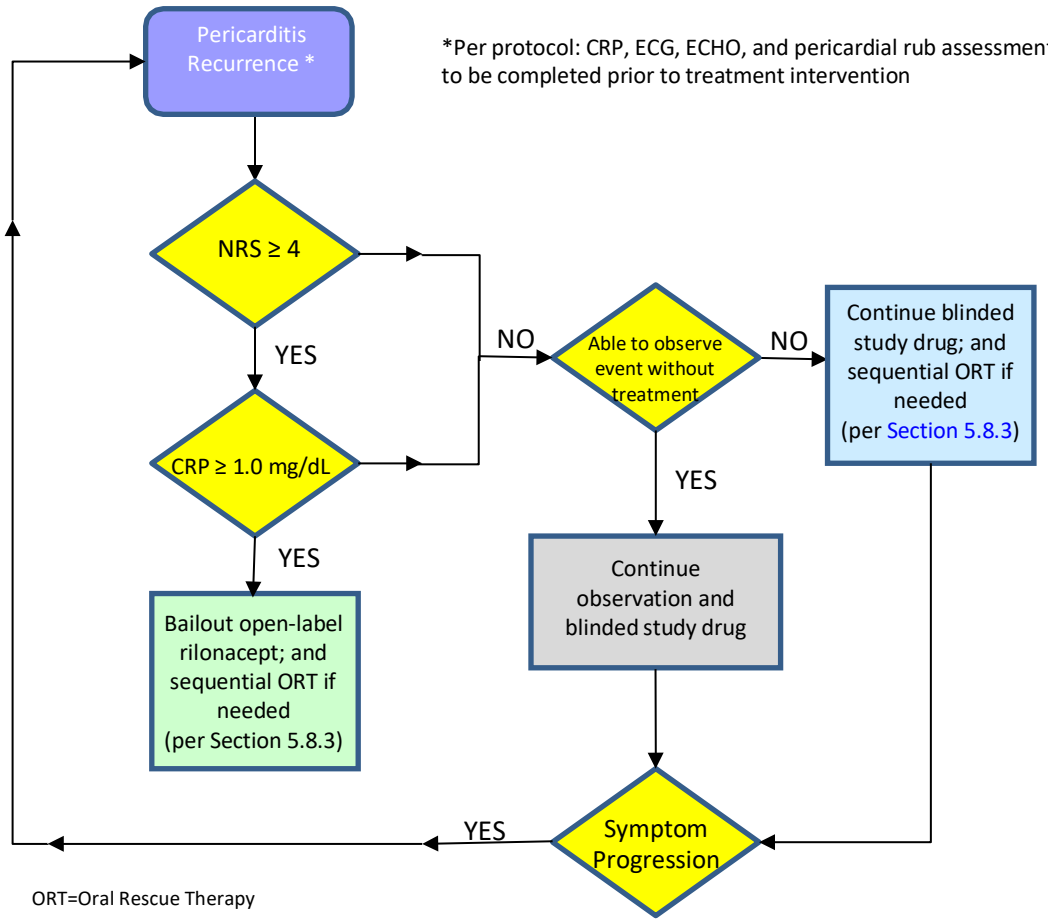
Following communication with the [redacted] medical monitor, if the event meets the criteria for bailout rilonacept (at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and one CRP value ≥1 mg/dL either on the same day or separated by no more than 7 days), and after the [redacted] medical monitor has confirmed with the investigator that the diagnostic workup is complete, the attainment of bailout criteria is confirmed in the IWRS, blinded study drug is discontinued, and open-label rilonacept treatment is dispensed. If needed, sequential ORT is allowed as outlined in Section 5.8.3. The subject will continue to be followed up according to the Study Schedule of Activities for the RW period.

Following communication with the [redacted] medical monitor, if the event does not meet the protocol criteria for bailout rilonacept but in the judgement of investigator requires treatment, after the [redacted] medical monitor has confirmed with the investigator that the diagnostic workup is complete, the investigator is allowed to add sequential ORT to blinded study drug, and as outlined in Section 5.8.3. Blinded study drug treatment will continue until a pericarditis recurrence that meets criteria for bailout rilonacept, or until the end of the RW period.

For a summary of management of suspected pericarditis recurrence, refer to Figure 3.

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. The event package will include, but may not be limited to, data on the subject's pericarditis pain level, CRP value, ECG tracing, ECHO result, the presence or absence of pericardial rub, and any additional source documentation relevant to the assessment of the suspected event. Details on endpoint package requirements will be described in the CEC charter. The CEC-confirmed pericarditis recurrences will be used for Primary Endpoint efficacy analysis. For more details on the CEC, refer to Section 6.7.2

Figure 3: Management of Suspected Pericarditis Recurrence in the Randomized-Withdrawal Period



6.3 Safety Assessments

Safety assessments to be performed at study visits are summarized in Study Schedule of Activities and include: assessment of AEs (Section 6.4), physical examinations (full and abbreviated) including vital signs measurements, chest x-ray, TB screening, and clinical laboratory tests (serology, hematology,

chemistry, urinalysis) (Section 6.6). A pregnancy test (Section 6.6.6) will be conducted at screening and as needed during the study and must be performed 6 weeks after the last study drug administration.

6.3.1 Physical Examination

A full physical examination should include at minimum an evaluation of vital signs, head, eyes, ears, 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. Body weight and height will be measured as per the Study Schedule of Activities and will be recorded in the eCRF. Any abnormality identified at baseline should be recorded on the medical history and physical examination eCRFs. At selected visits as specified in the Study Schedule of Activities, an abbreviated physical examination will be performed to evaluate vital signs, lung and heart sounds, including evaluation for pericardial rub.

At all visits at the study site, limited symptom-directed physical examinations may need to be performed in order to determine changes from baseline or abnormalities and should be recorded in the subject's trial notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

6.3.2 Vital Signs

Vital signs include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Blood pressure measurements should be obtained after the subject has been seated for at least 5 minutes.

6.3.3 Chest X-ray

Chest x-rays in accordance with local requirements will be obtained at screening (or an existing chest x-ray within 12 weeks of first study drug administration can be used) according to the Study Schedule of Activities. Chest x-rays should be reviewed by a qualified radiologist for clinically significant abnormalities and evidence of pulmonary disease that would exclude the potential subject.

6.3.4 Tuberculosis Screening

An IGRA test or another TB test based on acceptable clinical practice in each country will be performed in order to evaluate for the presence of active or latent TB infection at screening.

6.4 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

6.4.1 Definitions

6.4.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the reporting investigator to be clinically significant; and any untoward medical occurrence.

6.4.1.2 Treatment-emergent Adverse Event

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to the study drug or any event already present that worsens in either intensity or frequency after exposure to the study drug.

6.4.1.3 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence or effect that, at any dose:

- Results in *death*. Includes all deaths, even those that appear to be completely unrelated to the study drug (e.g., car accident where the subject is a passenger).
- Is *life-threatening*. In the view of the investigator, the subject was at immediate risk of death from the event at the time of the event (i.e., it does not include an AE that might have caused death if it had occurred in a more serious form).
- Requires *in-patient hospitalization* or prolongs an existing hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such pre-existing condition must be recorded on the medical history or physical examination page of the eCRF. Hospitalization is defined as an admission to the hospital ward, a short-stay type unit, or Emergency Room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay longer than originally anticipated for the event or development of a new AE as determined by the Investigator or treating physician.)
- Results in *persistent or significant disability/incapacity*. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.)
- Is a congenital anomaly/birth defect.

- Is an *important medical event*. Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above, i.e., any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the study drug.

All SAEs that occur after signing of study-related informed consent, whether or not the SAEs are related to the study drug or study procedures, must be reported.

6.4.1.4 Adverse Event of Special Interest

An adverse event of special interest (AESI) is defined as an AE of scientific and medical interest specific to the understanding of the study drug and requiring close monitoring and rapid communication by the investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of the study drug.

Treatments with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies. Therefore, malignancy is an AESI for rilonacept. Any AE of malignancy (excluding basal cell carcinoma of the skin) requires reporting to the [redacted] Pharmacovigilance (PHV) within 24 hours after the time the site personnel first learn about the event, following the process as described in Section 6.4.6.

6.4.1.5 Adverse Reaction

Any noxious and unintended response to the study drug (i.e., where a causal relationship between the study drug and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reaction.

6.4.1.6 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction that is “unexpected”, i.e., it is not listed (or not listed at the severity that has been observed) in the designated Reference Safety Information of the Investigator’s Brochure. Evaluation and reporting requirements for SUSARs are detailed in Section 6.4.8.

6.4.2 Assessing Adverse Events

6.4.2.1 Relationship to Study Drug

The investigator's assessment of an AE's relationship to the study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized by investigator using the following classification and criteria:

- **Not Related**: when the AE is definitely caused by the subject's clinical state or the study procedure/conditions
- **Unlikely Related**: when the temporal association between the AE and the study drug is such that the drug is not likely to have any reasonable association with the AE
- **Possibly Related**: when the AE follows a reasonable temporal sequence from the time of study drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- **Related**: when the AE follows a reasonable temporal sequence from administration of the study drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced

6.4.2.2 Intensity

The severity of an AE will be recorded as one of the following:

- **Mild**: easily tolerated, does not interfere with normal daily activities, does not require intervention
- **Moderate**: causes some interference with daily activities; minimal, local, or noninvasive intervention indicated
- **Severe**: as a consequence of the event, daily activities are limited or completely halted; hospitalization or prolongation of hospitalization indicated

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.3 Recording Adverse Events

Each subject should be monitored for the development of any AEs. This information should be collected by asking nonleading questions (such as "How are you feeling?") and from observations of and conversations with patients. AEs may also be collected by direct physical exam, diagnostic procedures, or any other appropriate source.

At every study visit (telephone or at the site), subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been admitted to the hospital, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

All AEs (serious and non-serious) will be documented in the subject's source documents and recorded in the eCRF. Any clinically relevant (as determined by the investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the subject's source documents and in the eCRF.

The AE term should be reported in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Information to be collected includes the following:

- Event term
- Date and time of onset
- Investigator-specified assessment of severity and relationship study drug
- Date of resolution of the event
- Seriousness
- Any required treatment or actions
- Outcome
- Whether or not it caused the subject to discontinue the study drug.
- Whether or not the AE is an Injection Site Reaction (ISR). ISR is defined as any AE that occurs at the study drug injection site. If an ISR is observed, the subject may be treated at the discretion of the investigator.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the condition deteriorates at any time during the study, it should be recorded as an AE.

6.4.3.1 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of a list of signs and

symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.3.2 Adverse Events Based on Examinations and Tests

If an abnormal laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical rather than the laboratory term (e.g., anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically significant findings on examinations and tests should be reported as AEs.

Any new or aggravated clinically significant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4.3.3 Pericarditis Disease Related Events

Signs, symptoms, and abnormal findings associated with pericarditis are to be captured as a pericarditis recurrence event rather than as an AE unless the event is more severe than expected for the subject. In any case, pericarditis recurrence is required to be captured in the eCRF (see Section 6.2.3) within 24 hours of learning of the event.

6.4.4 Time Period for Collection of Adverse Events

Adverse events will be assessed from the time the subjects signs the ICF and through the duration of the study, or at least through the SFU period (6 weeks after the last dose of study drug).

6.4.5 Follow-Up of Unresolved Adverse Events

Every reasonable effort will be made to follow subjects who have AEs.

Any AEs that are unresolved at the subject's SFU visit are to be followed up by the investigator until resolution or for as long as medically indicated. Additional information for any subject with an ongoing AE at the end of the SFU period may be requested by the [redacted] PHV, as needed.

6.4.6 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.4.1.3) must be reported to the [redacted] PHV using the EDC system, immediately (i.e., within 24 hours) after the time site personnel first learn about the event.

In the event the EDC entry is not possible (e.g., system failure or access problems), the study site should complete the paper SAE report form and fax the form to the [redacted] PHV within 24 hours of awareness. The EDC system should be updated as soon as it is available.

A full description of every SAE will need to be provided to the [redacted] PHV (this may be supported by source documentation such as discharge summary or laboratory report should these documents be

requested by the [redacted] PHV). Additional follow-up information, if required or available, should be sent to the [redacted] PHV as soon as possible and placed with the original SAE information.

The following contact information is to be used for SAE reporting:

[redacted]

Information on non-serious AEs that become serious must also be reported to the [redacted] PHV as soon as it is available.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as applicable per institutional policy.

The Sponsor or designee will provide regulatory authorities, IRBs, IECs, and principal investigators with clinical safety updates/reports according to local requirements.

6.4.6.1 Other Reasons for Immediate Reporting

The following events require reporting to the [redacted] PHV within 24 hours after the time the site personnel first learn about the event:

- Pregnancy in subject or female partner of male subject
- Overdose of the study drug or concomitant medication, regardless of whether it is considered AE
- Other study drug errors
- Any AE of malignancy (excluding basal cell carcinoma of the skin)

6.4.7 Pregnancy

Pregnancy is regarded as an AE only if there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. Nonetheless, any pregnancy that occurs during study participation (including pregnancy in a female partner of a male subject) must be reported to the [redacted] PHV in the same way and using the same procedures as for an SAE (Section 6.4.6). The subject with pregnancy must not receive (additional) study drug. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriage must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study, and considered by the investigator as possibly related to the study drug, must be promptly reported to the [redacted] PHV.

In the event that a subject is found to be pregnant after having received at least 1 study drug dose, the study drug must be discontinued, and the pregnancy will be followed to term and the status of mother and child will be reported to the [redacted] PHV after delivery. Instances of perinatal death or congenital abnormality, if brought to the attention of the investigator at any time after cessation of study drug, will be reported to the [redacted] PHV within 24 hours.

6.4.8 Evaluating and Reporting SUSARs

[redacted] Pharmacovigilance will promptly evaluate all SUSARs and nonserious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, [redacted] PHV staff in collaboration with Kiniksa Pharmaceuticals will assess the expectedness of these events using the Reference Safety Information (Section 6.2) of the rilonacept Investigator's Brochure.

[redacted] PHV will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by [redacted] PHV and Kiniksa Pharmaceuticals as needed.

All relevant information about suspected SUSARs that are fatal or life-threatening will be recorded and reported to the competent authorities in all the applicable countries, and IRBs/IECs in conjunction with Directive 2001/20/EC.

6.5 Other Assessments

6.5.1 Pharmacokinetic Sample

All subjects will have PK samples obtained according to the Study Schedule of Activities. For PK analyses, it is important that the exact time of the SC injection is recorded for each subject. When PK samples are to be collected on dosing days, serum will be collected pre-dose to measure rilonacept concentrations. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

A PK substudy will be conducted in a subset of subjects agreeing to provide a PK sample 24 hours after the first dose of study drug in the RI period. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

6.5.2 Anti-Drug Antibodies (ADAs) against Rilonacept (KPL-914)

Serum samples to measure the presence of ADAs against rilonacept will be collected according to the Study Schedule of Activities. Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the site.

6.5.3 Biomarkers

Serum and plasma will be collected according to the Study Schedule of Activities for biomarker analysis.

6.5.4 Pharmacogenomics

Whole blood will be collected for pharmacogenomics assessments after signing the separate Pharmacogenomics ICF.

6.6 Laboratory Analyses

Any abnormal laboratory test results (hematology, chemistry, or urinalysis) or other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

Laboratory assessments will be performed at study visits as summarized in Study Schedule of Activities. Unscheduled laboratory assessments for safety issues are permitted as deemed necessary by the investigator.

Whenever possible in pediatric subjects, local laboratory tests should be drawn using pediatric tubes.

6.6.1 Serology

Samples for local laboratory assessment of hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and HIV test will be collected at screening. If clinically indicated, those tests may be also collected during the study.

6.6.2 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.

6.6.3 Chemistry

Blood chemistry tests performed in the central study laboratory include albumin, total protein, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, total bilirubin, bicarbonate, chloride, potassium, sodium, creatinine, glucose.

In addition, the following chemistry tests may be performed together with local CRP measurement when using POC device: chloride, creatine kinase, creatinine, glucose, potassium, sodium, total carbon dioxide, blood urea nitrogen.

6.6.4 Non-fasting Lipid Panel

Subjects treated with rilonacept may experience increases in their lipids, including total cholesterol, LDL, 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 Study Schedule of Activities.

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.

6.6.5 Urinalysis

Urinalysis performed by the central study laboratory includes specific gravity, pH, protein, urobilinogen, ketones, glucose, blood, bilirubin, nitrites, leukocyte esterase. It will be performed as described in the Study Schedule of Activities.

6.6.6 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. The purpose of pregnancy test is to prevent embryo/fetal exposure to study drug. Subjects with positive or indeterminate pregnancy test during the screening are not eligible for the study.

6.6.7 Sample Collection

The procedures for the collection, handling, and shipment of laboratory samples are specified in the Laboratory Manual supplied to sites by the central laboratory.

6.7 Committees

6.7.1 Independent Data Monitoring Committee (DMC)

A DMC will be utilized in this study to ensure external objective medical and/or statistical (if needed) review of safety data in order to protect the ethical and safety interests of subjects. The DMC will review unblinded aggregate (and, where necessary, individual) subject safety data at pre-defined intervals according to a DMC charter. The analysis plan for the DMC review will be described in the DMC charter, which will also contain details of the composition and the responsibilities of the DMC.

6.7.2 Clinical Endpoint Committee (CEC)

An independent CEC will review and adjudicate all suspected recurrent pericarditis events that occur during the RW period of the study. The procedures for adjudicating events will be described in the CEC Charter. This will be done independent of the investigators, and in a manner blinded to treatment assignment. The CEC will complete assessments on an ongoing basis.

7 Statistical and Analytical Plan

7.1 Primary Efficacy Endpoint

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.

A sensitivity analysis will be done based on the investigator's assessment of the event.

Pericarditis recurrence is defined in Section 6.2.3.

Subjects who do not have a pericarditis recurrence will be censored at the date of the last available assessment during the RW period before data cutoff. Detailed censoring rules will be specified in the Statistical Analysis Plan (SAP).

7.2 Secondary Efficacy Endpoints for the RW Period

This Section defines secondary efficacy endpoints for the RW period. Endpoints for the RI period and for the LTE-TP are defined in Section 7.3.

7.2.1 Major Secondary Efficacy Endpoints

1. Proportion of subjects who maintained Clinical Response at Week 24 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.
2. Percentage of days with no or minimal pain in the first 24 weeks of the RW period. No or minimal pain is defined as non-missing NRS ≤1.
3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period.

7.2.2 Other Secondary Endpoints

All time-to-event endpoints start from the day of randomization. The following variables will be analyzed:

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

- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)
- Number (percentage) of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in EQ-5D-5L. There are 6 questions in this instrument (Section 6.2.1.8). Each of the first 5 questions has 5 levels, from level 1 (best) to level 5 (worst). They are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The sixth question is the health on the day, from 0 (the worst) to 100 (the best) (van Reenen and Janssen 2015). The levels of the first 5 questions (EQ-5D-5L profile) will be converted to an index value. Change from baseline in each one of these 7 values will be an endpoint.
- Change over time in subject's sleep quality assessed with the ISI (Section 6.2.1.9). There are 7 items in the ISI. Change in ISI total score, which is the sum of the 7 items over time, will be the endpoint.
- Change over time in ISI categories. The ISI total scores are divided to 4 categories:
  - 0–7 = No clinically significant insomnia
  - 8–14 = Subthreshold insomnia
  - 15–21 = Clinical insomnia (moderate severity)
  - 22–28 = Clinical insomnia (severe)
- Number (percentage) of subjects who receive sequential ORT for pericarditis (analgesics, NSAIDs, and/or colchicine) in the RW period

7.3 Other Endpoints

These include efficacy endpoints in the RI period and the LTE-TP. Since there is no control arm in these 2 periods, only descriptive statistics will be provided. All time-to-event endpoints start from the day of receiving rilonacept in that period.

7.3.1 Efficacy Endpoints for the RI Period

The following efficacy endpoints are included in this period:

- Proportion of subjects who achieved Clinical Response at the RI Week 12/RW baseline visit. Clinical Response is defined as a weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS and CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.
- Time to CRP normalization (≤0.5 mg/dL)
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12
- Change from baseline in CRP level at RI Week 12
- Resolution of ECHO and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L (Section 7.2.2 contains details about calculation)
- Change over time in the subject's sleep quality assessed with the ISI (Section 7.2.2 contains details about calculation)
- Change over time in ISI categories
- Number (percentage) of subjects who were off background pericarditis medication at RI Week 12

7.3.2 Efficacy Endpoints for the LTE-TP

The efficacy endpoints below are included in this period. Each endpoint will be summarized through Week 24, by subjects who did and did not have an adjudicated pericarditis recurrence in the RW period, respectively, and overall:

- Number (percentage) of subjects with pericarditis recurrences
- Proportion of subjects with Clinical Response
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain
- Percentage of days with no or minimal pain
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS

- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L (Section 7.2.2 contains details about calculation)
- Change over time in the subject's sleep quality assessed with the ISI (Section 7.2.2 contains details about calculation)
- Change over time in ISI categories
- Number (percentage) of subjects requiring addition of SOC pericarditis therapy

7.4 Sample Size Calculations

For the purpose of sample size estimation, 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) 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.

Patient 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 patients 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 patients may be enrolled and/or randomized at Kiniksa Pharmaceutical's discretion. However, at this time it is anticipated that no more than 75 subjects will be enrolled into this study. Since the data cutoff will be the event date of the 22nd adjudicated pericarditis recurrence AND all subjects still in the RW period have been treated for 24 weeks, the actual power could be higher if the assumed hazard ratio holds.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

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

Safety Analysis Set: 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.

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

Per-protocol Analysis Set: The per protocol (PP) analysis set is a subset of the ITT analysis set with the exclusion of subjects with major 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.

Pharmacokinetic Analysis Set: The PK analysis set includes subjects who receive at least 1 dose of study drug and have at least 1 PK sample. The PK analysis set will be used for all PK analyses.

7.6 Description of Subgroups to be Analyzed

Subgroup analyses for the primary endpoint will be performed by the stratification variable for randomization, as well as by important variables for baseline demographics and patient characteristics. These analyses are for the RW period only. Details will be provided in the SAP.

7.7 Statistical Analysis Methodology

This Section outlines the overall methodologies. Details of the statistical analyses, methods, and data conventions will be described in the SAP.

7.7.1 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 each of RI and RW periods and in the LTE-TP, 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.

7.7.2 Stratified Analysis

There will be 2 stratification variables for randomization:

- Oral CS use at RI baseline: yes or no
- Diagnosis of recurrent idiopathic pericarditis at RI baseline: yes or no

When a stratified analysis is used in the analysis and a stratum has no event of interest or no responder, the stratum will be pooled with the other stratum in the same stratification variable.

7.7.3 Testing Hypotheses and Multiplicity Adjustment

All statistical tests for the treatment comparison of efficacy endpoints in the RW period will be based on the ITT analysis set with 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 $\leq$0.025, a significant treatment effect on the primary endpoint will be claimed.

Section 7.2.1 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 24 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 $\leq$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 7.2.1 will be tested with Hochberg's procedure at overall 1-sided α=0.025. If both 1-sided unadjusted p-values are $\leq$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 $\leq$0.0125, claim significance of rilonacept on this endpoint.

7.7.4 Analysis of Primary Efficacy Endpoint

Primary analysis of this study will be done after 22nd CEC-confirmed pericarditis recurrence AND after all subjects in the RW period have been treated for 24 weeks. The log rank test will be the primary method for the analysis of time to recurrence, stratified by the stratification variables for randomization.

A sensitivity analysis will be performed based on the investigator's judgement of pericarditis recurrence. Additional sensitivity may be defined in the SAP.

7.7.5 Analysis of Secondary Efficacy Endpoints

7.7.5.1 Analysis of the Major Secondary Endpoints

1. Proportion of subjects who maintained Clinical Response at Week 24 of the RW period (defined as a weekly average of daily pericarditis pain ≤2.0 on the 11-point NRS and CRP ≤0.5 mg/dL at Week 24). The Cochran–Mantel–Haenszel (CMH) test will be used in this analysis, stratified by the stratification variables for randomization.
2. Percentage of days with minimal or no pain in the first 24 weeks post randomization. Minimal or no pain is defined as non-missing daily NRS ≤1. This endpoint will be analyzed with an analysis of covariance. In addition to treatment arm, the following covariates will be included in this analysis: the stratification variables for randomization, and baseline NRS weekly average in 2 categories: NRS ≤1 versus NRS >1.
3. Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 24 of the RW period. The CMH test will be used in this analysis, stratified by the stratification variables for randomization.

7.7.5.2 Analyses of Other Secondary Endpoints in the RW Period

The following endpoints will be analyzed using the same method for the primary endpoint:

- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO

A mixed model with repeated measures (MMRM) will be used in the analysis of the endpoints below. 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, and the variables for stratification at randomization. The p-value for treatment comparison will be calculated at each scheduled assessment for at least 24 weeks as part of the summary statistics. This is done with the understanding that the comparison could be biased due to dropouts or subjects with pericarditis recurrence.

- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L: Health score and Index value, respectively

- Change over time in the subject's sleep quality: sum of the ISI scores.

The CMH test will be used in the analysis of the endpoints below, stratified by the stratification variables for randomization.

- Proportion of patients without pericarditis recurrence in the first 24 weeks of the RW period
- Number (percent) of subjects with absent or minimal pericarditis activity based on the investigator's assessment
- Number (percentage) of subjects who receive SOC pericarditis therapy in the RW period

The following endpoints will be analyzed using the Mantel-Haenszel test with 1 degree of freedom:

- Change in each 1 of the first 5 questions in the EQ-5D-5L, i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
- Change over time in ISI categories

[redacted]

7.7.6 Analyses of Other Endpoints

Endpoints listed in Section 7.3 for the RI period and the LTE-TP will be descriptive in nature since there is no control arm. Summary statistics will be generated following the methodologies stated in Section 7.7.

Other analyses include anti-rilonacept antibodies and biomarker analyses. These analyses will be described in the SAP.

7.7.7 Pharmacokinetic Analyses

For all subjects, serum samples will be collected at time points shown in the Study Schedule of Activities in order to quantify concentrations of rilonacept. Descriptive statistics will be calculated for the serum concentrations of rilonacept by visit. Individual listings of serum concentrations will be provided.

Pharmacokinetic data may be used in a subsequent population PK evaluation that will be conducted outside of this study and described in a separate report.

7.7.8 Safety Analyses

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 the most recent version of MedDRA. TEAEs will be analyzed for all subjects combined and by treatment group in the RW period. Further analyses by severity and relationship to study drug as well as analyses of serious TEAEs will be presented.

Descriptive statistics will be used to summarize safety endpoints by visit for all subjects combined in the RI period and by treatment group in the RW period. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for clinical laboratory analyses (including safety laboratory measurements, ADAs, etc.), vital signs measurements, ECGs, and physical examination findings.

7.7.9 Interim Analyses

No interim analyses are planned for this study.

8 Data Quality Assurance

Assessment of subject compliance and adherence to study drug administration will be assessed by the site in collaboration with the visiting RN.

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management (ICH Q9).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

[redacted] will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant Standard Operating Procedures (SOPs) of [redacted]

Investigative site personnel will enter subject data into an EDC system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After the last study database lock, each study site will receive a CD-ROM containing all of their site

specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a Master DVD/CD-ROM copy of all of the site data from the study will be created and sent to Kiniksa for storage. [redacted] will maintain a duplicate Master DVD/CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to Kiniksa Pharmaceuticals.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Regulatory agencies and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, informed assent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by Kiniksa Pharmaceutical or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply Kiniksa Pharmaceutical or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Subject Information and Consent

A written informed consent in compliance approved by an IRB/IEC, as appropriate, at each center/country shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent for (or assent form, as applicable) template may be provided by Kiniksa Pharmaceutical or its designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by Kiniksa Pharmaceutical or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before screening, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

It should be emphasized to the subjects that they may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

For potential subjects under the age of 18, a parent or legal guardian is required to sign and date the ICF and the potential subject is also required to sign and date an informed assent form. The informed assent form explains the trial, it's purpose, procedures as well as risk and benefits in age-appropriate language. Both the ICF and informed assent form, as applicable, are required prior to participation in the trial. The investigator shall retain the signed original ICF(s)/assent form(s), as applicable, and give a copy of the signed original form to the subject or legal guardian.

For this study subjects will be required to sign and date the ICF (or assent form, if applicable) prior to entry to the study and prior to entry to LTE.

In addition, a separate ICF (assent, if applicable) will be needed for subjects participating in pharmacogenomic testing.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on local or country-specific industry and government standard operating procedures, working practice documents, or guidelines.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by Kiniksa Pharmaceuticals, its designee, the regulatory agencies/authorities, or the IRB/IEC.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Kiniksa Pharmaceuticals or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Kiniksa Pharmaceuticals or its designee to submit the complete and accurate certification or disclosure statements required under US Title 21 Code of Federal Regulations (CFR) Part 54. In addition, the investigator must provide to Kiniksa Pharmaceuticals a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 or local country-specific equivalent for outside the US
- Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572 or local country-specific equivalent for outside the US
- Financial disclosure information
- IRB/IEC-approved ICFs/assent forms, as applicable, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to [redacted] and/or IRB/IEC according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and Kiniksa Pharmaceuticals and regulatory authority(ies) with any reports required.

10.8 Records Retention

It is the responsibility of the investigator to ensure all essential trial documentation and source records (e.g., signed ICFs, study site/clinic files, subjects' hospital notes, copies of eCRFs) at their site are securely retained. The Sponsor will inform the investigator of the time periods for retaining study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations; otherwise, the retention period by default will be 15 years.

10.9 Publications

Kiniksa shall have the sole and exclusive right to publish information obtained from the study, including any data, results, and conclusions. Investigators are encouraged to participate in the study execution such that they may be invited to participate in the authorship of a potential publication in a manner commensurate with their participation in the study execution in accordance with International Committee of Medicinal Journal Editors standards. Any publication of the results will be subject to the terms and conditions provided in the study agreement.

11 Study Management

The administrative structure will include a Data Monitoring Committee (DMC) and a Clinical Endpoint Committee (CEC). Please refer to Section 6.7 for further details.

11.1 Monitoring

11.1.1 Monitoring of the Study

Data for each subject will be recorded in source records and in the eCRF. Data collection must be completed for each subject who signs an ICF.

For each subject enrolled, the investigator or designee will document in the source records of the subject that the subject is enrolled in this study along with all safety and efficacy information. The investigator is responsible for maintaining adequate case histories in the source records of each subject. Source data

should be preserved for the maximum period of time permitted by the hospital/institution and made available by the investigator in the cases described above.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow Kiniksa Pharmaceuticals, representatives of Kiniksa Pharmaceuticals, or a regulatory agency(ies) access to all study records.

The investigator should promptly notify Kiniksa Pharmaceuticals and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Kiniksa Pharmaceuticals and [redacted]

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Sponsor initiated amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval and to the regulatory authorities, if required, before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is any change, divergence, or departure from the study design or procedures defined in the protocol. No waivers will be granted for exemptions to inclusion/exclusion criteria. The Investigator will conduct the study in compliance with the protocol agreed to with the Sponsor and, if required, the regulatory authorities, and which was given approval/favorable opinion by the IRB/IEC. In the event of a protocol deviation, the Sponsor or a designee must be notified.

The Investigator, or person designated by the Investigator, must document and explain any deviation from the approved protocol. The Investigator will notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

11.3 Study Termination

Although Kiniksa Pharmaceuticals has every intention of completing the study, Kiniksa Pharmaceuticals reserves the right to discontinue the study at any time in case of safety concerns (e.g., SUSARs) or if special circumstances concerning the study drug or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, Kiniksa Pharmaceutical will ensure that the clinical study report(s) are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified to approve the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, Kiniksa Pharmaceutical will provide the investigator(s) with the full summary of the study results. The investigator(s) are encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers, as applicable.

12 Reference List

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13 Appendices

13.1 Appendix: ARCALYST® Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARCALYST safely and effectively. See full prescribing information for ARCALYST.

ARCALYST® (rilonacept)
Injection for Subcutaneous Use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. (1)

DOSAGE AND ADMINISTRATION

- Adult patients 18 yrs and older: Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg on the same day at two different sites. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. Do not administer ARCALYST more often than once weekly. (2)
- Pediatric patients aged 12 to 17 years: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. Do not administer ARCALYST more often than once weekly. (2)

DOSAGE FORMS AND STRENGTHS

Sterile, single-use 20-mL, glass vial containing 220 mg of rilonacept as a lyophilized powder for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Interleukin-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking ARCALYST. Discontinue treatment with ARCALYST if a patient develops a serious infection. Do not initiate treatment with ARCALYST in patients with active or chronic infections. (5.1)
- Hypersensitivity reactions associated with ARCALYST administration have been rare. If a hypersensitivity reaction occurs, discontinue administration of ARCALYST and initiate appropriate therapy. (5.5)
- Live vaccines should not be given concurrently with ARCALYST. Prior to initiation of therapy with ARCALYST, patients should receive all recommended vaccinations. (5.3)

ADVERSE REACTIONS

The most common adverse reactions reported by patients with CAPS treated with ARCALYST are injection-site reactions and upper respiratory tract infections. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-REGN-777 (1-877-734-6777) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with ARCALYST. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy – No human data. Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2016

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARCALYST® (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Injection for Subcutaneous Use Only.

2.2 Dosing

Adult patients 18 years and older: Treatment should be initiated with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg each given on the same day at two different sites. Dosing should be continued with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. ARCALYST should not be given more often than once weekly. Dosage modification is not required based on advanced age or gender.

Pediatric patients aged 12 to 17 years: Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. ARCALYST should not be given more often than once weekly.

2.3 Preparation for Administration

Each single-use vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection (supplied separately) is required prior to subcutaneous administration of the drug.

2.4 Administration

Using aseptic technique, withdraw 2.3 mL of preservative-free Sterile Water for Injection through a 27-gauge, ½-inch needle attached to a 3-mL syringe and inject the preservative-free Sterile Water for Injection into the drug product vial for reconstitution. The needle and syringe used for reconstitution with preservative-free Sterile Water for Injection should then be discarded and should not be used for subcutaneous injections. After the addition of preservative-free Sterile Water for Injection, the vial contents should be reconstituted by shaking the vial for approximately one minute and then allowing it to sit for one minute. The resulting 80-mg/mL solution is sufficient to allow a withdrawal volume of up to 2 mL for subcutaneous administration. The reconstituted solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Prior to injection, the reconstituted solution should be carefully

inspected for any discoloration or particulate matter. If there is discoloration or particulate matter in the solution, the product in that vial should not be used.

Using aseptic technique, withdraw the recommended dose volume, up to 2 mL (160 mg), of the solution with a new 27-gauge, ½-inch needle attached to a new 3-mL syringe for subcutaneous injection. EACH VIAL SHOULD BE USED FOR A SINGLE DOSE ONLY. Discard the vial after withdrawal of drug.

Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard.

2.5 Stability and Storage

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be protected from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded.

3 DOSAGE FORMS AND STRENGTHS

ARCALYST is supplied in sterile, single-use, 20-mL, glass vials. Each vial contains 220 mg of rilonacept as a white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted ARCALYST is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Interleukin-1 (IL-1) blockade may interfere with the immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking ARCALYST [*see Clinical Studies (14)*]. There was a greater incidence of infections in patients on ARCALYST compared with placebo. In the controlled portion of the study, one infection was reported as severe, which was bronchitis in a patient on ARCALYST.

In an open-label extension study, one patient developed bacterial meningitis and died [*see Adverse Reactions (6.3)*]. ARCALYST should be discontinued if a patient develops a serious infection. Treatment with ARCALYST should not be initiated in patients with an active or chronic infection.

In clinical studies, ARCALYST has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of

an IL-1 blocker in combination with TNF inhibitors. **Taking ARCALYST with TNF inhibitors is not recommended because this may increase the risk of serious infections.**

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as ARCALYST that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ARCALYST.

5.2 Immunosuppression

The impact of treatment with ARCALYST on active and/or chronic infections and the development of malignancies is not known [*see Adverse Reactions (6.3)*]. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.

5.3 Immunizations

Since no data are available on either the efficacy of live vaccines or on the risks of secondary transmission of infection by live vaccines in patients receiving ARCALYST, live vaccines should not be given concurrently with ARCALYST. In addition, because ARCALYST may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ARCALYST. No data are available on the effectiveness of vaccination with inactivated (killed) antigens in patients receiving ARCALYST.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ARCALYST adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current Recommended Immunizations schedules at the website of the Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/schedules/index.html).

5.4 Lipid Profile Changes

Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted [*see Adverse Reactions (6.7)*].

5.5 Hypersensitivity

Hypersensitivity reactions associated with ARCALYST administration in the clinical studies were rare. If a hypersensitivity reaction occurs, administration of ARCALYST should be discontinued and appropriate therapy initiated.

6 ADVERSE REACTIONS

Six serious adverse reactions were reported by four patients during the clinical program. These serious adverse reactions were *Mycobacterium intracellulare* infection; gastrointestinal bleeding and colitis; sinusitis and bronchitis; and *Streptococcus pneumoniae* meningitis [*see Adverse Reactions (6.3)*].

The most commonly reported adverse reaction associated with ARCALYST was injection-site reaction (ISR) [*see Adverse Reactions (6.2)*]. The next most commonly reported adverse reaction was upper respiratory infection [*see Adverse Reactions (6.3)*].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described herein reflect exposure to ARCALYST in 600 patients, including 85 exposed for at least 6 months and 65 exposed for at least one year. These included patients with CAPS, patients with other diseases, and healthy volunteers. Approximately 60 patients with CAPS have been treated weekly with 160 mg of ARCALYST. The pivotal trial population included 47 patients with CAPS. These patients were between the ages of 22 and 78 years (average 51 years). Thirty-one patients were female and 16 were male. All of the patients were White/Caucasian. Six pediatric patients (12-17 years) were enrolled directly into the open-label extension phase.

6.1 Clinical Trial Experience

Part A of the clinical trial was conducted in patients with CAPS who were naïve to treatment with ARCALYST. Part A of the study was a randomized, double-blind, placebo-controlled, six-week study comparing ARCALYST to placebo [*see Clinical Studies (14)*]. Table 1 reflects the frequency of adverse events reported by at least two patients during Part A.

Table 1: Most Frequent Adverse Reactions (Part A, Reported by at Least Two Patients)

Adverse Event	**ARCALYST 160 mg (n = 23)**	**Placebo (n= 24)**
Any AE	17 (74%)	13 (54%)
Injection-site reactions	11 (48%)	3 (13%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Nausea	1 (4%)	3 (13%)
Diarrhea	1 (4%)	3 (13%)
Sinusitis	2 (9%)	1 (4%)
Abdominal pain upper	0	2 (8%)
Cough	2 (9%)	0
Hypoesthesia	2 (9%)	0
Stomach discomfort	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)

6.2 Injection-Site Reactions

In patients with CAPS, the most common and consistently reported adverse event associated with ARCALYST was injection-site reaction (ISR). The ISRs included erythema, swelling, pruritus, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth and hemorrhage. Most injection-site reactions lasted for one to two days. No ISRs were assessed as severe, and no patient discontinued study participation due to an ISR.

6.3 Infections

During Part A, the incidence of patients reporting infections was greater with ARCALYST (48%) than with placebo (17%). In Part B, randomized withdrawal, the incidence of infections were similar in the ARCALYST (18%) and the placebo patients (22%). Part A of the trial was initiated in the winter months, while Part B was predominantly performed in the summer months.

In placebo-controlled studies across a variety of patient populations encompassing 360 patients treated with rilonacept and 179 treated with placebo, the incidence of infections was 34% and 27% (2.15 per patient-exposure year and 1.81 per patient-exposure year), respectively, for rilonacept and placebo.

Serious Infections: One patient receiving ARCALYST for an unapproved indication in another study developed an infection in his olecranon bursa with *Mycobacterium intracellulare*. The patient was on chronic glucocorticoid treatment. The infection occurred after an intraarticular glucocorticoid injection into the bursa with subsequent local exposure to a suspected source of mycobacteria. The patient recovered after the administration of the appropriate antimicrobial therapy. One patient treated for another unapproved indication developed bronchitis/sinusitis, which resulted in hospitalization. One patient died in an open-label study of CAPS from *Streptococcus pneumoniae* meningitis.

6.4 Malignancies

[*see Warnings and Precautions (5.2)*].

6.5 Hematologic Events

One patient in a study in an unapproved indication developed transient neutropenia (ANC < 1 x 10^9/L) after receiving a large dose (2000 mg intravenously) of ARCALYST. The patient did not experience any infection associated with the neutropenia.

6.6 Immunogenicity

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST. Nineteen of 55 patients (35%) who had received ARCALYST for at least 6 weeks tested positive for treatment-emergent binding antibodies on at least one occasion. Of the 19, seven tested positive at the last assessment (Week 18 or 24 of the open-label extension period), and five patients tested positive for neutralizing antibodies on at least one occasion. There was no correlation of antibody activity and either clinical effectiveness or safety.

The data reflect the percentage of patients whose test results were positive for antibodies to the rilonacept receptor domains in specific assays, and are highly dependent on the sensitivity and specificity of the assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is

highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to rilonacept with the incidence of antibodies to other products may be misleading.

6.7 Lipid Profiles

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with ARCALYST experienced increases in their mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were 19 mg/dL, 2 mg/dL, 10 mg/dL, and 57 mg/dL respectively after 6 weeks of open-label therapy. Physicians should monitor the lipid profiles of their patients (for example after 2-3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

7 DRUG INTERACTIONS

7.1 TNF-Blocking Agent and IL-1 Blocking Agent

Specific drug interaction studies have not been conducted with ARCALYST. Concomitant administration of another drug that blocks IL-1 with a TNF-blocking agent in another patient population has been associated with an increased risk of serious infections and an increased risk of neutropenia. The concomitant administration of ARCALYST with TNF-blocking agents may also result in similar toxicities and is not recommended [*see Warnings and Precautions (5.1)*]. The concomitant administration of ARCALYST with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of ARCALYST and other agents that block IL-1 or its receptors is not recommended.

7.2 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of ARCALYST, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of ARCALYST in pregnant women. Based on animal data, ARCALYST may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15 or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human doses of 160 mg based on body

surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100 or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). ARCALYST should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nonteratogenic effects. A peri- and post-natal reproductive toxicology study was performed in which mice were subcutaneously administered a murine analog of rilonacept at doses of 20, 100, 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F_1 offspring during maturation at all doses tested.

8.3 Nursing Mothers

It is not known whether rilonacept is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARCALYST is administered to a nursing woman.

8.4 Pediatric Use

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with ARCALYST at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24-weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g. Serum Amyloid A and C-Reactive Protein). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult patients.

The trough drug levels for four pediatric patients measured at the end of the weekly dose interval (mean 20 mcg/mL, range 3.6 to 33 mcg/mL) were similar to those observed in adult patients with CAPS (mean 24 mcg/mL, range 7 to 56 mcg/mL).

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

When administered to pregnant primates, rilonacept treatment may have contributed to alterations in bone ossification in the fetus. It is not known if ARCALYST will alter bone development in pediatric patients. Pediatric patients treated with ARCALYST should undergo appropriate monitoring for growth and development. [*see Use in Specific Populations (8.1)*]

8.5 Geriatric Use

In the placebo-controlled clinical studies in patients with CAPS and other indications, 70 patients randomized to treatment with ARCALYST were ≥ 65 years of age, and 6 were ≥ 75 years of age. In the CAPS clinical trial, efficacy, safety and tolerability were generally similar in elderly patients as compared to younger adults; however, only ten patients ≥ 65 years old participated in the trial. In an open-label extension study of CAPS, a 71 year old woman developed bacterial meningitis and died [*see Adverse*

Reactions (6.3)]. Age did not appear to have a significant effect on steady-state trough concentrations in the clinical study.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

There have been no reports of overdose with ARCALYST. Maximum weekly doses of up to 320 mg have been administered subcutaneously for up to approximately 18 months in a small number of patients with CAPS and up to 6 months in patients with an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, ARCALYST given intravenously at doses up to 2000 mg monthly in another patient population for up to six months were tolerated without dose-limiting toxicities. The maximum amount of ARCALYST that can be safely administered has not been determined.

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

ARCALYST is supplied in single-use, 20-mL glass vials containing a sterile, white to off-white, lyophilized powder. Each vial of ARCALYST is to be reconstituted with 2.3 mL of Sterile Water for Injection. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for subcutaneous administration only. The resulting solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Each vial contains 220 mg rilonacept. After reconstitution, each vial contains 80 mg/mL rilonacept, 46 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5 ± 0.3. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-

inflammatory Syndrome-1 [*CIAS1*]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

In most cases, inflammation in CAPS is associated with mutations in the NLRP-3 gene which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation.

Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1 receptor antagonist (IL-1ra) with reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.

12.2 Pharmacodynamics

C-Reactive Protein (CRP) and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Compared to placebo, treatment with ARCALYST resulted in sustained reductions from baseline in mean serum CRP and SAA to normal levels during the clinical trial. ARCALYST also normalized mean SAA from elevated levels.

12.3 Pharmacokinetics

The average trough levels of rilonacept were approximately 24 mcg/mL at steady-state following weekly subcutaneous doses of 160 mg for up to 48 weeks in patients with CAPS. The steady-state appeared to be reached by 6 weeks.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

No study was conducted to evaluate the effect of age, gender, or body weight on rilonacept exposure. Based on limited data obtained from the clinical study, steady state trough concentrations were similar between male and female patients. Age (26-78 years old) and body weight (50-120 kg) did not appear to have a significant effect on trough rilonacept concentrations. The effect of race could not be assessed because only Caucasian patients participated in the clinical study, reflecting the epidemiology of the disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of rilonacept. The mutagenic potential of rilonacept was not evaluated.

Male and female fertility was evaluated in a mouse surrogate model using a murine analog of rilonacept. Male mice were treated beginning 8 weeks prior to mating and continuing through female gestation day 15. Female mice were treated for 2 weeks prior to mating and on gestation days 0, 3, and 6. The murine analog of rilonacept did not alter either male or female fertility parameters at doses up to 200 mg/kg (this dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

14 CLINICAL STUDIES

The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS.

Part A was a 6-week, randomized, double-blind, parallel-group period comparing ARCALYST at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all patients received ARCALYST 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on ARCALYST 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with ARCALYST 160 mg weekly.

Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment.

The changes in mean symptom scores for the randomized parallel-group period (Part A) and the randomized withdrawal period (Part B) of the study are shown in Table 2. ARCALYST-treated patients had a larger reduction in the mean symptom score in Part A compared to placebo-treated patients. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on ARCALYST.

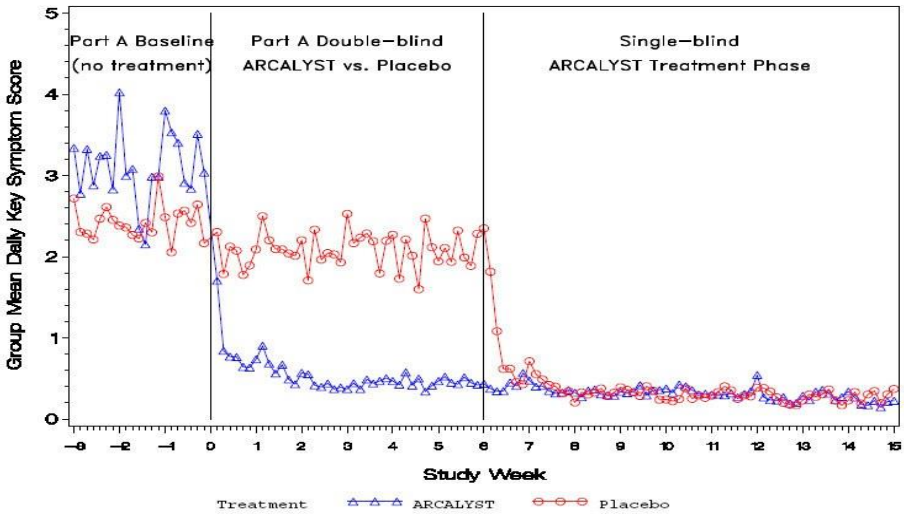
Table 2: Mean Symptom Scores

Part A	Placebo (n=24)	ARCALYST (n=23)	Part B	Placebo (n=23)	ARCALYST (n=22)
Pre-treatment Baseline Period (Weeks -3 to 0)	2.4	3.1	Active ARCALYST Baseline Period (Weeks 13 to 15)	0.2	0.3
Endpoint Period (Weeks 4 to 6)	2.1	0.5	Endpoint Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment groups	(-1.3, -0.4)**	

*Differences are adjusted using an analysis of covariance model with terms for treatment and Part A baseline.
**A confidence interval lying entirely below zero indicates a statistical difference favoring ARCALYST versus placebo.

Daily mean symptom scores over time for Part A are shown in Figure 1.

Figure 1: Group Mean Daily Symptom Scores by Treatment Group in Part A and Single-blind ARCALYST Treatment Phase from Week -3 to Week 15



Improvement in symptom scores was noted within several days of initiation of ARCALYST therapy in most patients.

In Part A, patients treated with ARCALYST experienced more improvement in each of the five components of the composite endpoint (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) than placebo-treated patients.

In Part A, a higher proportion of patients in the ARCALYST group experienced improvement from baseline in the composite score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%) and by at least 75% (70% vs. 0%) compared to the placebo group.

Serum Amyloid A (SAA) and C-Reactive Protein (CRP) levels are acute phase reactants that are typically elevated in patients with CAPS with active disease. During Part A, mean levels of CRP decreased versus baseline for the ARCALYST treated patients, while there was no change for those on placebo (Table 3). ARCALYST also led to a decrease in SAA versus baseline to levels within the normal range.

Table 3. Mean Serum Amyloid A and C-Reactive Protein Levels Over Time in Part A

Part A	ARCALYST	Placebo
SAA (normal range: 0.7 – 6.4 mg/L)	(n=22)	(n=24)
Pre-treatment Baseline	60	110
Week 6	4	110
CRP (normal range: 0.0 – 8.4 mg/L)	(n= 21)	(n=24)
Pre-treatment Baseline	22	30
Week 6	2	28

During the open-label extension, reductions in mean symptom scores, serum CRP, and serum SAA levels were maintained for up to one year.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each 20-mL glass vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. ARCALYST is supplied in a carton containing four vials (NDC 61755-001-01).

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be kept from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded. Discard the vial after a single withdrawal of drug.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

The first injection of ARCALYST should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer ARCALYST, he/she should be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously should be assessed to ensure proper administration of ARCALYST, including rotation of injection sites. (*See Patient Information Leaflet for ARCALYST®*). ARCALYST should be reconstituted with preservative-free Sterile Water for Injection to be provided by the pharmacy. A puncture-resistant container for disposal of vials, needles and syringes should be used. Patients or caregivers should be instructed in proper vial, syringe, and needle disposal, and should be cautioned against reuse of these items.

Injection-site Reactions: Physicians should explain to patients that almost half of the patients in the clinical trials experienced a reaction at the injection site. Injection-site reactions may include pain, erythema, swelling, pruritus, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Patients should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Infections: Patients should be cautioned that ARCALYST has been associated with serious, life-threatening infections, and not to initiate treatment with ARCALYST if they have a chronic or active infection. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ARCALYST. Treatment with ARCALYST should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ARCALYST, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ARCALYST with other IL-1 blocking agents, such as anakinra, is not recommended.

Vaccinations: Prior to initiation of therapy with ARCALYST physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ARCALYST.

REGENERON

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Regeneron Pharmaceuticals, Inc.

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V 5.0

Patient Information

ARCALYST® (ARK-a-list)

(rilonacept)

Injection for Subcutaneous Use

Read the patient information that comes with ARCALYST before you start taking it and each time you refill your prescription. There may be new information. The information in this leaflet does not take the place of talking with your healthcare provider about your medical condition and your treatment.

What is the most important information I should know about ARCALYST?

ARCALYST can affect your immune system. ARCALYST can lower the ability of your immune system to fight infections. Serious infections, including life-threatening infections and death have happened in patients taking ARCALYST. **Taking ARCALYST can make you more likely to get infections, including life-threatening serious infections, or may make any infection that you have worse.**

You should not begin treatment with ARCALYST if you have an infection or have infections that keep coming back (chronic infection).

After starting ARCALYST, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have any open sores on your body, call your healthcare provider right away. **Treatment with ARCALYST should be stopped if you develop a serious infection.**

You should not take medicines that block Tumor Necrosis Factor (TNF), such as Enbrel® (etanercept), Humira® (adalimumab), or Remicade® (infliximab), while you are taking ARCALYST. You should also not take other medicines that block Interleukin-1 (IL-1), such as Kineret® (anakinra), while taking ARCALYST. Taking ARCALYST with any of these medicines may increase your risk of getting a serious infection.

Before starting treatment with ARCALYST, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as fever, cough, or flu-like symptoms
- have any open sores on your body
- have a history of infections that keep coming back
- have asthma. Patients with asthma may have an increased risk of infection.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis.
- have or have had HIV, Hepatitis B, or Hepatitis C
- take other medicines that affect your immune system

Before you begin treatment with ARCALYST, talk with your healthcare provider about your vaccination history. Ask your healthcare provider whether you should receive any vaccinations, including pneumonia vaccine and flu vaccine, before you begin treatment with ARCALYST.

What is ARCALYST?

ARCALYST is a prescription medicine called an interleukin-1 (IL-1) blocker. ARCALYST is used to treat adults and children 12 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle Wells Syndrome (MWS). ARCALYST can help lessen the signs and symptoms of CAPS, such as rash, joint pain, fever, and tiredness, but it can also lead to serious side effects because of the effects on your immune system.

What should I tell my healthcare provider before taking ARCALYST?

ARCALYST may not be right for you. **Before taking ARCALYST, tell your healthcare provider about all of your medical conditions, including if you:**

- are scheduled to receive any vaccines. You should not receive live vaccines if you take ARCALYST.
- are pregnant or planning to become pregnant. It is not known if ARCALYST will harm your unborn child. Tell your healthcare provider right away if you become pregnant while taking ARCALYST.
- are breast-feeding or planning to breast-feed. It is not known if ARCALYST passes into your breast milk.

See "What is the most important information I should know about ARCALYST?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take other medicines that affect your immune system, such as:

- other medicines that block IL-1, such as Kineret® (anakinra).
- medicines that block Tumor Necrosis Factor (TNF), such as Enbrel® (etanercept), Humira® (adalimumab), or Remicade® (infliximab).
- corticosteroids.

See "What is the most important information I should know about ARCALYST?"

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist every time you get a new prescription.

If you are not sure or have any questions about any of this information, ask your healthcare provider.

How should I take ARCALYST?

See the "Patient Instructions for Use" at the end of this leaflet.

- Take ARCALYST exactly as prescribed by your healthcare provider.
- ARCALYST is given by injection under the skin (subcutaneous injection) one time each week.
- Your healthcare provider will tell and show you or your caregiver:
    - how much ARCALYST to inject
    - how to prepare your dose
    - how to give the injection
- Do not try to give ARCALYST injections until you are sure that you or your caregiver understands how to prepare and inject your dose. Call your healthcare provider or pharmacist if you have any questions about preparing and injecting your dose, or if you or your caregiver would like more training.
- If you miss a dose of ARCALYST, inject it as soon as you remember, up to the day before your next scheduled dose. The next dose should be taken at the next regularly scheduled time. If you have any questions, contact your healthcare provider.
- If you accidentally take more ARCALYST than prescribed, call your healthcare provider.

What are the possible side effects of ARCALYST?

Serious side effects may occur while you are taking and after you finish taking ARCALYST including:

- **Serious Infections. See "What is the most important information I should know about taking ARCALYST?"** Treatment with ARCALYST should be discontinued if you develop a serious infection.
- **Allergic Reaction.** Call your healthcare provider or seek emergency care right away if you get any of the following symptoms of an allergic reaction while taking ARCALYST:
  - rash
  - swollen face
  - trouble breathing

Common side effects with ARCALYST include:

- **Injection-site reaction**. This includes: pain, redness, swelling, itching, bruising, lumps, inflammation, skin rash, blisters, warmth, and bleeding at the injection site.
- **Upper respiratory infection.**
- **Changes in your blood cholesterol and triglycerides (lipids).** Your healthcare provider will check you for this.

These are not all the possible side effects of ARCALYST. Tell your healthcare provider about any side effects that bother you or that do not go away. For more information ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ARCALYST?

- Keep ARCALYST in the carton it comes in.
- Store ARCALYST in a refrigerator between 36°F to 46°F (2°C to 8°C). Call your pharmacy if you have any questions.
- Always keep ARCALYST away from light.
- Refrigerated ARCALYST can be used until the expiration date printed on the vial and carton.
- ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing**.** Keep ARCALYST away from light.
- If you need to take ARCALYST with you when traveling, store the carton in a cool carrier with a cold pack and protect it from light.

Keep ARCALYST, injection supplies, and all other medicines out of reach of children.

What are the ingredients in ARCALYST?

Active ingredient: rilonacept.

Inactive ingredients: histidine, arginine, polyethylene glycol 3350, sucrose, and glycine.

General Information about ARCALYST

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use ARCALYST for a condition for which it was not prescribed. Do not give ARCALYST to other people even if they have the same condition. It may harm them.

This leaflet summarizes the most important information about ARCALYST. If you would like more information, speak with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ARCALYST that was written for healthcare professionals. For more information about ARCALYST, call 1-877-REGN-777 (1-877-734-6777), or visit www.ARCALYST.com.

Patient Instructions for Use

It is important for you to read, understand and follow the instructions below exactly. Following the instructions correctly will help to make sure that you use, prepare and inject the medicine the right way to prevent infection.

How do I prepare and give an injection of ARCALYST?

STEP 1: Setting up for an injection

1. Choose a table or other flat surface area to set up the supplies for your injection. Be sure that the area is clean or clean it with an antiseptic or soap and water first.
2. Wash your hands well with soap and water, and dry with a clean towel.
3. Put the following items on a table, or other flat surface, for each injection (see Figure 1):

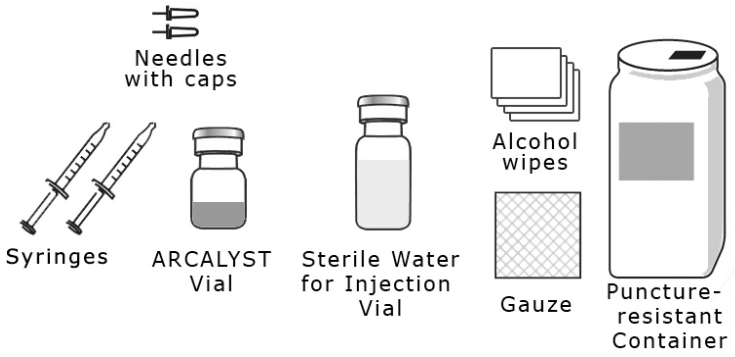

Figure 1

- 2 sterile, 3-milliliter (mL) disposable syringes with markings at each 0.1 mL (see Figure 2):
    - one needed for mixing (reconstitution) ARCALYST
    - one needed for injection

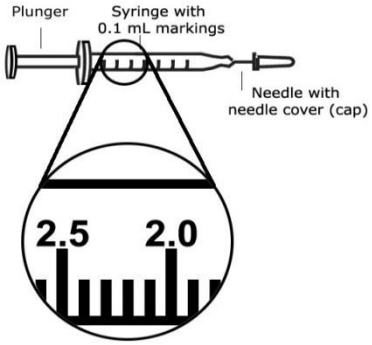

Figure 2

- 2 sterile disposable needles (27-gauge, ½-inch)
    - one needed for mixing
    - one needed for injection
- 4 alcohol wipes
- 1 2x2 gauze pad
- 1 vial of ARCALYST (powder in vial)
- 1 vial of preservative-free Sterile Water for Injection
- 1 puncture-resistant container for disposal of used needles, syringes, and vials

Note:

- Do not use Sterile Water for Injection, syringes or needles other than those provided by your pharmacy. Contact your pharmacy if you need replacement syringes or needles.
- Do not touch the needles or the rubber stoppers on the vials with your hands. If you do touch a stopper, clean it with a fresh alcohol wipe.
- If you touch a needle or the needle touches any surface, throw away the entire syringe into the puncture-resistant container and start over with a new syringe.
- **Do not reuse needles or syringes.**

- To protect yourself and others from possible needle sticks, it is very important to throw away every syringe, with the needle attached, in the puncture proof container right after use. ***Do not try to recap the needle.***

STEP 2: Preparing Vials

1. Check the expiration date on the carton of ARCALYST. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
2. Check the expiration date on the vial of Sterile Water for Injection. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
3. Remove the protective plastic cap from both vials.
4. Clean the top of each vial with an alcohol wipe. Use one wipe for each vial and wipe in one direction around the top of the vial (see Figure 3).

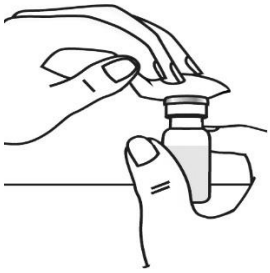

Figure 3

5. Open the wrapper that contains the 27-gauge needle by pulling apart the tabs and set it aside for later use. Do not remove the needle cover. This needle will be used to mix the water with powder. Open the wrapper that contains the syringe by pulling apart the tabs. Hold the barrel of the syringe with one hand and twist the 27-gauge needle onto the tip of the syringe until it fits snugly with the other hand (see Figure 4).

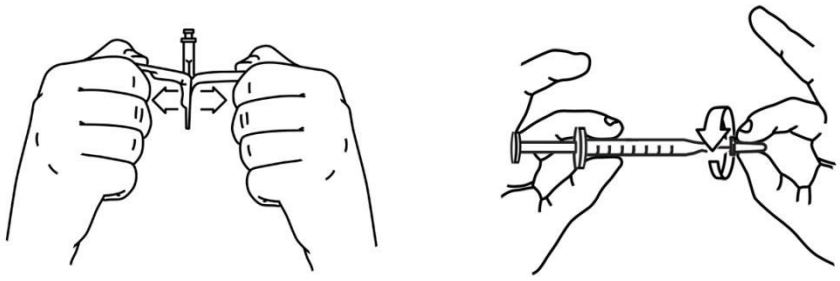

Figure 4

6. Hold the syringe at eye level. With the needle covered pull back the plunger to the 2.3 mL mark, filling the syringe with air (see Figure 5).

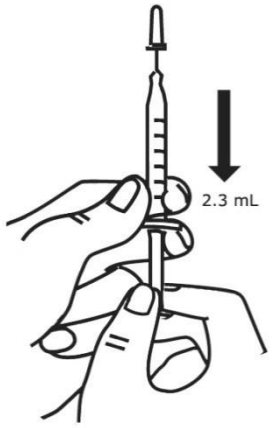

Figure 5

7. Hold the syringe in one hand, use the other hand to pull the needle cover straight off. Do not twist the needle as you pull off the cover. Place the needle cover aside. Hold the syringe in the hand that you will use to mix (reconstitute) your medicine. Hold the Sterile Water vial on a firm surface with your other hand. Slowly insert the needle straight through the rubber stopper. Do not bend the needle. Push the plunger in all the way to push the air into the vial (see Figure 6).

Figure 6

8. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up.
9. Make sure the tip of the needle is covered by the liquid and slowly pull back on the plunger to the 2.3 mL mark to withdraw the Sterile Water from the vial (see Figure 7).

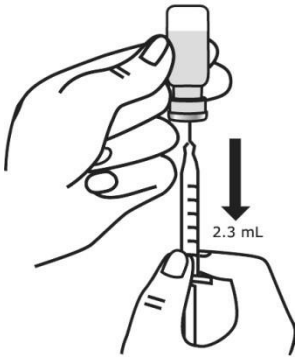

Figure 7

10. Keep the vial upside down and tap or flick the syringe with your fingers until any air bubbles rise to the top of the syringe.
11. To remove the air bubbles, gently push in the plunger so only the air is pushed out of the syringe and back into the bottle.
12. After removing the bubbles, check the syringe to be sure that the right amount of Sterile Water has been drawn into the syringe (see Figure 8).

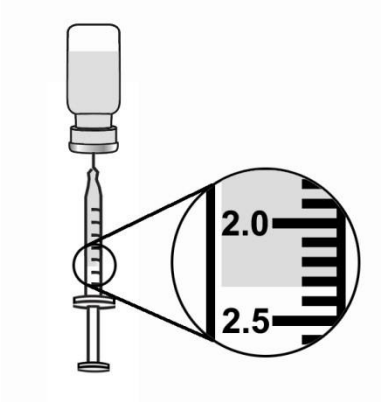

Figure 8

13. Carefully remove the syringe with needle from the Sterile Water vial. Do not touch the needle.

STEP 3: Mixing (Reconstituting) ARCALYST

1. With one hand, hold the ARCALYST vial on a firm surface.

2. With the other hand, take the syringe with the Sterile Water and the same needle, and slowly insert the needle straight down through the rubber stopper of the ARCALYST vial. Push the plunger in all the way to inject the Sterile Water into the vial.
3. Direct the water stream to gently go down the side of the vial into the powder (see Figure 9).

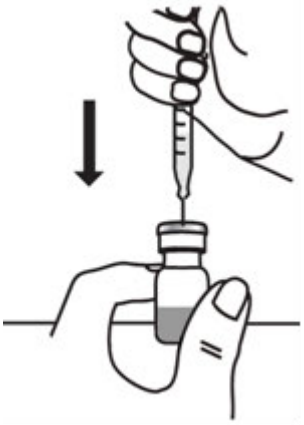

Figure 9

4. Remove the syringe and needle from the stopper and throw away the needle, syringe, and Sterile Water vial in the puncture-resistant container. Do not try to put the needle cover back on the needle.
5. Hold the vial containing the ARCALYST and sterile water for injection sideways (not upright) with your thumb and a finger at the top and bottom of the vial, and quickly shake the vial back and forth (side-to-side) for about 1 minute (see Figure 10).

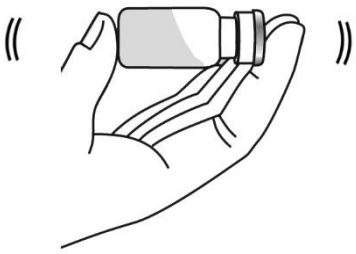

Figure 10

6. Put the vial back on the table and let the vial sit for about 1 minute.
7. Look at the vial for any particles or clumps of powder which have not dissolved.

8. If the powder has not completely dissolved, shake the vial quickly back and forth for 30 seconds more. Let the vial sit for about 1 minute.
9. Repeat Step 8 until the powder is completely dissolved and the solution is clear.
10. The mixed ARCALYST should be thick, clear, and colorless to pale yellow. Do not use the mixed liquid if it is discolored or cloudy, or if small particles are in it (see Figure 11).

    NOTE: Contact your pharmacy to report any mixed ARCALYST that is discolored or contains particles.

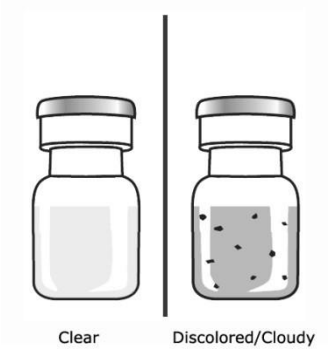

Figure 11

11. ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing. Keep ARCALYST away from light.

STEP 4: Preparing the injection

1. Hold the ARCALYST vial on a firm surface and wipe the top of the ARCALYST vial with a new alcohol wipe (see Figure 12).

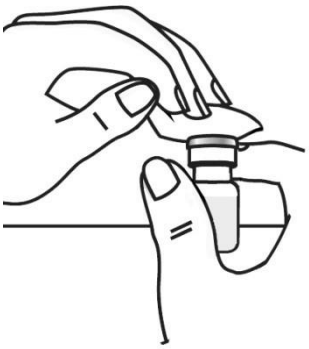

Figure 12

2. Take a new sterile, disposable needle and attach securely to a new syringe without removing the needle cover (see Figure 13).

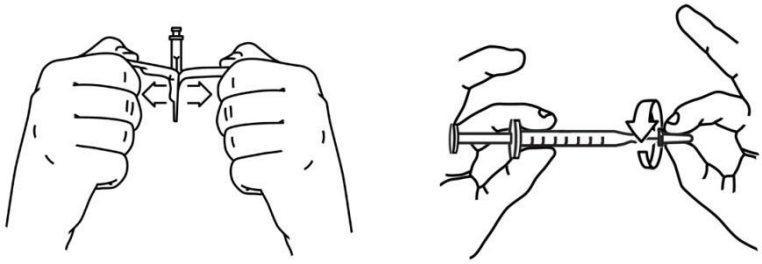

Figure 13

3. The amount of air you draw into the syringe should equal the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject.
4. To draw air into the syringe, hold the syringe at eye level. Do not remove the needle cover. Pull back the plunger on the syringe to the mark that is equal to the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject (see Figure 14).

Figure 14

5. Remove the needle cover and be careful not to touch the needle. Keep the ARCALYST vial on a flat surface and slowly insert the needle straight down through the stopper. Push the plunger down and inject all the air into the vial (see Figure 15).

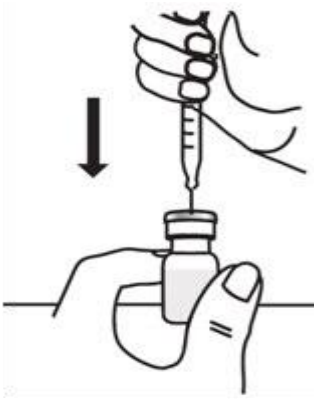

Figure 15

6. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up. Hold the vial at eye level.
7. Keep the tip of the needle in the liquid and slowly pull back on the plunger to the mark on the syringe that matches the amount of medicine prescribed by your healthcare provider (see Figure 16).

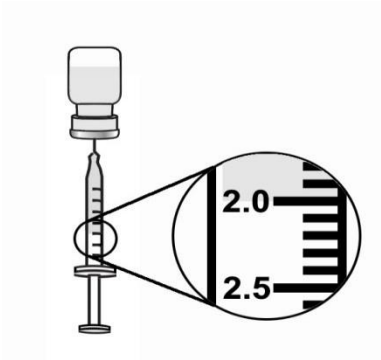

Figure 16

NOTE: The maximum adult dose of ARCALYST is 2 mL.

8. Keep the vial upside down with the needle straight up, and gently tap the syringe until any air bubbles rise to the top of the syringe (see Figure 17).

   It is important to remove air bubbles so that you withdraw up the right amount of medicine from the vial.

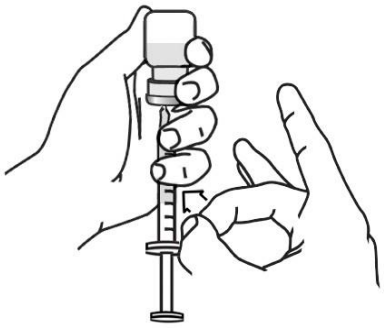

Figure 17

9. To remove the air bubbles, slowly and gently push in the plunger so only the air is pushed through the needle.
10. Check to make sure that you have the amount of medicine prescribed by your healthcare provider in the syringe.
11. Throw away the ARCALYST vial in the puncture-resistant container even if there is any medicine left in the vial (see Figure 18). Do not use any vial of ARCALYST more than one time.

Figure 18

STEP 5: Giving the Injection

1. ARCALYST is given by subcutaneous injection, an injection that is given into the tissue directly below the layers of skin. It is not meant to go into any muscle, vein, or artery.

   You should change (rotate) the sites and inject in a different place each time in order to keep your skin healthy.

Rotating injection sites helps to prevent irritation and allows the medicine to be completely absorbed. Ask your healthcare provider any questions that you have about rotating injection sites.

- Do not inject into skin that is tender, red, or hard. If an area is tender or feels hardened, choose another site for injection until the tenderness or "hardening" goes away.
- Tell your healthcare provider about any skin reactions including redness, swelling, or hardening of the skin.
- Areas where you may inject ARCALYST include the left and right sides of the abdomen, and left and right thighs. If someone else is giving the injection, the upper left and right arms may also be used for injection (see Figure 19):

  (Do not inject within a 2-inch area around the navel)

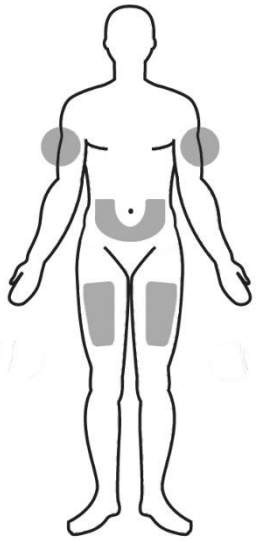

Figure 19

2. Choose the area for the injection. Clean the area in a circular motion with a new alcohol wipe. Begin at the center of the site and move outward. Let the alcohol air dry completely.
3. Take the cover off the needle and be careful not to touch the needle.
4. Hold the syringe in one hand like you would hold a pencil.
5. With the other hand gently pinch a fold of skin at the cleaned site for injection (see Figure 20).

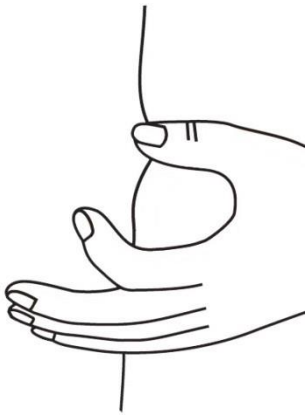

Figure 20

6. Use a quick "dart like" motion to insert the needle straight into the skin (90 degree angle) (see Figure 21). Do not push down on the plunger while inserting the needle into the skin.

   For small children or persons with little fat under the skin, you may need to hold the syringe and needle at a 45 degree angle (see Figure 21).

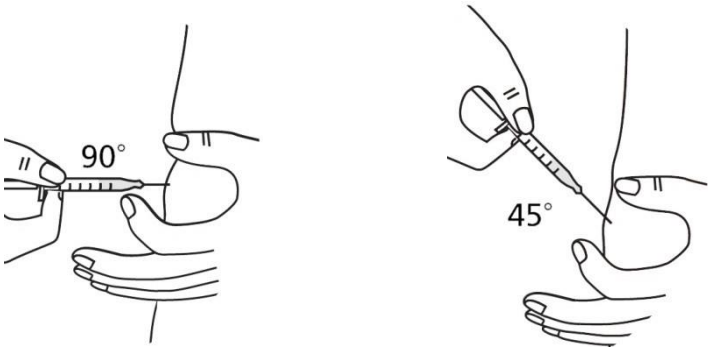

Figure 21

7. After the needle is completely in the skin, let go of the skin that you are pinching.
8. With your free hand hold the syringe near its base. Gently pull back the plunger. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle, discard the syringe and needle. Start over with "STEP 1: Setting up for an injection" using new supplies (syringes, needles, vials, alcohol swabs and gauze pad).
9. If no blood appears, inject all the medicine in the syringe at a slow, steady rate, pushing the plunger all the way down. It may take up to 30 seconds to inject the entire dose.
10. Pull the needle out of the skin, and hold a piece of sterile gauze over the injection site for several seconds (see Figure 22).

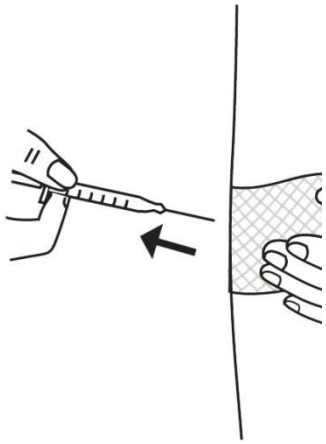

Figure 22

11. Do not replace the needle cover. Throw away the vials, used syringes and needles in the puncture-resistant container (see Figure 23). Do not recycle the container. DO NOT throw away vials, needles, or syringes in the household trash or recycle.

Figure 23

12. Keep the puncture-resistant container out of reach of children. When the container is about two-thirds full, dispose of it as instructed by your healthcare provider. Follow any special state or local laws about the right way to throw away needles and syringes.
13. Used alcohol wipes can be thrown away in the household trash.

Contact your healthcare provider right away with any questions or concerns about ARCALYST.

Notes: 1. Enbrel®, Humira®, Kineret®, and Remicade®, respectively, are trademarks of Immunex Corporation, AbbVie Biotechnology Ltd., Amgen Inc., and Janssen Biotech, Inc., respectively.

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V 4.0

13.2 Appendix: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Subjects will be asked to select the score that best describes their average level of pericarditis pain over the previous 24 hours using an 11-point NRS, where zero (0) indicates 'no pain' and ten (10) means indicates 'pain as bad as it could be'.

On this scale of 0-10, zero (0) indicates 'no pain' and ten (10) indicates 'pain as bad as it could be', please rate your pericarditis pain on average in the last 24 hours

Kiniksa Pharmaceuticals, Ltd

Protocol KPL-914-C002

Amendment 1 Summary of Changes

Version 1.1. 05 October 2018 to Version 2.0 dated 12 Apr 2019

Rationale for Amendment

This is an amendment to revise one of the criteria for permanent study drug discontinuation, add baseline PK drug level measurement, remove the 10 subject cap in the cardiac MRI substudy, revise full physical examination text, revise statement on FDA Form 1572 outside the US, and correct minor inconsistencies among the protocol synopsis and protocol text, and among protocol text and Informed Consent and Investigators Brochure. In addition, Kiniksa study contacts were updated to reflect changes in study personnel.

Table 1 lists the modifications made in Amendment 1 along with the rationale for each change.

Minor editorial changes for improved readability are not included in the table.

Table 1 List of Changes

Change	Section	Current Text	Revised Text	Rationale
1	KPL-914-C002	[redacted]	[redacted] m	Update reflects changes in Kiniksa study personnel.
2	Study Synopsis	**Study Pharmacokinetic or Pharmacodynamic Assessments:** Pharmacokinetic or pharmacodynamic assessments will include: • PK analysis • Anti-rilonacept antibodies • Biomarkers • Peripheral blood mononuclear cell isolation (for subjects who sign the separate informed consent for pharmacogenomics assessments)	**Study Pharmacokinetic or Pharmacodynamic Assessments:** Pharmacokinetic or pharmacodynamic assessments will include: • PK analysis • Anti-rilonacept antibodies • Biomarkers • Pharmacogenomics (for subjects who sign the separate informed consent for pharmacogenomics assessments)	Text in the 4th bullet (Pharmacogenomics) in the synopsis was updated to remove "peripheral blood mononuclear cells isolation" for consistency with main protocol. Collection of nucleated cells for DNA isolation is stipulated in the protocol as a "whole blood for pharmacogenomics assessment."

Change	Section	Current Text	Revised Text	Rationale
3	Table 1-1 Study Schedule of Activities-Screening and Run-In Period (Part 1 of 2) Table 1-2 Study Schedule of activities-Randomized Withdrawal (part 1 of 2) Table 1-3 Study Schedule of Activities-Long Term Extension (Part 1 of 2) Table 1-4 Study Schedule of Activities-Supplemental Visits (Part 1 of 2)	Footnotes: [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.	Footnotes: [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 judgment.	Change was done to allow genitourinary system examination to be performed as a part of full physical examination, based on clinical judgement.
	6.3.1 Physical Examination	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.	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 judgment.	

Change	Section	Current Text	Revised Text	Rationale
4	1.3.1 Safety of Rilonacept	**Malignancies** The impact of treatment with rilonacept on the development of malignancies is not known. However, treatment with immunosuppressants, including rilonacept, may result in an increase in the risk for malignancies.	**Malignancies** Although malignancies have been reported in some subjects treated with rilonacept during clinical trials, the effect of rilonacept on the development of cancer is not known. Treatment with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies.	Change was done to coordinate the protocol content with current Informed Consent and Investigator Brochure content.

Change	Section	Current Text	Revised Text	Rationale
5	4.2.2.1 Discontinuation of Study Drug	The study drug dosing will be permanently stopped if any of the following occurs: • The subject develops a serious or intolerable AE, TB, or malignancy, excluding non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma • Initiation of protocol-prohibited medication (Section 5.8.6) • Subject requires treatment with CS for pericarditis during RW or LTE-TP periods of the study • Pregnancy or pregnancy planned during the study or within 3 months after the last study drug administration • ALT or AST values ≥3 × ULN associated with total bilirubin ≥2 × ULN, with no underlying medical conditions to explain the elevated values • Treatment with a live (attenuated) vaccine during the study • Investigator or Sponsor's medical monitor or [redacted] medical monitor decides that, for safety reasons, it is in the subject's best interest • Termination of the study by Kiniksa Pharmaceuticals Permanent or temporary study drug discontinuation should be strongly considered at the time if any of the following occurs: • Subject develops an opportunistic infection. • Subject develops moderate or severe infection • Neutrophil count <1.0 × 103/µL • Isolated ALT or AST values >5 × ULN • Surgical procedure	The study drug dosing will be permanently stopped if any of the following occurs: • The subject develops TB or malignancy, excluding non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma • Initiation of protocol-prohibited medication (Section 5.8.6) • Subject requires treatment with CS for pericarditis during RW or LTE-TP periods of the study • Pregnancy or pregnancy planned during the study or within 3 months after the last study drug administration • ALT or AST values ≥3 × ULN associated with total bilirubin ≥2 × ULN, with no underlying medical conditions to explain the elevated values • Treatment with a live (attenuated) vaccine during the study • Investigator or Sponsor's medical monitor or [redacted] medical monitor decides that, for safety reasons, it is in the subject's best interest • Termination of the study by Kiniksa Pharmaceuticals Permanent or temporary study drug discontinuation should be strongly considered at the time if any of the following occurs: • Subject develops an opportunistic infection • Subject develops moderate or severe infection • Neutrophil count <1.0 × 103/µL • Isolated ALT or AST values >5 × ULN • Surgical procedure	First bullet was modified to remove: - requirement for permanent study drug discontinuation for any SAE. This is done to avoid stopping the drug in case of hospitalization for recurrent pericarditis or other events which would otherwise not require study drug discontinuation - requirement for permanent study drug discontinuation for intolerable AE, as this concept is covered in bullet #7 where it's stated that Investigator or Sponsor's medical monitor or [redacted] medical monitor can decide that discontinuation of study drug for safety reasons is in the subject's best interest

Change	Section	Current Text	Revised Text	Rationale
6	6.1 Study Visits	Subjects can be brought to the clinic in place of a scheduled outpatient visit or for an unscheduled visit at the discretion of the investigator.	Subjects can be brought to the clinic in place of a scheduled outpatient visit or for an unscheduled visit at the discretion of the investigator or if arranging a visiting nurse for an at-home visit is logistically not feasible.	The statement was added to allow clinic visit in case arranging a nurse home visit is logistically not feasible.
7	6.1.2.1 Enrollment (Run-In Baseline): Clinic Visit	• Obtain central laboratory chemistry, hematology, lipid panel, CRP, anti-drug antibodies (ADAs), biomarkers, and urinalysis (laboratory tests should be drawn prior to the first study drug administration, but results of those tests are not required before enrollment).	• Obtain central laboratory chemistry, hematology, lipid panel, CRP, anti-drug antibodies (ADAs [ADA sample will be also used for PK measurement]), biomarkers, and urinalysis (laboratory tests should be drawn prior to the first study drug administration, but results of those tests are not required before enrollment).	Statement added that Run-In Baseline ADA sample will be also used for PK measurement.
8	6.1.2.7 RI Week 6: Clinic Visit	Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur: • Have the subject administer the next scheduled injection of study drug (if within the study drug window) and have the subject record in the medication diary. • Dispense study drug through the IWRS and record the amount (number of vials) dispensed. • Review the study drug dosing schedule, administration techniques, and documentation.	Upon completion of the above study activities, the study drug dispensing can commence. The following procedures occur: • Dispense study drug through the IWRS and record the amount (number of vials) dispensed. • Have the subject administer the next scheduled injection of study drug (if within the study drug window) and have the subject record in the medication diary. • Review the study drug dosing schedule, administration techniques, and documentation.	First and second bullet were switched to clarify order of procedures. Site should dispense study drug through the IWRS prior to the subject administering the next injection of study drug.

Change	Section	Current Text	Revised Text	Rationale
9	6.2 Efficacy Assessments	In a substudy at selected sites in approximately 10 subjects, a cardiac MRI will be performed.	In a substudy at selected sites, a cardiac MRI will be performed.	Removed the limitation of 10 subjects in the MRI substudy.
10	10.3 Investigator Documentation	• Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572	• Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572 or local country-specific equivalent for outside the US	Added statement that in lieu of FDA1572 Form, outside the US, a local country-specific equivalent of 1572 Form can be used.

CLINICAL STUDY PROTOCOL

PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY WITH OPEN-LABEL EXTENSION, TO ASSESS THE EFFICACY AND SAFETY OF RILONACEPT TREATMENT IN SUBJECTS WITH RECURRENT PERICARDITIS – **R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY** **(RHAPSODY)**

AMENDMENT #2; PROTOCOL VERSION 3.0 10 MARCH 2020

IND: 136,896

EudraCT: 2018-002719-87

CONFIDENTIALITY STATEMENT

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KPL-914-C002

Sponsor:	[redacted]
Sponsor Study Contact:	[redacted]
Sponsor Medical Contact:	[redacted]
Medical Monitor:	[redacted]
Protocol Version:	Amendment 2 / Version 3.0
	(Supersedes Version 2.0 dated 12 April 2019)
Protocol Date:	10 March 2020

PROTOCOL APPROVAL - SPONSOR SIGNATORY

Protocol Number:	KPL-914-C002
Protocol Title:	Phase 3, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study with Open-Label Extension, to Assess the Efficacy and Safety of Rilonacept Treatment in Subjects with Recurrent Pericarditis (RHAPSODY)
Protocol Version:	Amendment 2 / Version 3.0 (Supersedes Version 2.0 dated 12 April 2019)
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[redacted]

Signature

Date

PROTOCOL APPROVAL – LEAD STATISTICIAN

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Protocol accepted and approved by:

Lead Statistician

[redacted]

Signature

Date

DECLARATION OF INVESTIGATOR

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I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation (ICH) Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.
- I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Kiniksa Pharmaceuticals.

Signature of Investigator:

_____ _____

Signature Date

Name, academic qualification _____

Position (job title) _____

Address of Institution _____

Phone, fax, email information _____

PROTOCOL SYNOPSIS

Protocol Number:	KPL-914-C002
Title:	Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis
Study Acronym:	RHAPSODY **(R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY)**
Sponsor:	[redacted]
Study Phase:	3
Study Sites:	Multicenter, global
Indication:	Recurrent pericarditis

Study Rationale:

Recurrent pericarditis is a rare autoinflammatory condition with no approved therapies. Current treatments, utilizing nonspecific inhibitors of inflammation (nonsteroidal anti-inflammatory drugs [NSAIDs], colchicine, corticosteroids [CS]), result in significant morbidity with chronic use. Some patients develop CS dependency or require surgical pericardiectomy to treat the symptoms of their disease.

The interleukin-1 (IL-1) pathway plays a major role in the pathophysiology of recurrent pericarditis. Rilonacept (KPL-914) is a recombinant fusion protein that blocks IL-1 signaling. It is currently approved for treatment of another autoinflammatory condition, Cryopyrin-Associated Periodic Syndrome (CAPS). Based on its IL-1–antagonistic properties and pharmacokinetics (PK), which allow for once-weekly subcutaneous (SC) injections, it is reasonable to evaluate the efficacy and safety of rilonacept in subjects with recurrent pericarditis to address the unmet need in treatment of this disease.

Study Objectives:

Primary Objective**:** To assess the efficacy of rilonacept treatment in subjects with recurrent pericarditis.

Secondary Objective: To assess the safety of rilonacept treatment in subjects with recurrent pericarditis.

Study Population:

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 prior pericarditis episodes (including the first episode and 1 recurrence). Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present at screening with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale (NRS) and C-reactive protein (CRP) value ≥1 mg/dL (either on the same day or separated by no more than 7 days) within 7 days prior to first study drug administration.

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to first administration of study drug, and that changes in medications made within this time period (for instance, 1-time use of NSAIDs) are not anticipated by the Investigator to significantly alter assessments of baseline disease activity.

Study Design:

This study has 4 periods:

(1) Screening period, during which assessment of disease characteristics, baseline therapy, and the pretreatment workup is completed (up to 4 weeks).

(2) Single-blind Run-In (RI) period (12 weeks), during which blinded rilonacept is administered SC once weekly in all subjects. 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 NRS within the 7 days prior to and including the day of randomization on RI Week 12/Randomization

Withdrawal (RW) baseline and a 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 LTE without having to proceed through the RW period.

(3) 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.

(4) 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 again 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 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 also 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 long-term extension by the Data Monitoring Committee.

Estimated Study Duration:

Subjects completing the randomized withdrawal period are projected to be dosed with rilonacept for a minimum of approximately 36 weeks and a maximum of 2 years based on enrollment assumptions and pericarditis recurrence events accrual time. Subjects who enter the long-term extension period will be dosed for up to 24-months longer.

Study Efficacy Assessments:

- Daily pericarditis pain on the 11-point NRS
- CRP level
- Electrocardiogram (ECG)
- Echocardiography (ECHO)
- Patient Global Impression of Pericarditis Severity (PGIPS)
- Physician Global Assessment of Pericarditis Activity (PGA-PA)
- 36-Item Short Form Health Survey (SF-36)
- 5-Level EuroQoL-5D (EQ-5D-5L)
- Insomnia Severity Index (ISI)
- Cardiac magnetic resonance imaging

Study Pharmacokinetic or Pharmacodynamic Assessments:

- PK analysis
- Anti-rilonacept antibodies
- Biomarkers
- Pharmacogenomics (for subjects who sign the separate informed consent for pharmacogenomics assessments)

Study Safety Assessments:

- Physical examination
- Vital signs measurements
- Adverse event (AE) monitoring
- Chest x-ray

- Tuberculosis screening
- Laboratory tests

Investigational Medicinal Product, Dosage, and Route of Administration:

Rilonacept (KPL-914) is a recombinant fusion protein consisting of the extracellular domains of human IL-1 cytokine receptor and the Fc portion of human immunoglobulin G1 (IgG1). It acts as a soluble decoy receptor binding IL-1α/IL-1β and prevents their interaction with the IL-1 cell-surface receptor.

Study drug (rilonacept or placebo) is supplied in a single use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml of placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

The first injection of rilonacept loading dose at the RI baseline visit will be administered at the study site by study site staff. The second injection of rilonacept loading dose at the RI baseline visit will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration.

Sample Size: Up to approximately 100 subjects with recurrent pericarditis will be enrolled, which will allow accrual of at least 22 adjudicated primary efficacy endpoint (pericarditis recurrence) events.

Statistical Methods: 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 efficacy analysis. A sensitivity analysis will be done based on the Investigator's assessment of the pericarditis recurrence.

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 efficacy endpoints.

<u>Major secondary efficacy endpoints for the RW period include:</u>

- Proportion of subjects who maintained Clinical Response at Week 16 of the RW period
- Percentage of days with no or minimal pain (pain ≤2 on the 11-point NRS) in the first 16 weeks of the RW period
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point rating scale of PGIPS) at Week 16 of the RW period

Other secondary efficacy endpoints for the RW period include:

- Proportions of subjects who maintained Clinical Response at Week 8 and Week 24 of the RW period, respectively
- Percentages of days with no or minimal pain (pain ≤2 on the 11-point NRS) in the first 8 weeks and 24 weeks of the RW period, respectively
- Proportions of subjects with absent or minimal pericarditis symptoms (based on the 7-point rating scale of PGIPS) at Week 8 and Week 24 of the RW period, respectively
- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST segment elevation or PR segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO
- Change in category of ECHO pericardial effusion size at week 24 and end of RW based on central labs
- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain (weekly average)
- Proportion of subjects with absent or minimal pericarditis activity based on Physician Global Assessment of Pericarditis Activity (PGA PA) over time
- Proportion of subjects with absent or minimal pericarditis activity over time based on the PGIPS over time
- Change over time in SF 36 Physical and Mental Component Scores and domain scores
- Changes in SF-6D, 6 domain scores and utility index
- Change in EQ-5D-5L individual scores and index value
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Cumulative number (percentage) of subjects who receive sequential ORT, prednisone, or bailout rilonacept for pericarditis every 4 weeks in the RW period

Efficacy endpoints for the RI period include:

- Time to pain response defined as a rolling average of NRS score of 2 or less on three consecutive days.
- Time to CRP normalization (≤0.5 mg/dL)
- Time to monotherapy

- Time to clinical response (monotherapy + NRS ≤2 + CRP ≤0.5 mg/dL)
- Proportion of subjects who achieved Clinical Response at the RI Week 12. Clinical Response is defined as reaching monotherapy on or before week 10 and a weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS and CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12 and over time
- Change from baseline in CRP level at RI Week 12 and over time
- Resolution of echocardiographic and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain (NRS≤2) while on treatment
- Proportion of subjects with absent or minimal pericarditis symptoms based on the PGIPS
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in SF-36 Physical and Mental Component Scores and domain scores
- Change in the SF-6D 6 domain scores and the utility index
- Change in EQ-5D-5L individual scores and index value
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who were off background pericarditis medication on or before weeks 4, 8, 10, and 12

The analysis for treatment comparison will be triggered after at least the 22nd CEC-confirmed pericarditis recurrence events have been accrued. At that time, randomization will be closed, and subjects will return to study sites for the EORW visit. At that point study treatment will stop (completing the database for the primary efficacy endpoint analysis), and subjects will either continue into the LTE or complete their study participation. Missing data due to end of RW period will be considered as missing at random. Handling of missing values will be described in the SAP.

Details of the analyses will be specified in the Statistical Analysis Plan.

Protocol Version and Date: Version 3.0 dated 10 March 2020

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Definition/ Explanation
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAPS	Cryopyrin Associated Periodic Syndrome
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CMH	Cochran–Mantel–Haenszel
CRP	C-reactive protein
CS	corticosteroids
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiography; echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EORW	End of Randomized-Withdrawal(visit)
EOS	End of Study
EOT	End of Treatment (visit)
EQ-5D-5L	5-level EuroQoL-5D
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form

Abbreviation or Specialist Term	Definition/ Explanation
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG1	human immunoglobulin G1
IGRA	Interferon Gamma Release Assay
IL-1	interleukin-1
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ISR	injection site reaction
ITT	intent to treat
IV	intravenous(ly)
IWRS	interactive web response system
KPL-914	rilonacept
LDL	low-density lipoprotein
LTE	Long Term Extension Treatment Period
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MWS	Muckle-Wells Syndrome
NSAID	nonsteroidal anti-inflammatory drug
NRS	Numerical Rating Scale
ORT	Oral Rescue Therapy
PHV	Pharmacovigilance
PGA-PA	Physician Global Assessment of Pericarditis Activity
PGIPS	Patient Global Impression of Pericarditis Severity
PK	pharmacokinetic(s)
POC	point of care
PRO	patient-reported outcome
RI	Run-In (period)
RN	visiting registered nurse
RW	Randomized-Withdrawal (period)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)

Abbreviation or Specialist Term	Definition/ Explanation
SF-36	36-Item Short Form Health Survey
SFU	safety follow-up
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TC	site telephone visit (telephone contact)
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell
WFI	Water for Injection

1. INTRODUCTION

Pericarditis is inflammation of the pericardium, the double-walled sac surrounding the heart. Etiologies of pericarditis include infectious causes (viral, bacterial, fungal, and parasitic) and non-infectious causes (idiopathic, autoimmune, neoplastic, metabolic, traumatic, post-surgical, and drug-related) (Adler et al 2015). In 80% of cases in developed countries, the cause of pericarditis is either post-viral or "idiopathic" in that it cannot be attributed to a specific condition (Imazio et al 2010; Zayas et al 1995).

The underlying pathogenesis of recurrent pericarditis remains unclear, although a growing body of evidence suggests that abnormal immune responses play a role in the pathogenic processes. While the adaptive immune system plays a role in autoimmune disorders that manifest with pericarditis as one of the many organ systems involved (such as in systemic lupus erythematosus or rheumatoid arthritis), the innate immune system, including interleukin-1 (IL-1) signaling, is often the major effector in autoinflammatory disorders, such as isolated pericarditis (Baskar et al 2016; Brucato et al 2016; Imazio et al 2016, Dinarello et al 2012).

Diagnosis of pericarditis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic changes, pericardial effusion, or elevated levels of inflammation markers (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Adler et al 2015). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define an acute pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rubs, new widespread ST-segment elevation or PR-segment depression based on electrocardiogram (ECG) findings, and pericardial effusion (new or worsening). Elevations of certain markers of inflammation (i.e., CRP, ESR, and WBC) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]) are used as supportive findings (Adler et al 2015).

Recurrent pericarditis is characterized by the recurrence of pericarditis signs and symptoms after a symptom-free period of at least 4 to 6 weeks (Adler et al 2015). Recurrent pericarditis affects 20% to 30% of patients with acute pericarditis (Imazio 2014) and can be debilitating for patients due to pain and limitations in physical function during pericarditis episodes. Pericarditis recurrences result in increased emergency room admissions and hospitalizations. In the United States, 5% of patients presenting to the emergency room with non-ischemic chest pain are diagnosed with pericarditis (Agarwal et al 2015).

The estimated prevalence of recurrent pericarditis in the US and Europe is 70,000 to 160,000 patients including approximately 8,000 to 21,000 patients who are refractory or intolerant to current therapies or who require long-term administration of corticosteroids (CS) to control their disease (Brucato et al 2016; Lazaros et al 2016; Imazio et al 2010; Khandaker et al 2010; Imazio et al 2008).

1.1. Current Therapeutic Management of Pericarditis

There are no approved therapies for the treatment of recurrent pericarditis. Current treatments include nonspecific inhibitors of inflammation, i.e., aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and CS (Lilly et al 2013).

Aspirin and other NSAIDs are the first-line approach. Because high doses of aspirin and NSAIDs are often required, consideration must be given to gastric protection therapy, as potential risks of therapy include stomach ulcers and gastrointestinal (GI) bleeding, as well as renal and cardiovascular toxicity. Colchicine is another mainstay therapy for pericarditis and is commonly used with NSAIDs to hasten the response to NSAIDs and reduce the risk of subsequent recurrences. However, its use may be associated with the risk of fatal overdosing, significant drug interactions, and neuromuscular toxicity. In addition, approximately 10% to 15% of patients experience significant GI side effects with colchicine, including GI intolerance or severe diarrhea, requiring treatment discontinuation (Imazio et al 2016).

Available ESC guidelines stipulate that CS should be prescribed for the management of pericarditis episodes only in cases of incomplete response, intolerance, or contraindications to NSAIDs and colchicine because of their unfavorable long-term benefit-risk profile. Corticosteroid use is associated with side effects, including weight gain, diabetes, osteoporosis, avascular bone necrosis, and increased risk for infections (Imazio et al 2008). For the management of pericarditis, CS are usually administered at low to moderate doses and can provide rapid control of symptoms. However, they often require many months of tapering after the normalization of CRP levels. In addition, there is a high rate of pericarditis relapse when CS use is tapered or stopped (Lotriionte et al 2010; Imazio et al 2005; Maisch et al 2004), particularly in the absence of concurrent colchicine treatment.

Patients with recurrent pericarditis who are refractory or intolerant to current therapeutic management options or who require long-term administration of CS to control their disease can be particularly challenging to manage. As a last resort, some refractory patients are being referred to the surgical procedure of pericardiectomy, with variable outcomes. Multiple immunosuppressive medications have been used without consistent benefit (Baskar et al 2016).

[redacted]

1.2. Pathogenesis of Recurrent Pericarditis: Role of IL-1

Interleukin-1 is a key cytokine that drives the pathophysiology of many inflammatory processes, and it is implicated as a causative factor in various inflammatory diseases in humans.

The two distinct IL-1 genes, *IL1A* and *IL1B*, encode IL-1α and IL-1β, respectively. IL-1α and IL-1β bind to the universally-expressed cell surface receptor, IL-1 receptor type-1, triggering a cascade of inflammatory mediators. The precursor form of IL-1α is expressed in keratinocytes, mucous membrane epithelial cells, and organs such as the liver and vascular endothelium in healthy individuals. During pathological states, IL-1α moves to the cell surface or is released after cell death to activate IL-1 receptors in adjacent cells, thus beginning the cascade of sterile inflammation. IL-1β, however, is not expressed in healthy individuals until a stimulus, such as microbial products or other chemokines, triggers its transcription in monocytes, tissue macrophages, and dendritic cells via the inflammasome. IL-1 drives the inflammatory cascade in classic autoinflammatory conditions, such as tumor necrosis factor (TNF)-associated periodic syndrome (TRAPS) and familial Mediterranean

fever (FMF) and plays a significant role in systemic onset of juvenile idiopathic arthritis and in autoimmune diseases such as rheumatoid arthritis (Baskar et al 2016).

IL-1–blocking therapies are effective at controlling end-organ disease and damage in patients with various autoinflammatory disorders, and different strategies to block IL-1 have been used in clinical trials and demonstrated substantial success in controlling episodes of fever and elevations in acute-phase reactants (Cantarini et al 2015).

This mechanistic plausibility of IL-1 antagonism in addressing pathophysiology related to the inflammasome extends to other conditions characterized by sterile acute inflammation, such as recurrent pericarditis.

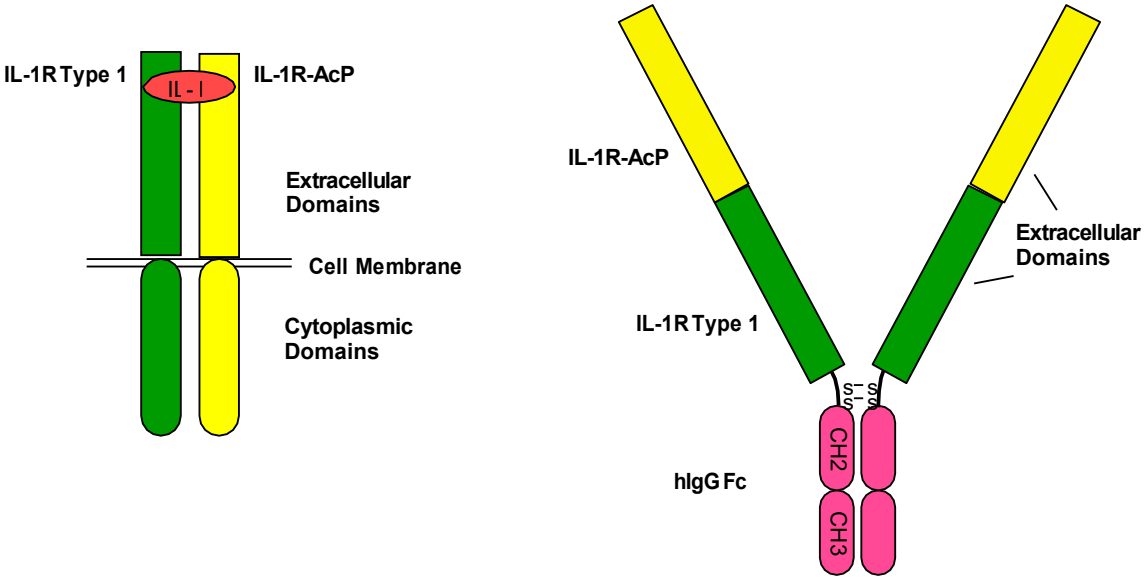
1.3. Rilonacept (KPL-914)

Rilonacept (designated as KPL-914 in the development program by Kiniksa Pharmaceuticals, Ltd) was developed by Regeneron Pharmaceuticals, Inc. (Regeneron) of Tarrytown, NY, and is approved with the trade name ARCALYST® in the US for the treatment of CAPS, including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children age 12 and older. Rilonacept is currently manufactured and marketed as ARCALYST® by Regeneron. Rilonacept received marketing authorization in the European Union for the treatment of CAPS with severe symptoms, including FCAS and MWS in adults and children aged 12 years and older, but based on a request from Regeneron, the marketing authorization was withdrawn. The withdrawal was a business decision and was not related to any concern with the safety or efficacy of rilonacept.

Rilonacept is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human IgG1. Rilonacept is a dimeric glycoprotein with a total molecular weight of approximately 250 kDa. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1 type I receptor (IL-1R1) and the IL-1 receptor accessory protein (IL-1R-AcP) (Figure 1).

Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells. Rilonacept blocks IL-1 by acting as a soluble decoy receptor that binds IL-1 and prevents its interaction with cell surface receptors.

Figure 1: Schematic of Rilonacept (KPL-914)



1.3.1. Safety of Rilonacept

For a detailed review of the available rilonacept safety data, please refer to the current Investigator Brochure and the ARCALYST® package insert located in the Pharmacy Manual. Rilonacept has been evaluated in 23 studies, including 22 complete and 1 ongoing. In the completed studies, 2243 subjects (2152 patients and 91 healthy volunteers) were exposed to rilonacept. Thirty of these patients were pediatric (<18 years of age). Doses up to 320 mg subcutaneously (SC) once weekly and 2000 mg intravenously (IV) monthly have been studied for different indications, including CAPS, gout, and other inflammatory disorders.

Injection Site Reactions

In clinical studies with rilonacept, the most common and consistently reported AE associated with rilonacept was injection site reaction (ISR). The ISRs included erythema, swelling, pruritus, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth, and hemorrhage. Most ISRs were mild to moderate. In the gout clinical studies, approximately 1% of subjects treated with rilonacept discontinued due to ISRs. Similar results have been seen in other patient populations.

Infections

Interleukin-1 blockade may interfere with immune response to infections. Serious life-threatening infections have been reported in clinical trials in subjects treated with rilonacept.

Changes in Laboratory Parameters

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Subjects treated with rilonacept in clinical trials experienced increases in their mean total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Antibodies directed against the receptor domains of rilonacept were detected using an enzyme-linked immunosorbent assay (ELISA). In clinical trials with rilonacept, approximately 30% to 35% of subjects tested positive for treatment-emergent antibodies to rilonacept on at least 1 occasion.

Systemic Hypersensitivity Reactions

Hypersensitivity reactions are a potential risk with protein therapeutics in general. In clinical studies with rilonacept, systemic hypersensitivity reactions have been rare.

Malignancies

Although malignancies have been reported in some subjects treated with rilonacept during clinical trials, the effect of rilonacept on the development of cancer is not known. Treatment with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies.

Fetal Defects

There are no adequate and well-controlled studies of rilonacept in pregnant women. Based on animal data, rilonacept may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15, or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human dose of 160 mg based on body surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100, or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

Nonteratogenic effects: A peri- and postnatal reproductive toxicology study was performed in which mice were administered a murine analog of rilonacept at doses of 20, 100, and 200 mg/kg SC 3 times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F1 offspring during maturation at all doses tested.

1.3.2. KPL-914-C001 (Study with Rilonacept [KPL-914] in Recurrent Pericarditis)

Study KPL-914-C001 is an open-label, single active-arm Phase 2 proof-of-concept study in subjects age ≥6 to 75 years old with recurrent idiopathic or post-pericardiotomy syndrome (PPS) pericarditis. The study includes a 6-week Treatment Period in which all the subjects receive once-weekly rilonacept 160 mg SC (2.2 mg/kg for subjects ≥6 and <18 years old) following a loading dose of 320 mg SC in subjects ≥18 years old (4.4 mg/kg in subjects ≥6 and <18 years old) in addition to background pericarditis therapies (NSAIDS, colchicine,

CS). After completing the 6-week Treatment Period and based on response status, the subjects have the option to enter the 18-week Extension Period during which they will continue to receive rilonacept at the same dose, but during which time Investigators are encouraged to wean and stop background pericarditis medications.

The primary objectives of the study are to explore clinical and biochemical endpoints of recurrent pericarditis symptomatology, as well as to assess feasibility to wean from concomitant pericarditis medication in the Extension Period while continuing treatment with rilonacept. The study population includes the following 5 subject categories (Parts):

- Part 1 enrolls symptomatic subjects with recurrent idiopathic pericarditis with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 2 enrolls symptomatic subjects with recurrent idiopathic pericarditis with CRP level ≤1 mg/dL that, in the opinion of the Investigator, can be attributed to concomitant medications (e.g., CS) and with pericardial inflammation present on cardiac MRI confirmed by the imaging core lab.
- Part 3 enrolls subjects with CS-dependent recurrent idiopathic pericarditis not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.
- Part 4 enrolls symptomatic subjects with recurrent PPS with an elevated marker of systemic inflammation (CRP level >1 mg/dL).
- Part 5 enrolls subjects with CS-dependent recurrent PPS not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.

The clinical phase of the study was completed in May 2019 (clinicaltrials.gov/NCT03980522); the final clinical study report is in preparation.

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objective

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

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase 3, multi-center, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis. This study has 4 periods (Figure 2).

3.1.1. Screening Period (up to 4 weeks)

During the screening period, assessment of disease characteristics, baseline therapy, and the pre-treatment workup will be completed during a period of up to 4 weeks. Additional information provided in Section 6.1.2.

3.1.2. Single-blind Run-In (RI) Period (12 weeks)

During the single-blind RI period, treatment with blinded rilonacept is administered and subjects are weaned off background standard of care (SOC) therapy for their pericarditis disease. Subjects will be blinded regarding the time of transition from the single-blind to the double-blind period; i.e., they will not be aware of the duration of the RI period.

In the single-blind RI period, subjects ≥18 years old will receive blinded 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 blinded 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 the RI period.

The RI period includes:

- 1-week Stabilization period, during which blinded rilonacept is administered in addition to 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. The dosages of CS, NSAIDs, and colchicine will be tapered according to the guidelines for weaning in the Pharmacy Manual (for the purpose of the protocol, aspirin is considered an NSAID). In general, CS doses will be tapered off starting at RI Week 1 and will be withdrawn by RI Week 10 (over a total of 9 weeks). NSAID and colchicine doses will be tapered off starting at RI Week 4 and will be withdrawn by RI Week 10 (over a total of 6 weeks).
- 2-week Monotherapy period: Subjects who have been successfully weaned off background SOC pericarditis therapy will continue to receive blinded rilonacept.

Subjects who stopped background pericarditis medications and achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will proceed into the double-blind placebo-controlled Randomized-Withdrawal (RW) period of the study. For definition of Clinical Response, refer to Section 6.2.2.

Subjects who are unable to achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline are to 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 LTE without having to proceed through the RW period.

3.1.3. Double-blind Placebo-controlled RW Period (pericarditis recurrence event-driven duration)

During the RW period, subjects who were able to stop background pericarditis medications and who achieve Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline will be randomized 1:1 to double-blinded administration of study drug:

- Rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects ≥12 and <18 years old) SC injections once weekly OR
- Matching placebo SC injections once weekly

Pericarditis Recurrence in the RW Period: For the definition of pericarditis recurrence, refer to Section 6.2.3.

Upon pericarditis recurrence, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale [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 prior RW period treatment assignment. 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 Section 5.6.3 and detailed in the Pharmacy Manual.

Subjects with pericarditis recurrence who do not meet the protocol criteria for bailout rilonacept will continue blinded study drug until they meet the protocol criteria for bailout rilonacept 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 Section 5.6.3 and detailed in the 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.

The RW period will continue until the prespecified number of primary efficacy endpoint (CEC-confirmed pericarditis recurrence) events has occurred. Based on projected event accrual and subject randomization, Kiniksa Pharmaceutical will determine the end of the RW period and announce to sites so that subject End of Randomized Withdrawal (EORW) visits

can occur. All subjects, including those who have transitioned to open-label rilonacept or who prematurely discontinued study drug, should complete an EORW visit.

3.1.4. Long Term Extension Treatment Period (LTE) (up to 24 months)

Upon completion of the RW period and the EORW visit, all subjects that did not discontinue study drug will have an option to continue treatment with open-label rilonacept in the LTE or to withdraw from the study. Subjects still in the RI period at the time that the RW period has ended and the LTE is opened will have the option to enter the LTE directly when they have completed the RI period and have met the definition of clinical response or to withdraw from the study.

Treatment in the extension period may continue until the earliest of the following dates:

- Rilonacept is approved for commercial use or is available for reimbursement to treat pericarditis in the region
- The subject has received 24 months of treatment in the LTE or the Investigator and subject decide to continue in the study off-treatment
- Additional reasons for discontinuation of treatment can be found in section 4.3.1.

Any subject who, in the opinion of the Investigator, should not continue open-label rilonacept will be withdrawn from the study.

Subjects will be reviewed again 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 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 also 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.

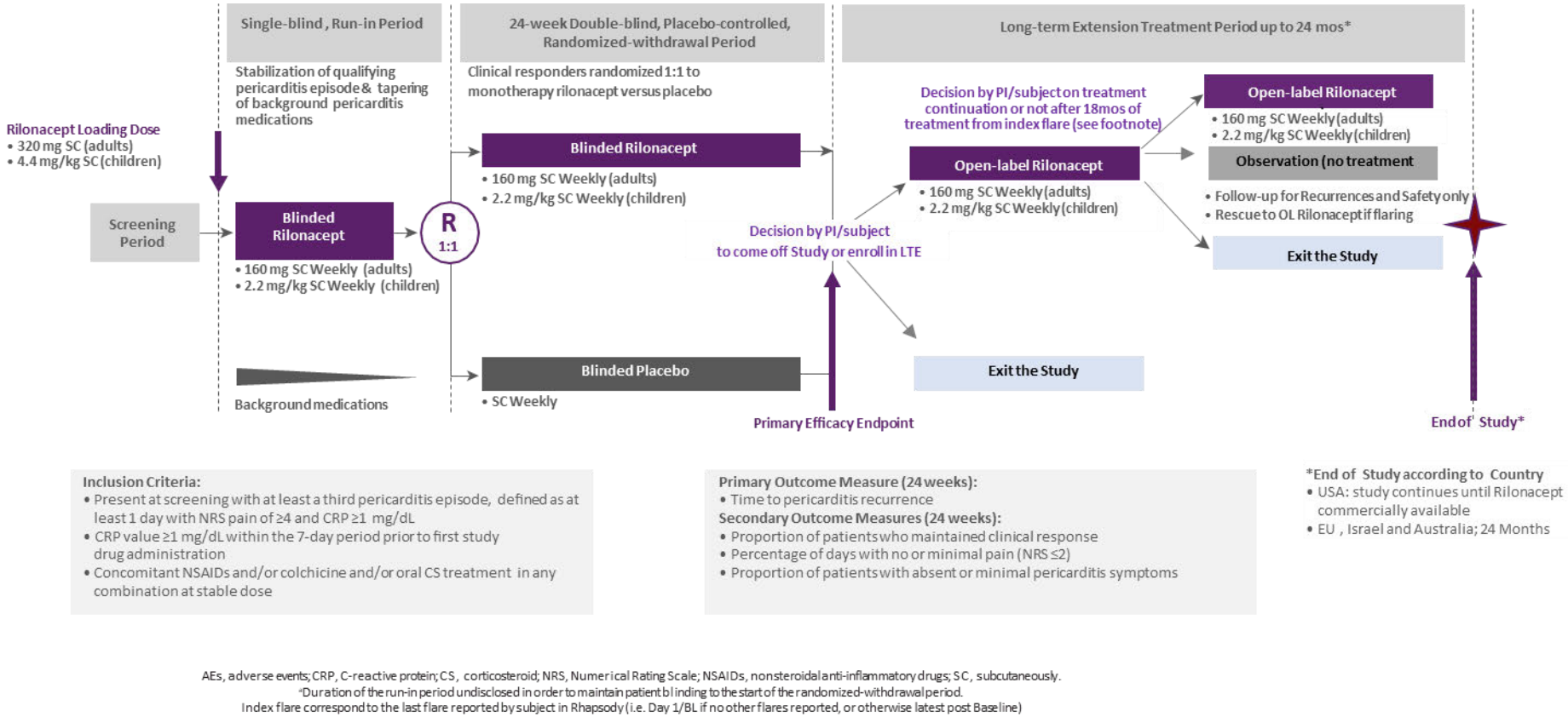
Subjects completing the RW period are projected to be dosed with rilonacept for a minimum of approximately 36 weeks and a maximum of 2 years based on enrollment assumptions and pericarditis recurrence events accrual time. Subjects who enter the LTE will be dosed for up to 24-months longer.

Pericarditis Recurrence in the LTE Period (Observation arm)

For those subjects who, upon the 18-month post-most-recent-recurrence assessment, opt to continue in the LTE for observation only while off-treatment: should they have a further pericarditis recurrence, in the opinion of the Investigator, during that observation period, may resume open-label rilonacept after completion of a recurrence visit as outlined in Section 6.1.4. Resumption of rilonacept will follow the procedures for bailout as outlined in Section 3.1.3.

Subjects who experience a recurrence of pericarditis in the LTE while receiving open label rilonacept will attend for a recurrence visit and may then continue on rilonacept or transition to SOC treatment at the discretion of the investigator.

Figure 2: Overview of KPL-914-C002 Study Design



AEs, adverse events; CRP, C-reactive protein; CS, corticosteroid; NRS, Numerical Rating Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneously.
*Duration of the run-in period undisclosed in order to maintain patient blinding to the start of the randomized-withdrawal period.
Index flare correspond to the last flare reported by subject in Rhapsody (i.e. Day 1/BL if no other flares reported, or otherwise latest post Baseline)

3.2. Rationale of Study Design

Subjects eligible for this KPL-914-C002 study will be subjects with recurrent pericarditis presenting with an acute pericarditis episode at screening.

The KPL-914-C002 study design ensures that during the RI period all subjects will receive rilonacept, a drug with evidence supporting clinical activity based on the clinical data with rilonacept from the Phase 2 proof-of-concept study (KPL-914-C001). During the RI period, pericarditis will be stabilized with symptoms controlled and background pericarditis medications (NSAIDs, colchicine, CS) will be tapered and withdrawn, while rilonacept treatment continues.

The design then allows half of the subjects to continue receiving active treatment after having achieved Clinical Response on that treatment, which maximizes subject exposure to a potentially beneficial therapy. The temporary withdrawal of rilonacept (by switching to placebo) in the half of the subjects who were randomly assigned to placebo is expected to result in an accelerated time to pericarditis recurrence and a higher recurrence rate compared to those who continue on active treatment, a finding that demonstrates that the underlying pericarditis etiology is still ongoing and will provide further support for the anticipated observation of the clinical effect of rilonacept during the RI period of the study. The period of exposure to an ineffective treatment is minimized in this design, as subjects will be removed from blinded treatment when the condition returns to a specified severity (i.e., for having met the criteria of pericarditis pain ≥4 on the 11-point NRS and CRP level ≥1 mg/dL) without unblinding them to prior treatment assignment, thus protecting the primary efficacy endpoint of the study. All subjects who meet the pain and CRP criteria described above will be treated with open-label bailout rilonacept using a loading dose, followed by once-weekly SC injections. In addition, sequential ORT such as NSAIDs and/or colchicine will be allowed upon recurrence at the Investigator's discretion based on the subject's clinical status, as outlined in Section 5.6.3 and as stipulated in the Pharmacy Manual. Subjects with pericarditis recurrence not meeting criteria for bailout rilonacept, can be treated with sequential ORT based on Investigator judgement and as described in protocol Section 5.6.3 and the Pharmacy Manual. If the subject requires the addition of CS treatment to control the pericarditis recurrence, the subject will be discontinued from study drug. All subjects will be followed for the duration of RW period.

In summary, the proposed RW trial with rilonacept allows all enrolled subjects an opportunity to receive the active drug during the acute episode of pericarditis yet provides pivotal-quality data on the efficacy of rilonacept in this enriched cohort by subsequently randomly assigning subjects to placebo versus active treatment after they achieve a predefined clinical response. Subjects with pericarditis recurrences after randomization will receive bailout rilonacept treatment and/or sequential ORT according to the protocol. This approach minimizes the exposure to placebo, which is important for a study that requires active disease upon enrollment and includes a pediatric population. The available regulatory guidance supports the use of an RW study design in the setting of recurrent pericarditis as a

means of establishing the long-term effectiveness of rilonacept, an approved product for the treatment of another rare autoinflammatory condition (CAPS).

3.3. Justification for Dose Selection

[redacted] i.e., 320 mg SC loading dose (4.4 mg/kg in subjects ≥12 and <18 years old), followed by once-weekly SC doses at 160 mg (2.2 mg/kg in subjects ≥12 and <18 years old).

In the rilonacept development program in CAPS, gout, rheumatoid arthritis, and other inflammatory conditions, over 2000 subjects were exposed to rilonacept, including 1650 subjects receiving a rilonacept dose of 160 mg or higher. A total of 103 and 169 subjects were exposed to any rilonacept dose for at least 1 year or 6 months, respectively. Most of the real-life experience with rilonacept comes from the CAPS population treated at this marketed dose. As of March 2018, approximately 365 CAPS patients have been exposed to rilonacept in the post-marketing setting since 2008. The safety data accumulated so far support the benefit/risk ratio for the rilonacept dose intended to be evaluated in subjects with recurrent pericarditis.

Based on the clinical data with rilonacept from the Phase 2 proof of concept study (KPL-914-C001), it is expected that rilonacept doses [redacted] (320 mg followed by 160 mg SC once weekly and corresponding pediatric doses), and evaluated in the KPL-914-C001 study, will consistently provide adequate suppression of clinical inflammatory response, including CRP levels, in patients with recurrent pericarditis.

Subjects who meet the protocol criteria for **bailout rilonacept** upon pericarditis recurrence in the RW period of the study (Sections 3.1 and 6.2.3), irrespective of treatment assignment at randomization, will receive open-label rilonacept (loading dose of 320 mg SC followed by once-weekly SC injections of 160 mg, or the corresponding pediatric doses). [redacted]

The rationale for bailout rilonacept treatment upon pericarditis recurrence for subjects who were randomly assigned to placebo is that rilonacept had controlled their disease activity during the RI period; therefore, re-initiation of rilonacept is justified to regain control of pericarditis signs and symptoms upon recurrence. Subjects who were randomly assigned to rilonacept and qualify for bailout rilonacept upon pericarditis recurrence in the RW period were initial responders to rilonacept treatment during the RI period; thus it could be assumed that the loss of response during the RW period could be due to development of resistance to rilonacept due to different mechanisms, e.g., higher IL-1 levels or a change in rilonacept pharmacokinetics (PK)/ pharmacodynamics. Therefore, re-administration of a loading dose of rilonacept may help to restore Clinical Response.

4. SELECTION OF STUDY POPULATION

Up to approximately 100 subjects with recurrent pericarditis will be enrolled, which will allow accrual of at least 22 adjudicated pericarditis recurrence events in randomized subjects at approximately 50 sites globally. Subjects will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 pericarditis episodes (including the first episode and 1 recurrence) prior to screening. Enrollment of pediatric subjects will be limited to up to 20% of the study population. To be eligible for the study, subjects must present with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and CRP level ≥1 mg/dL within 7 days prior to the first study drug administration.

4.1. Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent form (ICF) or assent form (for pediatric subjects ≥12 and <18 years old), has provided signed and witnessed written informed consent or assent (as applicable), and agrees to comply with protocol requirements.
2. Is male or female 12 years of age or older with body weight of at least 23.6 kg (52 Lbs).
3. Has a diagnosis of recurrent pericarditis.
4. At least 1 of the pericarditis episodes experienced prior to screening has met at least 2 of the following 4 criteria, in the opinion of the Investigator and based on the documented available data, according to the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al 2015):
    a. Pericarditic chest pain
    b. Pericardial rub
    c. New widespread ST-segment elevation or PR-segment depression according to ECG findings
    d. Pericardial effusion (new or worsening)
5. Presents with at least the third episode of pericarditis during screening (i.e., at least the second pericarditis recurrence following the first pericarditis episode), and within 7 days* prior to and including RI baseline (first administration of study drug) has:
    a. At least 1 day with pericarditis pain ≥4 on the 11-point NRS, **AND**

b. CRP level ≥1.0 mg/dL (for details of CRP collection see Section 6.1.1)
*Pericarditis pain ≥4 and CRP ≥1 mg/dL are not required to be present on the same day.

6. Has received NSAIDs and/or colchicine and/or CS (in any combination), if used, at stable dose levels (or at least not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs) are not anticipated, in the opinion of the Investigator, to significantly alter assessments of baseline disease activity.
7. If using NSAIDs and/or colchicine and/or CS at the time of RI baseline (first administration of study drug), is willing and able, in the opinion of the Investigator, to taper and discontinue those medications within the 9-week weaning time in the RI period of the study while continuing rilonacept treatment.
8. Female subjects must be:
   a. Postmenopausal, defined as at least 12 months after the cessation of menses (without an alternative medical cause) OR
   b. Incapable of pregnancy OR
   c. Permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation or having a male partner with vasectomy as affirmed by the subject OR
   d. If of childbearing potential, must agree to use a highly effective method of contraception during the study and for 3 months after the last study drug administration (e.g., hormonal contraceptives associated with inhibition of ovulation, intrauterine device [IUD], intrauterine hormone-releasing system [IUS], or sexual abstinence)
9. If male and sexually active, must have documented vasectomy or must practice birth control and not donate sperm during the study and for 3 months after the last study drug administration.
10. Must be up-to-date with all immunizations, in agreement with current local immunization guidelines for immunosuppressed subjects, before RI baseline (first administration of study drug).
11. Is able to adequately maintain a daily subject diary according to protocol.
12. Must be able to adhere to the study visit schedule and understand and comply with the other protocol requirements.
13. Agrees to refrain from making any new, major lifestyle changes that may affect pericarditis symptoms (e.g., changing exercise pattern) from the time of the ICF is signed through the end of the double-blind RW period.

4.2. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Has a diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis; or systemic autoimmune diseases with exception of Still's disease.
2. Is pregnant, breastfeeding, or planning a pregnancy or fathering a child during the study or within 3 months after the last study drug administration.
3. Has a history of immunosuppression, including positive human immunodeficiency virus (HIV) test results.
4. Is currently receiving CS at a dose of >60 mg/day prednisone (or equivalent) for adult subjects, or >0.5 mg/kg/day (or >60 mg/day, whichever is lower) prednisone (or equivalent) in pediatric subjects (≥12 and <18 years old).
5. Has ever received cytotoxic drugs, including cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.
6. Has ever received agents that deplete B or T cells (e.g., rituximab, alemtuzumab).
7. Has received systemic immunomodulatory agents (with exception of CS) within the following time frames prior to RI baseline (first administration of study drug):
    a. Azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, or mercaptopurine within 24 weeks.
    b. TNF inhibitors, IL-6 inhibitors, or janus-activating kinase inhibitors within 12 weeks.
    c. Canakinumab within 12 weeks. Canakinumab could not have been discontinued due to safety unless it was discontinued due to local injection site reactions.
    d. Rilonacept within 6 weeks. Rilonacept could not have been discontinued due to lack of efficacy or due to safety.
    e. Methotrexate within 2 weeks.
    f. Anakinra within 5 days. Anakinra could not have been discontinued due to lack of efficacy or due to safety unless it was discontinued due to local injection site reactions.
8. Has a history of myeloproliferative disorder.
9. Has a history of demyelinating disease or symptoms suggestive of multiple sclerosis.
10. Meets the following TB criteria:
    a. History of active TB prior to screening OR
    b. History of latent TB that was not adequately treated prior to screening OR
    c. Signs or symptoms suggestive of active TB (e.g., new cough of >14 days in duration or a change in chronic cough, persistent fever, unintentional weight loss, or night sweats) upon review of medical history and/or physical examination at screening OR

d. Recent close contact with a person with active TB OR
e. Positive or indeterminate Interferon Gamma Release Assay (IGRA) test results or results from another positive TB test at screening based on acceptable clinical practice for the country in which the subject is enrolling.

11. Has chest x-ray (posterior-anterior view) at screening (or history of results within 12 weeks before receiving first administration of study drug), with evidence of malignancy or abnormality consistent with prior or active TB infection.
12. Has received immunization with a live (attenuated) vaccine within 12 weeks before screening or is expected to receive live (attenuated) vaccine during the study or within 12 weeks after the last study drug administration.
13. Has a history of positive or intermediate results for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening.
14. Has an estimated glomerular filtration rate (eGFR) <30 ml/min.
15. Has a history of malignancy of any organ system within the past 5 years before screening (other than a successfully treated non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
16. Has a known or suspected current active infection or a history of chronic or recurrent infectious disease, including, but not limited to, chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, or an open, draining infected skin wound.
17. Has had a serious infection, has been admitted to the hospital for an infection, has been treated with oral antibiotics for a documented infection within 2 weeks of RI baseline (first administration of study drug), or has been treated with IV antibiotics for an infection within 8 weeks of RI baseline.
18. Has had an organ transplant.
19. Has screening laboratory test results meeting any of the following criteria:
    - Hemoglobin level <10.0 g/dL
    - WBC count $<3.0 \times 10^3/\mu L$
    - Neutrophil count $<1.5 \times 10^3/\mu L$
    - Platelet count $<100 \times 10^3/\mu L$
    - Total bilirubin level >1.5 × the upper limit of normal (ULN) unless the test results are consistent with those for Gilbert's syndrome
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 × ULN
20. In the Investigator's opinion, has a history of alcoholism or drug/chemical abuse within 2 years before screening.
21. Has a known hypersensitivity to ARCALYST® (rilonacept) or to any of its excipients.

22. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before screening or is planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
23. In the Investigator's opinion, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations. This includes significant concomitant illnesses such as, but not limited to, cardiac, renal, neurological, endocrinological, metabolic, pulmonary, GI, or psychiatric diseases.
24. In the opinion of the Investigator, is not likely to be compliant with the study protocol.
25. In the opinion of the Investigator, should not participate in this study.

4.3. Subject Completion, Withdrawal from Study, and Study Drug Discontinuation

4.3.1. Completion

A subject will be considered to have completed the study if she/he has completed the RW period and has completed assessments at the EORW visit. At the EORW visit all subjects who are still receiving study treatment (blinded therapy or open-label bailout) will be offered an opportunity to receive up to an additional 24 months of open-label rilonacept treatment based on their clinical status and at the discretion of the investigator, and after signing the LTE informed consent.

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 LTE without having to proceed through the RW period.

Any subject who in the opinion of the Investigator should not continue open-label rilonacept in LTE will be withdrawn from the study.

Subjects who elect not to enter the LTE will be followed for 6 weeks (safety follow up) after receiving the last study drug administration.

4.3.2. Reasons for Discontinuation of Study Drug and Study Withdrawal

Subjects have the right to stop taking study drug before the end of the study or to withdraw their consent for further participation in the study (i.e., precluding continued data collection). A subject also may be asked to stop study drug at the investigator's discretion. In the event that a subject permanently discontinues study drug but does not withdraw the informed consent, the investigator should continue to follow up with the subject by telephone contact (TC) visits, in the clinic, or by other means through the EORW visit if the subject discontinues in RI, RW, or LTE unless consent is withdrawn.

The reasons for premature study drug discontinuation will be recorded in the electronic case report form (eCRF).

4.3.2.1. Discontinuation of Study Drug

The study drug dosing will be permanently stopped if any of the following occurs:

- The subject develops TB or malignancy, excluding non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma
- Initiation of protocol-prohibited medication (Section 5.6.5)
- Subject requires treatment with CS for pericarditis during RW or LTE periods of the study
- Pregnancy or pregnancy planned during the study or within 3 months after the last study drug administration
- ALT or AST values ≥3 × ULN associated with total bilirubin ≥2 × ULN, with no underlying medical conditions to explain the elevated values
- Treatment with a live (attenuated) vaccine during the study
- Investigator or Sponsor's medical monitor or [redacted] medical monitor decides that, for safety reasons, it is in the subject's best interest
- Termination of the study by Kiniksa Pharmaceuticals

Permanent or temporary study drug discontinuation should be strongly considered at the time if any of the following occurs:

- Subject develops an opportunistic infection.
- Subject develops moderate or severe infection
- Neutrophil count $<1.0 \times 10^3/\mu L$
- Isolated ALT or AST values >5 × ULN
- Surgical procedure

4.3.2.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time and for any reason, without prejudice to their future medical care by the Investigator or at the study site. However, prior to withdrawal of consent, it should be confirmed that the subject will not allow any form of follow up including options such as less frequent follow up calls or visits, follow up with a family member or friend, or follow up through a local physician or medical records. Follow up options will be summarized on a withdrawal of consent checklist source document that must be reviewed and signed by the Investigator for any subject who withdraws consent for further participation in the study. The checklist must be completed for all enrolled subjects who have withdrawn consent. The reasons for a subject's withdrawal from the study are also required to be recorded in the eCRF.

A subject may be considered withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Documented withdrawal of informed consent
- Death

In subjects who are documented as having withdrawn consent from all study activities, no further study visits or study-related TCs can be conducted. All data collected prior to the date of the subject's confirmed withdrawal of consent will be included in the study, as specified in the subject's signed ICF.

5. STUDY TREATMENTS

5.1. Method of Assigning Subjects to Treatment Groups

In the single-blind RI period, all subjects will receive blinded rilonacept at the same dose through Week 12; subjects will be blinded to the time of transitioning to RW. Subjects who stopped background SOC pericarditis therapy and who achieve Clinical Response on rilonacept at RI Week 12/RW baseline will be randomly assigned in a double-blind manner to continue to receive blinded rilonacept or matching placebo using a 1:1 allocation ratio. The definition of Clinical Response is provided in Section 6.2.2. An interactive web response system (IWRS) will be used to administer the randomization schedule. 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

5.2. Treatments Administered

Throughout this protocol, "study drug" refers to the investigational medicinal products: rilonacept and matching placebo. Both will be administered as applicable by SC injection. For additional information on rilonacept please refer to the Prescribing Information for Arcalyst® located in the Pharmacy Manual.

Study drug administration will be performed once a week (every 7 ± 2 days). The interval between study drug administrations must be at least 5 days.

5.2.1. Adult Subjects (≥18 years old)

Rilonacept: Loading dose 320 mg administered as 2 SC injections, 160 mg each (2 ml) at RI baseline, followed by once-weekly SC injections of 160 mg (2ml).

Placebo: administered as once-weekly SC injections of 2 ml each in the RW period

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 320 mg administered as 2 SC injections, 160 mg each (2 ml) at the next scheduled study drug administration date, followed by once-weekly SC injections of 160 mg (2ml).

5.2.2. Pediatric Subjects (≥12 and <18 years old)

Rilonacept: Loading dose 4.4 mg/kg administered as 2 SC injections, 2.2 mg/kg each (maximum 160 mg each) at RI baseline, followed by once-weekly SC injections of 2.2 mg/kg (maximum 160 mg). The volume of injections will be based on the subject's weight (Table 1).

Placebo (in RW): once-weekly SC injections with volume based on the subject's weight (Table 1 , maximum 2 ml).

Upon meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) in the RW period, subjects will be transitioned to open-label rilonacept 4.4 mg/kg administered as 1 (maximum 2 ml) or 2 SC injections at the next scheduled study drug administration date, followed by once-weekly SC injections of 2.2 mg/kg (maximum 2 ml). The volume of injections will be based on the subject's weight (Table 1).

Study drug dose/volume will be calculated by the Investigator or pharmacist during site clinic visits based on body weight (as specified in Section 13.1) using a weight-based dosing chart in **kilograms** (Table 1).

Table 1: Study Drug Dose Volume (After Reconstitution) by Body Weight in Kilograms for Pediatric Subjects Aged ≥12 and <18 Years

Weight Range (kg)	Loading Dose Volume (ml)	Weekly Dose Volume (ml)
23.6 to 27.2	2 x 0.7	0.7
27.3 to 30.8	2 x 0.8	0.8
30.9 to 34.4	2 x 0.9	0.9
34.5 to 38.1	2 x 1.0	1.0
38.2 to 41.7	2 x 1.1	1.1
41.8 to 45.4	2 x 1.2	1.2
45.5 to 49.0	2 x 1.3	1.3
49.1 to 52.6	2 x 1.4	1.4
52.7 to 56.3	2 x 1.5	1.5
56.4 to 59.9	2 x 1.6	1.6
60.0 to 63.5	2 x 1.7	1.7
63.6 to 67.2	2 x 1.8	1.8
67.3 to 70.8	2 x 1.9	1.9
70.9 or greater	2 x 2.0	2.0

5.2.3. Study Drug Self-Administration

The first study drug dose on RI baseline will be administered at the study site. During this visit, the subject will be trained on study drug preparation and injection. In case the subject is unwilling or unable to prepare and self-inject the study drug, the subject's caregiver will be trained.

The first study drug administration for adult and pediatric subjects on RI baseline will consist of 2 SC injections, constituting a loading dose. The first injection will be prepared and administered by study site staff. The second injection will be prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once-weekly study drug doses will be self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient SC administration. If the subject or subject's caregiver is unable to prepare and inject the study dug, the subject may report for once-weekly injections to a study site, or injections can be administered by the visiting registered nurse (RN).

5.3. Identity of Investigational Medicinal Product

Rilonacept (KPL-914) is the drug being evaluated in the current study. Refer to Section 1.3 for a detailed description of rilonacept's mechanism of action.

Study drug (rilonacept or placebo) is supplied in a single-use, 20 ml glass vial containing a sterile, white to off-white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

Each placebo vial contains lyophilized powder. After reconstitution with 2.3 ml sterile WFI, the placebo vial contains 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

5.4. Management of Clinical Supplies

5.4.1. Study Drug Product Packaging and Storage

Additional information regarding the preparation, dispensation, administration, and storage of rilonacept or placebo will be described in the Pharmacy Manual.

Study drug will be provided by Kiniksa Pharmaceuticals to the study sites in the lyophilized formulation in glass vials as described in Section 5.3. Each single-use vial will have a clinical label adhered to the vial. One labeled vial will be placed into a carton. Each carton will have

a clinical label adhered to the outside of the carton. One tamper-evident seal will be placed on the top of the carton to securely close the lid.

Study drug is to be stored and shipped refrigerated at 2°C to 8°C (36°F to 46°F) inside the original carton to protect it from light.

5.4.2. Study Drug Accountability

The sites will receive study drug for on-site administration at study site visits. Upon receipt of study drug, the Investigator (or delegate) will conduct an inventory of the supplies and verify that the supplies are received intact, at the appropriate temperature, and in the correct amounts prior to completing a supplies receipt. The Investigator will confirm receipt of study drug in the IWRS and retain a copy of this receipt at the study site. The inventory of supplies at each study site will be reviewed by the study monitor.

Study drug will be dispensed to the study subjects for outpatient self-administration according to the supply chain described in the Pharmacy Manual.

The Investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviating from the expected dispensing regimen must also be recorded. The full process for drug dispensing, documentation, and destruction will be described in the Pharmacy Manual.

A full drug accountability log will be maintained at the study site at all times.

5.4.3. Other Supplies

The Sponsor will provide the materials needed to prepare and administer study drug. The Sponsor also will provide coolers and refrigerated gel packs to ensure that the subjects transport the study drug at the proper temperature. On occasion, sites may be asked to locally procure ancillary materials. Please see the Pharmacy Manual for additional information.

5.5. Study Drug Overdose

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose must be promptly reported to the [redacted] Pharmacovigilance (PHV) in the same way and using the same procedures as for a serious adverse event (SAE) (Section 6.4.6), regardless of whether any AEs are associated with the overdose.

If there are AEs associated with the overdose, these should be recorded on the relevant AE/SAE Sections in the eCRF; however, overdoses without signs or symptoms do not need to be recorded as AEs in the eCRF.

5.6. Prior and Concomitant Medications

Use of all concomitant medications and any changes in concomitant medications will be recorded in the subject's eCRF. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF. The initiation of protocol prohibited medication (Section 5.6.5) requires discontinuation of study drug.

Guidelines regarding the use of concomitant medication will be detailed in the Pharmacy Manual and are summarized in the following Sections.

5.6.1. Screening

Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine, and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs), in the opinion of the Investigator, are not anticipated to significantly alter assessments of baseline disease activity.

Analgesics can be used at the discretion of the Investigator during screening activities prior to the first study drug dose, but only after the subject has documented a pericarditis pain level ≥4 on the 11-point NRS within 7 days prior to and including RI baseline (first administration of study drug).

Subjects can enter the study on prednisone (or equivalent dose) not exceeding 60 mg/day for adults and not exceeding 0.5 mg/kg/day (with a maximum dose of 60 mg/day) in pediatric subjects.

5.6.2. Single-blind RI Period

- 1-week Stabilization period, during which rilonacept is administered in addition to SOC pericarditis therapy and ongoing pericarditis episode is treated. All concomitant pericarditis medications including NSAIDs, analgesics, colchicine and CS will remain stable, unless the dosing must be decreased or stopped in the judgement of the Investigator due to an AE.
- 9-week background medication Weaning period, during which subjects are weaned off background SOC pericarditis therapy, as applicable, while treatment with blinded rilonacept continues. The guidelines for background medication taper and discontinuation will be provided in the Pharmacy Manual.
  - Corticosteroids
    - Starting at Week 1 and through Week 10, CS will be tapered and discontinued at a rate dependent on the dose at study entry.
  - Analgesics
    - Starting at Week 1 and through Week 10, analgesics (non-opioid and opioid) will be tapered and discontinued. Opioid analgesics can continue beyond Week 10 at stable doses through the end of the RW

period if it is not feasible to discontinue them without causing withdrawal symptoms.

  - NSAIDs and Colchicine
    - Starting at Week 4 and through Week 10, NSAIDs and colchicine will be tapered and discontinued.

- 2-week Monotherapy period during which rilonacept administration continues: Subjects are required to be off all background SOC pericarditis therapy, with the exception of opioid analgesics if their discontinuation is not feasible.

5.6.3. Double-blind Placebo-controlled RW Period

During the RW period, subjects should not be receiving any concomitant medications for pericarditis, with the exception of opioid analgesics in case their taper down and discontinuation was not feasible in the RI period.

The use of concomitant medication is permitted upon pericarditis recurrence based on the subject meeting protocol criteria for bailout rilonacept as follows:

Subjects meeting protocol criteria for bailout rilonacept

Upon pericarditis recurrence and meeting protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) and completing the diagnostic workup as confirmed by the [redacted] medical monitor, subjects will be transitioned to open-label rilonacept, as described in Section 3.1. Because open-label rilonacept can be administered only if at least 5 days have passed from the last blinded study drug administration, the Investigators are allowed to use sequential ORT, i.e., analgesics, NSAIDs, and colchicine, if necessary, at their discretion. The use of those medications will be detailed in the Pharmacy Manual; it is briefly given as follows:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to open-label rilonacept based on the subject's clinical status and at the discretion of the Investigator.
- If, after transition to open-label rilonacept, the Investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from rilonacept and followed through the EORW visit.

Subjects not meeting protocol criteria for bailout rilonacept

If, based on the Investigator's judgement, the subject is experiencing pericarditis recurrence that does not meet the protocol criteria for bailout rilonacept (Sections 3.1 and 6.2.3) but does

require additional treatment, the subject will continue blinded study drug, and the Investigator should manage the pericarditis recurrence using sequential ORT for pericarditis, i.e., analgesics, NSAIDs, colchicine as described in the Pharmacy Manual and outlined briefly below:

- Analgesics (including non-opioid and opioid) can be used for pain control prior to completing the diagnostic workup for a recurrent pericarditis episode. The use of analgesics during pericarditis recurrence evaluation will provide pain relief for subjects without impacting their CRP levels or other objective components of the diagnostic workup.
- After the diagnostic workup is completed based on the [redacted] medical monitor's assessment, NSAIDs followed by colchicine can be added to blinded study drug based on the subject's clinical status and at the discretion of the Investigator.
- If, after the addition of NSAIDs and colchicine, the Investigator decides that the subject requires CS for pericarditis therapy, the subject will be discontinued from blinded study drug and followed through the EORW visit.

5.6.4. Long Term Extension

Subjects who opt to continue open-label rilonacept in the LTE will have their concomitant pericarditis medications managed at the discretion of the Investigator and based on the subject's clinical status. If addition of CS is required to manage recurrent pericarditis, rilonacept should be discontinued.

5.6.5. Prohibited Concomitant Medicines During the Study

The following concomitant medications are prohibited throughout the duration of the study including the LTE:

- Interleukin-1 (IL-1) blockers other than rilonacept
- IL-6 blockers
- Janus-activating kinase inhibitors
- TNF inhibitors
- Potent immunosuppressants (azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, mercaptopurine, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents, agents that deplete B or T cells [e.g., rituximab, alemtuzumab])
- Live (attenuated) vaccines, which are prohibited during the study and within 12 weeks after the last study drug administration

5.7. Method of Blinding

In the single-blind RI period, all subjects will receive rilonacept but will be blinded to the duration of the RI period and the timing of randomization. The RW period is a double-blind period in which rilonacept and placebo are identical in appearance. Neither the subject nor any of the Investigator/site staff, [redacted] or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Council for Harmonisation [ICH] E9).

In the event of a pericarditis recurrence that meets the criteria for bailout rilonacept (Sections 3.1 and 6.2.3), the subject will be transitioned to open-label rilonacept but will remain blinded to their prior RW treatment assignment.

If the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, the Sponsor and [redacted] must be notified immediately. The Investigator may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study drug is essential for the appropriate clinical management or welfare of the subject. In most cases, the management of a medical emergency would be the same, regardless of whether the subject received active drug. The treatment assignment will be unblinded through the IWRS.

The [redacted] PHV staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the blinded report may be sent to clinical Investigators in accordance with local regulations.

5.8. Treatment Compliance

Subjects will record the administration of all doses of study drug (whether as an outpatient or in the clinic) in a subject's diary. In addition, throughout all study periods, adherence to study drug administration will be assessed by the study site in collaboration with the visiting RN, if applicable (Section 6).

6. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential subjects will provide informed consent or an assent, if applicable. Potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all questions answered for them. Subjects will undergo screening procedures specific to the study only after the ICF has been provided by the subject unless performed as part of SOC practice. The investigator or designee will also sign the ICF.

6.1. Study Visits

Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities.

Following screening assessments, qualifying subjects will be enrolled and enter the RI period. Subjects who stop background pericarditis medications and achieve Clinical Response at RI Week 12 (Section 6.2.2), will be randomized and enter the RW period. During both the RI and RW period, a combination of clinic and outpatient visits will occur. Outpatient visits may consist of telephone or virtual contacts as well as home visits conducted by a visiting nurse. For each scheduled visit of the study (including outpatient and clinic), assessments should occur prior to scheduled injections of study drug. Subjects can be brought to the clinic in place of a scheduled outpatient visit, for an unscheduled visit at the discretion of the Investigator, or if arranging a visiting nurse for an at home visit is logistically not feasible.

The visit schedule is derived from the day of the RI baseline visit. One week is equal to 7 calendar days. Although visits do not occur every week, subjects will be provided an electronic device to record daily pericarditis pain NRS measurements and administration of study drug from the beginning of the RI period through the end of the RW period. If a subject is unable to independently complete the daily entries, a caregiver may help the subject with data entry only. Throughout all study periods, compliance with study drug administration will be assessed by the site in collaboration with the visiting RN.

Any subject who prematurely discontinues study drug will complete an EOT visit and will be followed for the duration of the trial according to the SOA unless the subject withdraws consent. In addition, throughout all study periods, compliance with study drug administration will be assessed by the site in collaboration with the visiting RN.

6.1.1. Screening Visit(s)

Subjects will undergo screening procedures for the study only after the signing of informed consent or assent by the subject. Potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all questions answered for them. The Investigator or designee will also sign the ICF. All subjects that sign the informed consent will be registered in IWRS and will be assigned a unique subject ID.

The screening period begins at the signing of the ICF and must be completed within 28 days. Procedures performed per SOC prior to consent for the study, may be used for screening and do not need to be repeated for the study if performed within the 28 days of enrollment, except for the following procedures below:

- IGRA, hepatitis serology and HIV within 8 weeks of enrollment
- Chest X-ray within 12 weeks enrollment
- Qualifying 11-point pericarditis pain NRS assessment ≥4 and CRP ≥ 1 mg/dL within 7 days prior to enrollment (the qualifying NRS assessment and CRP are not required to occur on the same day.)

Procedures may be repeated at the discretion of the Investigator during the screening period. Subjects that are deemed not eligible must be screen failed in IWRS and can be rescreened at the discretion of the Investigator. Rescreened subjects will receive a new Subject ID through IWRS at the re-screening visit.

It is possible that the screening and enrollment visit will occur on the same day. If the screening and the enrollment visit (RI Baseline Visit) is performed on the same day, procedures that are required at both visits do not need to be repeated. Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities for this visit.

6.1.2. Enrollment (RI Baseline Visit)

Subjects meeting entry criteria will be enrolled at the RI Baseline visit. All procedures for the RI Baseline visit should be performed prior to enrollment in IWRS and the first administration of study drug. Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities for this visit.

6.1.3. Randomization (RI Week 12/RW Baseline Visit)

All procedures for the RI Week 12 visit should be performed prior to randomization in IWRS. Subjects who stopped background SOC pericarditis therapy and who achieve Clinical Response (see Section 6.2.2) at RI Week 12 visit will be randomized in the IWRS and will complete the procedures for the RW Baseline visit. If randomization has been closed, subjects achieving Clinical Response after completing the RI period may transition directly to the LTE.

For subjects that do not qualify for randomization, the Sponsor or [redacted] medical monitor is to be immediately contacted to evaluate the reasons for non-qualification. Following medical monitor consultation, if the subject is deemed to not be a treatment responder, study drug will be discontinued, and the subject will not proceed to randomization. The subject will complete the EOT visit and continue with follow-up according to the SOA until the end of the RW period. Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities for this visit.

6.1.4. Pericarditis Recurrence Assessment: Clinic Visit

If a subject experiences symptoms consistent with pericarditis recurrence, he/she should contact the study Investigator immediately for evaluation (including in the LTE). It is possible that a subject may have assessments performed remotely, however, assessments are also expected be performed at the study site as soon as possible. Required assessments include:

- Evaluate pericarditis pain on the 11-point NRS.
- Evaluate concomitant medications as well as pericarditis concomitant medications.
- Obtain laboratory samples for CRP (local and central) (the POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment).
- Acquire a 12 lead ECG.
- Acquire a cardiac ECHO per core laboratory imaging parameters; this ECHO is read locally for the purpose of pericarditis recurrence assessment and is then submitted to the ECHO core laboratory for central review.
- Perform an abbreviated physical examination, height and body weight.
- For subjects >18 years, complete the SF-36, EQ-5D-5L, ISI.
- For all subjects, complete the PGIPS score.
- The Investigator is to complete the PGA PA.
- Obtain central laboratory samples for PK, ADAs, and biomarkers.
- Other procedures deemed necessary per the Investigator or delegated site personnel (e.g. MRI for sub-study subjects).

Upon having completed the evaluation, if the Investigator makes a clinical diagnosis that the subject is having a pericarditis recurrence event, he/she should contact the [redacted] medical monitor to review and confirm that all assessments have been performed and collected. Upon [redacted] medical monitor confirmation of completion of the assessment, the Investigator commences as described in Section 6.2.3.

Subjects treated for a pericarditis recurrence event will continue to follow the same visit schedule described for the RW period (Section 6.1.5).

Source documentation including the assessments and evaluations used to confirm a pericarditis recurrence event, are required to be sent to CEC.

6.1.5. Randomized Withdrawal Period Visits

During the RW period, subjects will continue with once-weekly study drug administration as well as daily 11-point pericarditis pain NRS scoring. Visits will occur every 4 weeks, alternating TC/RN visits and clinic visits, with the first visit during the RW period (RW Week 4) being a TC/RN visit. Additional unscheduled visits may occur at any time for evaluation of suspected pericarditis recurrence (Section 6.1.4) or for other reasons as deemed necessary by the study Investigator. Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities for these visits.

6.1.6. End of Randomized Withdrawal and LTE Baseline (EORW and LTE Baseline Visits)

All subjects, including those that have had pericarditis recurrence or have permanently discontinued study drug will have an EORW visit at the end of the RW period. Upon completion of the EORW visit procedures those subjects who have not discontinued treatment previously will provide informed consent to participate in the LTE period. The LTE Baseline visit will be completed on the same day as the EORW visit. During the LTE subjects will return to the site every 12 weeks for up to 24 months thereafter from the first dose of open-label rilonacept in the LTE. Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities for these visits.

6.1.7. End of Treatment Visit

If at any time throughout the course of the study a subject prematurely discontinues study drug, an End of Treatment (EOT) visit is to occur as soon as possible. If the EOT visit coincides with the last study visit completed by the subject, procedures that are required at both visits do not need to be repeated and should be applied to complete the EOT requirements. Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities for this visit.

6.1.8. Safety Follow-up Visit

The SFU visit is to be conducted 6 weeks after the last dose of study drug. In the event that a subject permanently discontinues study drug but does not withdraw the informed consent, the Investigator should continue to follow the subject per protocol for the remainder of that study period. Refer to Section 13.1 for a comprehensive list of procedures in the Schedule of Activities for this visit.

6.2. Efficacy Assessments

Efficacy assessments to be performed at study visits are summarized in Section 13.1 and include: CRP, daily pericarditis pain assessment (11-point NRS), ECG, ECHO, Patient Global Impression of Pericarditis Severity (PGIPS), Physician Global Assessment of Pericarditis Activity (PGA-PA), and subject's quality of life assessments (SF-36, EQ-5D-5L) and insomnia questionnaire (ISI). In a sub-study at selected sites, a cardiac MRI will be performed.

Note that in case the electronic versions of the PROs and assessments/questionnaires (PGIPS, PGA-PA, SF-36, EQ-5D-5L, and ISI) are not available, the paper forms must be completed until the electronic versions are available again.

6.2.1. Individual Efficacy Assessments

6.2.1.1. C-Reactive Protein

Central and local laboratory assessments of CRP will be performed at study visits as described in Section 13.1. Centrally assayed CRP values will be used for statistical evaluations of changes from baseline. Locally assayed CRP will be used for screening,

evaluation of treatment response prior to randomization, and assessment of suspected pericarditis recurrence in the RW period. The POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment.

6.2.1.2. 11-Point Pericarditis Pain Numerical Rating Scale

Subjects will be asked to provide a daily assessment of pericarditis pain starting at RI baseline until EORW visit. A validated 11-point pericarditis NRS (see Section 13.2) will be used to measure the subject's level of pain intensity on a daily basis throughout the study (Hawker et al 2011; Mannion et al 2007; Dworkin et al 2005).

It is recommended that daily pericarditis pain measurements using the 11-point pericarditis NRS are performed by subjects at the same time of the day each day, and prior to study drug injection on days with study drug administration.

6.2.1.3. Electrocardiogram

Twelve-lead ECGs will be performed at study visits as described in Section 13.1. Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-segment elevation or PR-segment depression.

6.2.1.4. Echocardiogram

Echocardiographic assessment of presence of pericardial effusion including new or worsening of pericardial effusion should be obtained at study visits as described in Section 13.1. Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart, and pericarditis is one of the main causes of pericardial effusion. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening. Echocardiograms are to be acquired per the ECHO core imaging parameters. Upon local assessment and interpretation, the ECHO is then to be submitted to the designated central imaging laboratory.

6.2.1.5. Patient Global Impression of Pericarditis Severity

Patient Global Impression questionnaires have been developed for a variety of indications. The PGIPS is a single-item PRO measure that assesses the subject's impression of overall severity of pericarditis symptoms at the time the questionnaire is administered, using a 7-point rating scale ranging from absent (no recurrent pericarditis symptoms) to very severe (recurrent pericarditis symptoms cannot be ignored) (Guy 1976). The PGIPS can be completed in less than 30 seconds.

The subject will select from the following that best describes the severity of pericarditis symptoms at the time of occurrence of the event:

- Absent: no symptoms
- Minimal: can be easily ignored without effort
- Mild: can be ignored with effort

- Moderate: cannot be ignored but does not influence my daily activities
- Moderately severe: cannot be ignored and occasionally limits my daily activities
- Severe: cannot be ignored and often limits my concentration on daily activities
- Very severe: cannot be ignored and markedly limits my daily activities

The PGIPS will be collected as described in Section 13.1.

6.2.1.6. Physician Global Assessment of Pericarditis Activity

Physician Global Assessment questionnaires have been developed for a variety of indications. The PGA-PA is a single-item clinician-reported outcome measure that Investigators use to rate their impression of the patient's overall pericarditis disease activity at the time the assessment is completed, using a 7-point rating scale ranging from absent to very severe (Guy 1976). Like the PGIPS, the PGA-PA can be completed in less than 30 seconds.

The Investigator will select the box that best describes subject's pericarditis activity at the time of occurrence of the assessment.

- Absent
- Minimal
- Mild
- Moderate
- Moderately severe
- Severe
- Very severe

The PGA-PA will be collected as described in Section 13.1.

6.2.1.7. 36-Item Short Form Health Survey

The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. The SF-36 was developed at RAND Corporation as part of its Medical Outcomes Study. The SF-36 assesses 8 health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health.

SF-36 will be collected in subjects ≥18 years or older as described in Section 13.1.

6.2.1.8. EQ-5D-5L

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EQ VAS. The descriptive

system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The rating scale records the subject's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgement. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles (https://euroqol.org/eq-5d-instruments).

The EQ-5D-5L will be collected in subjects ≥18 years or older as described in Section 13.1.

6.2.1.9. Insomnia Severity Index

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. The total score is interpreted as follows: no clinically significant insomnia (0–7); subthreshold insomnia (8–14); clinical (moderate) insomnia (15–21); and clinical (severe) insomnia (22–28) (Morin et al 2011).

The ISI will be collected in subjects ≥18 years or older as described in Section 13.1.

6.2.1.10. Cardiac Magnetic Resonance Imaging

Cardiac MRI will be performed as described in Section 13.1 in subjects at selected sites in the cardiac MRI substudy. Cardiac MRI will be performed to assess any changes in pericardial inflammation. Cardiac MRI readings will be performed by a central imaging laboratory. The study site/clinic reading of the MRI at the time of the examination may be used by the Investigator for clinical decision-making.

6.2.2. Assessment of Clinical Response at the End of the Run-In Period Week 12/RW Baseline

At RI Week 12/RW baseline visit, all subjects receiving rilonacept who are able to discontinue background SOC pericarditis therapy during the RI period (Section 3.1) are assessed for Clinical Response. Only subjects who achieve Clinical Response at RI Week 12 and have discontinued background medications for pericarditis are eligible for randomization in the RW period.

Clinical Response at RI Week 12 is defined as follows:

- A weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS during the 7 days prior to and including the day of randomization, **AND**
- CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.

6.2.3. Management of Suspected Pericarditis Recurrence in the RW Period

Pericarditis Recurrence Definition: Pericarditis recurrence, for the purpose of the protocol, is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis.

At any time point during the RW period, subjects who experience suspected recurrence of their pericarditis will have been instructed to inform their site Investigator as soon as possible. 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 (Section 6.1.4). The Investigator will evaluate all assessments performed for a diagnostic workup, whether at the study site or at locations outside.

Upon completion of pericarditis workup, the Investigator is required to contact the [redacted] medical monitor to confirm that the protocol required diagnostic workup is complete prior to implementing treatment for the event.

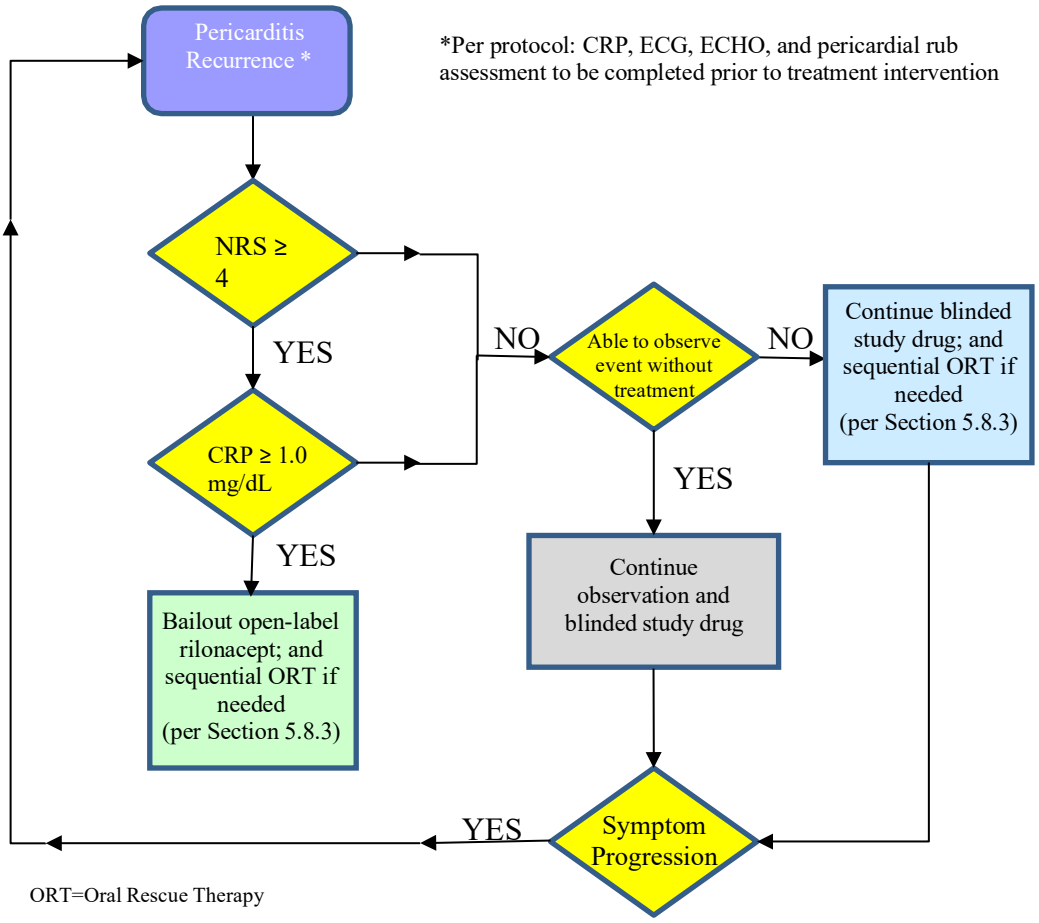
Following communication with the [redacted] medical monitor, if the event meets the criteria for bailout rilonacept (at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and one CRP value ≥1 mg/dL either on the same day or separated by no more than 7 days), and after the [redacted] medical monitor has confirmed with the Investigator that the diagnostic workup is complete, the attainment of bailout criteria is confirmed in the IWRS, blinded study drug is discontinued, and open-label rilonacept treatment is dispensed. If needed, sequential ORT is allowed as outlined in Section 5.6.3. The subject will continue to be followed up according to Section 13.1 for the RW period.

Following communication with the [redacted] medical monitor, if the event does not meet the protocol criteria for bailout rilonacept but in the judgement of Investigator requires treatment, after the [redacted] medical monitor has confirmed with the Investigator that the diagnostic workup is complete, the Investigator is allowed to add sequential ORT to blinded study drug, and as outlined in Section 5.6.3. Blinded study drug treatment will continue until a pericarditis recurrence that meets criteria for bailout rilonacept, or until the end of the RW period.

For a summary of management of suspected pericarditis recurrence, refer to Figure 3.

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. The event package will include, but may not be limited to, data on the subject's pericarditis pain level, CRP value, ECG tracing, ECHO result, the presence or absence of pericardial rub, and any additional source documentation relevant to the assessment of the suspected event. Details on endpoint package requirements will be described in the CEC charter. The CEC-confirmed pericarditis recurrences will be used for Primary Endpoint efficacy analysis. For more details on the CEC, refer to Section 6.7.2

Figure 3: Management of Suspected Pericarditis Recurrence in the Randomized-Withdrawal Period



6.3. Safety Assessments

Safety assessments to be performed at study visits are summarized in Section 13.1 and include: assessment of AEs (Section 6.4), physical examinations (full and abbreviated) including vital signs measurements, chest x-ray, TB screening, and clinical laboratory tests (serology, hematology, chemistry, urinalysis) (Section 6.6). A pregnancy test (Section 6.6.6) will be conducted at screening and as needed during the study and must be performed 6 weeks after the last study drug administration.

6.3.1. Physical Examination

A full physical examination should include at minimum an evaluation of vital signs, head, eyes, ears, 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. Body weight and height will be measured as per Section 13.1 and will be recorded in the eCRF. Any abnormality identified at baseline should be recorded on the medical history and physical

examination eCRFs. At selected visits as specified in Section 13.1, an abbreviated physical examination will be performed to evaluate vital signs, lung and heart sounds, including evaluation for pericardial rub.

At all visits at the study site, limited symptom-directed physical examinations may need to be performed in order to determine changes from baseline or abnormalities and should be recorded in the subject's trial notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

6.3.2. Vital Signs

Vital signs include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Blood pressure measurements should be obtained after the subject has been seated for at least 5 minutes.

6.3.3. Chest X-ray

Chest x-rays in accordance with local requirements will be obtained at screening (or an existing chest x-ray within 12 weeks of first study drug administration can be used) according to Section 13.1. Chest x-rays should be reviewed by a qualified radiologist for clinically significant abnormalities and evidence of pulmonary disease that would exclude the potential subject.

6.3.4. Tuberculosis Screening

An IGRA test or another TB test based on acceptable clinical practice in each country will be performed in order to evaluate for the presence of active or latent TB infection at screening (see Section 4.2).

6.4. Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

6.4.1. Definitions

6.4.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the reporting Investigator to be clinically significant; and any untoward medical occurrence.

6.4.1.2. Treatment-emergent Adverse Event

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to the study drug or any event already present that worsens in either intensity or frequency after exposure to the study drug.

6.4.1.3. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence or effect that, at any dose:

- Results in *death*. Includes all deaths, even those that appear to be completely unrelated to the study drug (e.g., car accident where the subject is a passenger).
- Is *life-threatening*. In the view of the Investigator, the subject was at immediate risk of death from the event at the time of the event (i.e., it does not include an AE that might have caused death if it had occurred in a more serious form).
- Requires *in-patient hospitalization* or prolongs an existing hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such pre-existing condition must be recorded on the medical history or physical examination page of the eCRF. Hospitalization is defined as an admission to the hospital ward, a short-stay type unit, or Emergency Room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay longer than originally anticipated for the event or development of a new AE as determined by the Investigator or treating physician.)
- Results in *persistent or significant disability/incapacity*. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.)
- Is a congenital anomaly/birth defect.
- Is an *important medical event*. Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above, i.e., any event that the Investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the study drug.

All SAEs that occur after signing of study-related informed consent, whether or not the SAEs are related to the study drug or study procedures, must be reported.

6.4.1.4. Adverse Event of Special Interest

An adverse event of special interest (AESI) is defined as an AE of scientific and medical interest specific to the understanding of the study drug and requiring close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of the study drug.

Treatments with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies. Therefore, malignancy is an AESI for rilonacept. Any AE of malignancy (excluding basal cell carcinoma of the skin) requires reporting to the [redacted] Pharmacovigilance (PHV) within 24 hours after the time the site personnel first learn about the event, following the process as described in Section 6.4.6.

6.4.1.5. Adverse Reaction

Any noxious and unintended response to the study drug (i.e., where a causal relationship between the study drug and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reaction.

6.4.1.6. Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse reaction that is "unexpected", i.e., it is not listed (or not listed at the severity that has been observed) in the designated Reference Safety Information of the Investigator's Brochure. Evaluation and reporting requirements for SUSARs are detailed in Section 6.4.8.

6.4.2. Assessing Adverse Events

6.4.2.1. Relationship to Study Drug

The Investigator's assessment of an AE's relationship to the study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized by Investigator using the following classification and criteria:

- **Not Related**: when the AE is definitely caused by the subject's clinical state or the study procedure/conditions
- **Unlikely Related**: when the temporal association between the AE and the study drug is such that the drug is not likely to have any reasonable association with the AE
- **Possibly Related**: when the AE follows a reasonable temporal sequence from the time of study drug administration but could have been produced by the subject's clinical state or the study procedures/conditions

- **Related**: when the AE follows a reasonable temporal sequence from administration of the study drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced

6.4.2.2. Intensity

The severity of an AE will be recorded as one of the following:

- **Mild**: easily tolerated, does not interfere with normal daily activities, does not require intervention
- **Moderate**: causes some interference with daily activities; minimal, local, or noninvasive intervention indicated
- **Severe**: as a consequence of the event, daily activities are limited or completely halted; hospitalization or prolongation of hospitalization indicated

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.3. Recording Adverse Events

Each subject should be monitored for the development of any AEs. This information should be collected by asking nonleading questions (such as “How are you feeling?”) and from observations of and conversations with patients. AEs may also be collected by direct physical exam, diagnostic procedures, or any other appropriate source.

At every study visit (telephone or at the site), subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been admitted to the hospital, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

All AEs (serious and non-serious) will be documented in the subject’s source documents and recorded in the eCRF. Any clinically relevant (as determined by the Investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the subject’s source documents and in the eCRF.

The AE term should be reported in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Information to be collected includes the following:

- Event term
- Date and time of onset
- Investigator-specified assessment of severity and relationship study drug
- Date of resolution of the event

- Seriousness
- Any required treatment or actions
- Outcome
- Whether or not it caused the subject to discontinue the study drug.
- Whether or not the AE is an Injection Site Reaction (ISR). ISR is defined as any AE that occurs at the study drug injection site. If an ISR is observed, the subject may be treated at the discretion of the Investigator.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the condition deteriorates at any time during the study, it should be recorded as an AE.

6.4.3.1. Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.3.2. Adverse Events Based on Examinations and Tests

If an abnormal laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical rather than the laboratory term (e.g., anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically significant findings on examinations and tests should be reported as AEs.

Any new or aggravated clinically significant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4.3.3. Pericarditis Disease-related Events

Signs, symptoms, and abnormal findings associated with pericarditis are to be captured as a pericarditis recurrence event rather than as an AE unless the event is more severe than expected for the subject. In any case, pericarditis recurrence is required to be captured in the eCRF (see Section 6.2.3) within 24 hours of learning of the event.

6.4.4. Time Period for Collection of Adverse Events

Adverse events will be assessed from the time the subject's signs the ICF and through 6 weeks after the last dose of study drug.

6.4.5. Follow-Up of Unresolved Adverse Events

Every reasonable effort will be made to follow subjects who have AEs.

Any AEs that are unresolved at the end of the subject's SFU visit are to be followed up by the Investigator until resolution or for as long as medically indicated. Additional information for any subject with an ongoing AE at the end of the SFU period may be requested by the [redacted] PHV, as needed.

6.4.6. Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.4.1.3) must be reported to the [redacted] PHV using the EDC system, immediately (i.e., within 24 hours) after the time site personnel first learn about the event.

In the event the EDC entry is not possible (e.g., system failure or access problems), the study site should complete the paper SAE report form and fax the form to the [redacted] PHV within 24 hours of awareness. The EDC system should be updated as soon as it is available.

A full description of every SAE will need to be provided to the [redacted] PHV (this may be supported by source documentation such as discharge summary or laboratory report should these documents be requested by the [redacted] PHV). Additional follow-up information, if required or available, should be sent to the [redacted] PHV as soon as possible and placed with the original SAE information.

The following contact information is to be used for SAE reporting:

[redacted]

Information on non-serious AEs that become serious must also be reported to the [redacted] PHV as soon as it is available.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as applicable per institutional policy.

The Sponsor or designee will provide regulatory authorities, IRBs, IECs, and principal Investigators with clinical safety updates/reports according to local requirements.

6.4.6.1. Other Reasons for Immediate Reporting

The following events require reporting to the [redacted] PHV within 24 hours after the time the site personnel first learn about the event:

- Pregnancy in subject or female partner of male subject

- Overdose of the study drug or concomitant medication, regardless of whether it is considered AE
- Other study drug errors
- Any AE of malignancy (excluding basal cell carcinoma of the skin)

6.4.7. Pregnancy

Pregnancy is regarded as an AE only if there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. Nonetheless, any pregnancy that occurs during study participation (including pregnancy in a female partner of a male subject) must be reported to the [redacted] PHV in the same way and using the same procedures as for an SAE (Section 6.4.6). The subject with pregnancy must not receive (additional) study drug. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriage must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the subject has completed the study, and considered by the Investigator as possibly related to the study drug, must be promptly reported to the [redacted] PHV.

In the event that a subject is found to be pregnant after having received at least 1 study drug dose, the study drug must be discontinued, and the pregnancy will be followed to term and the status of mother and child will be reported to the [redacted] PHV after delivery. Instances of perinatal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of study drug, will be reported to the [redacted] PHV within 24 hours.

6.4.8. Evaluating and Reporting SUSARs

[redacted] Pharmacovigilance will promptly evaluate all SUSARs and nonserious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, [redacted] PHV staff in collaboration with Kiniksa Pharmaceuticals will assess the expectedness of these events using the Reference Safety Information (Section 6.2) of the rilonacept Investigator's Brochure.

[redacted] PHV will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by [redacted] PHV and Kiniksa Pharmaceuticals as needed.

All relevant information about suspected SUSARs that are fatal or life-threatening will be recorded and reported to the competent authorities in all the applicable countries, and IRBs/IECs in conjunction with Directive 2001/20/EC.

6.5. Other Assessments

6.5.1. Pharmacokinetic Sample

All subjects will have PK samples obtained according to Section 13.1. For PK analyses, it is important that the exact time of the SC injection is recorded for each subject. When PK samples are to be collected on dosing days, serum will be collected pre-dose to measure rilonacept concentrations. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

A PK substudy will be conducted in a subset of subjects agreeing to provide a PK sample 24 hours after the first dose of study drug in the RI period. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

6.5.2. Anti-Drug Antibodies (ADAs) against Rilonacept (KPL-914)

Serum samples to measure the presence of ADAs against rilonacept will be collected according to Section 13.1. Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the site.

6.5.3. Biomarkers

Serum and plasma will be collected according to Section 13.1 for biomarker analysis.

6.5.4. Pharmacogenomics

Whole blood will be collected for pharmacogenomics assessments after signing the separate Pharmacogenomics ICF.

6.6. Laboratory Analyses

Any abnormal laboratory test results (hematology, chemistry, or urinalysis) or other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgement of the Investigator are to be recorded as AEs or SAEs.

Laboratory assessments will be performed at study visits as summarized in Section 13.1. Unscheduled laboratory assessments for safety issues are permitted as deemed necessary by the Investigator.

Whenever possible in pediatric subjects, local laboratory tests should be drawn using pediatric tubes.

6.6.1. Serology

Samples for local or central laboratory assessment of hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and HIV test will be collected at screening. If clinically indicated, those tests may be also collected during the study.

6.6.2. 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.

6.6.3. Chemistry

Blood chemistry tests performed in the central study laboratory include albumin, total protein, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, total bilirubin, bicarbonate, chloride, potassium, sodium, creatinine, glucose.

In addition, the following chemistry tests may be performed together with local CRP measurement when using POC device: chloride, creatine kinase, creatinine, glucose, potassium, sodium, total carbon dioxide, blood urea nitrogen.

6.6.4. Non-fasting Lipid Panel

Subjects treated with rilonacept may experience increases in their lipids, including total cholesterol, LDL, HDL, and triglycerides.

Non fasting measurements of total cholesterol, triglycerides, HDL, and direct LDL will be performed by central study laboratory as described 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.

6.6.5. Urinalysis

Urinalysis performed by the central study laboratory includes specific gravity, pH, protein, urobilinogen, ketones, glucose, blood, bilirubin, nitrites, leukocyte esterase. It will be performed as described in Section 13.1.

6.6.6. 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. When needed, serum pregnancy test should be performed. The purpose of pregnancy test is to prevent embryo/fetal exposure to study drug. Subjects with positive or indeterminate pregnancy test during the screening are not eligible for the study.

6.6.7. Sample Collection

The procedures for the collection, handling, and shipment of laboratory samples are specified in the Laboratory Manual supplied to sites by the central laboratory.

6.7. Committees

6.7.1. Independent Data Monitoring Committee (DMC)

A DMC will be utilized in this study to ensure external objective medical and/or statistical (if needed) review of safety data in order to protect the ethical and safety interests of subjects. The DMC will review unblinded aggregate (and, where necessary, individual) subject safety data at pre-defined intervals according to a DMC charter. The analysis plan for the DMC review will be described in the DMC charter, which will also contain details of the composition and the responsibilities of the DMC.

6.7.2. Clinical Endpoint Committee (CEC)

An independent CEC will review and adjudicate all suspected recurrent pericarditis events that occur during the RW period of the study. The procedures for adjudicating events will be described in the CEC Charter. This will be done independent of the Investigators, and in a manner blinded to treatment assignment. The CEC will complete assessments on an ongoing basis.

7. STATISTICAL AND ANALYTICAL PLAN

7.1. Primary Efficacy Endpoint

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.

A sensitivity analysis will be done based on the Investigator's assessment of the event.

Pericarditis recurrence is defined in Section 6.2.3.

Subjects who do not have a pericarditis recurrence will be censored at the date of the last available assessment for pericarditis recurrence during the RW period before data cutoff. Detailed censoring rules will be specified in the Statistical Analysis Plan (SAP).

7.2. Secondary Efficacy Endpoints for the RW Period

This Section defines secondary efficacy endpoints for the RW period. Endpoints for the RI period and for the LTE are defined in Section 7.3.

7.2.1. Major Secondary Efficacy Endpoints

- 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.
- Percentage of days with no or minimal pain in the first 16 weeks of the RW period. No or minimal pain is defined as non-missing NRS ≤2.
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 16 of the RW period.

7.2.2. Other Secondary Endpoints

All time-to-event endpoints start from the day of randomization. The following variables will be analyzed:

- Proportion of subjects who maintained Clinical Response at Week 8 and Week 24 of the RW period, respectively
- Percentage of days with no or minimal pain (pain ≤2 on the 11-point NRS) in the first 8 weeks and 24 weeks of the RW period, respectively
- Proportions of subjects with absent or minimal pericarditis symptoms (based on the 7 point rating scale of PGIPS) at Week 8 and Week 24 of the RW period, respectively
- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL. This is for elevation of CRP for which no other cause other than pericarditis was identified.
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG, whichever occurs first
- Time to new or worsening pericardial effusion on ECHO
- Change in category of ECHO pericardial effusion size at week 24 and end of RW based on central labs
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA over time

- Proportion of subjects with absent or minimal pericarditis activity over time based on the PGIPS over time
- Change over time in SF-36 Physical and Mental Component Scores and domain scores (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health domains)
- Changes in SF-6D, 6 domain scores and utility index
- Change in EQ-5D-5L. There are 6 questions in this instrument (Section 6.2.1.8). Each of the first 5 questions has 5 levels, from level 1 (best) to level 5 (worst). They are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The sixth question is the health on the day, from 0 (the worst) to 100 (the best) (van Reenen and Janssen 2015). The levels of the first 5 questions (EQ-5D-5L profile) will be converted to an index value. Change from baseline in each one of these 7 values will be an endpoint.
- Change in subject's sleep quality assessed with the ISI (Section 6.2.1.9). There are 7 items in the ISI. Change in ISI total score, which is the sum of the 7 items over time, will be the endpoint.
- Change in ISI categories. The ISI total scores are divided to 4 categories:
  - 0–7 = No clinically significant insomnia
  - 8–14 = Subthreshold insomnia
  - 15–21 = Clinical insomnia (moderate severity)
  - 22–28 = Clinical insomnia (severe)
- 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 following endpoints are for subjects enrolled in the MRI substudy. There will be no hypothesis testing performed. Only summary statistics will be provided.
  - Proportion of subjects with pericardial Delayed Hyperenhancement at RW baseline and week 24 based on the MRI assessment
  - Proportion of subjects with Myocardial Delayed Hyperenhancement at RW baseline and week 24 based on the MRI assessment
  - Proportion of subjects with pericardial Effusion and Effusion size at RW baseline and week 24 based on the MRI assessment

7.3. Other Endpoints

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. All time-to-event endpoints start from the day of receiving rilonacept in that period.

The annualized event rate for recurrence of pericarditis will be calculated for the combined RW and LTE periods.

7.3.1. Efficacy Endpoints for the RI Period

The following efficacy endpoints are included in this period:

- Time to pain response. Pain response is defined as a rolling average of NRS score of 2 or less on three consecutive days
- Time to CRP normalization (≤0.5 mg/dL)
- Time to monotherapy
- Time to clinical response (monotherapy + NRS ≤2 + CRP ≤0.5 mg/dL)
- Proportion of subjects who achieved Clinical Response at the RI Week 12. Clinical Response is defined as reaching monotherapy on or before week 10 and a weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS and CRP level ≤0.5 mg/dL at the RI Week 12/RW baseline visit.
- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12 and over time
- Change from baseline in CRP level at RI Week 12 and over time
- Resolution of ECHO and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain while on treatment
- Proportion of subjects with absent or minimal pericarditis symptoms based on PGIPS over time
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA over time
- Change over time in the SF-36 Physical and Mental Component Scores and domain scores
- Change in the SF-6D 6 domain scores and the utility index
- Change in the EQ-5D-5L (Section 7.2.2 contains details about calculation)
- Change in the subject's sleep quality assessed with the ISI (Section 7.2.2 contains details about calculation)
- Change in ISI categories
- Number (percentage) of subjects who were off background pericarditis medication on or before weeks 4, 8, 10, and 12

7.3.2. Efficacy Endpoints for the LTE Period

Efficacy endpoints for the LTE will be defined in the Statistical Analysis Plan.

7.4. Sample Size Calculations

For the purpose of sample size estimation, 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) 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.

Patient 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 patients 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 patients 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.

7.5. Analysis Sets

The following analysis sets will be used in the statistical analyses.

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

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.

Safety Analysis Set: All subjects who received 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.

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

Run-in Week 12 Analysis Set: All subjects who received the first dose in the RI period at least 12 weeks before data cutoff. This analysis set will be used for secondary efficacy endpoints measured at Week 12 in the RI period.

Long Term Extension Analysis Set: All subjects who received at least 1 dose of study drug in the long-term extension period will be included in the long-term extension analysis set

Per-protocol Analysis Set: The per protocol (PP) analysis set is a subset of the ITT analysis set with the exclusion of subjects with major 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.

Pharmacokinetic Analysis Set: The PK analysis set includes subjects who receive at least 1 dose of study drug and have at least 1 PK sample. The PK analysis set will be used for all PK analyses.

7.6. Description of Subgroups to be Analyzed

Subgroup analyses for the primary endpoint will be performed by the stratification variable for randomization, as well as by important variables for baseline demographics and patient characteristics. These analyses are for the RW period only. Details will be provided in the SAP.

7.7. Statistical Analysis Methodology

This Section outlines the overall methodologies. Details of the statistical analyses, methods, and data conventions will be described in the SAP.

7.7.1. 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 25th, 50th, and 75th percentiles with 95% CI, if estimable.

Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

At each of RI and RW periods and in the LTE, 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.

The analysis for treatment comparison will be triggered after at least the 22nd CEC-confirmed pericarditis recurrence events have been accrued. At that time, randomization will be closed, and subjects will return to study sites for the EORW visit. At that point study treatment will stop (completing the database for the primary efficacy endpoint analysis), and subjects will either continue into the LTE or complete their study participation. Missing data due to end of RW period will be considered as missing at random. Handling of missing values will be described in the SAP.

7.7.2. Stratified Analysis

There will be 2 stratification variables for randomization:

- Oral CS use at RI baseline: yes or no
- Diagnosis of recurrent idiopathic pericarditis at RI baseline: yes or no

When a stratified analysis is used in the analysis and a stratum has no event of interest or no responder, the stratum will be pooled with the other stratum in the same stratification variable.

7.7.3. Testing Hypotheses and Multiplicity Adjustment

All statistical tests for the treatment comparison of efficacy endpoints in the RW period will be based on the ITT analysis set with 1-sided α=0.025 unless otherwise specified. 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 $\leq$0.025, a significant treatment effect on the primary endpoint will be claimed.

Section 7.2.1 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 24 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 $\leq$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 7.2.1 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.

7.7.4. Analysis of Primary Efficacy Endpoint

Primary analysis of this study will be triggered after at least the 22nd CEC-confirmed pericarditis recurrence events have been accrued. The log rank test will be the primary method for the analysis of time to recurrence, stratified by the stratification variables for randomization. Detailed censoring rules will be described in the SAP.

A sensitivity analysis will be performed based on the Investigator's judgement of pericarditis recurrence. Additional sensitivity analyses may be defined in the SAP.

7.7.5. Analysis of Secondary Efficacy Endpoints

7.7.5.1. Analysis of the Major Secondary Endpoints

The analyses for the 3 major secondary endpoints will be based on the ITT Week 16 analysis set, with the Week 8 and Week 24 ITT analysis sets providing supportive sensitivity analyses.

- Proportion of subjects who maintained Clinical Response at Week 16 of the RW period (defined as a weekly average of daily pericarditis pain ≤2.0 on the 11-point NRS, CRP ≤0.5 mg/dL, and on monotherapy of randomized study drug at Week 24). The Cochran–Mantel–Haenszel (CMH) test will be used in this analysis, stratified by the stratification variables for randomization.
- Percentage of days with no or minimal pain in the first 16 weeks post randomization. Minimal or no pain is defined as non-missing daily NRS ≤2 on the 11-point NRS. This endpoint will be analyzed with an analysis of covariance. In addition to treatment arm, the following covariates will be included in this analysis: the stratification variables for randomization, and RI baseline NRS weekly average in 2 categories: NRS ≤2 versus NRS >2.
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGIPS) at Week 16 of the RW period. The CMH test will be used in this analysis, stratified by the stratification variables for randomization.

7.7.5.2. Analyses of Other Secondary Endpoints in the RW Period

The following endpoints will be analyzed using the same method for the major secondary endpoints:

- Proportion of subjects who maintained Clinical Response at Week 8 and Week 24 of the RW period
- Percentage of days with no or minimal pain (pain ≤2 on the 11 point NRS) in the first 8 weeks and 24 weeks of the RW period

- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point rating scale of PGIPS) at Week 8 and Week 24 of the RW period

The following endpoints will be analyzed using the same method for the primary endpoint:

- Time to pericarditis pain NRS ≥4
- Time to CRP level ≥1 mg/dL. This is for elevation of CRP for which no other cause other than pericarditis was identified.
- Time to pericardial rub
- Time to widespread ST segment elevation or PR segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO

A mixed model with repeated measures (MMRM) will be used in the analysis of the endpoints below. In the model, subjects will have repeated measures for the response variable change from baseline of the endpoint. For endpoints without repeated measures with subjects, e.g., health-related quality-of-life assessment, the analysis of covariance will be applied. The explanatory variables will include the baseline value, treatment arm, and the variables for stratification at randomization. The p-value for treatment comparison will be calculated at each scheduled assessment for at least 24 weeks as part of the summary statistics. This is done with the understanding that the comparison could be biased due to dropouts or subjects with pericarditis recurrence.

- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain (weekly average)

The CMH test will be used in the analysis of the endpoints below, stratified by the stratification variables for randomization.

- Proportion of patients without pericarditis recurrence in the first 24 weeks of the RW period
- Number (percent) of subjects with absent or minimal pericarditis activity based on the PGA-PA

The following endpoints will be summarized without formal hypothesis testing:

- Change in the SF 36 Physical and Mental Component Scores and domain scores
- Change in the EQ 5D 5L: Health score and Index value, respectively
- Change in the subject's sleep quality: sum of the ISI scores.

The following exploratory endpoint in the MRI sub-study will be summarized by treatment

[redacted]

7.7.6. Analyses of Other Endpoints

Endpoints listed in Section 7.3 for the RI period and the LTE will be descriptive in nature since there is no control arm. Summary statistics will be generated following the methodologies stated in Section 7.7. Analysis for efficacy endpoints measured at week 12 will be done using the run-in Week 12 analysis set.

Other analyses include anti-rilonacept antibodies and biomarker analyses. These analyses will be described in the SAP.

7.7.7. Pharmacokinetic Analyses

For all subjects, serum samples will be collected at time points shown in the Schedule of Activities in order to quantify concentrations of rilonacept. Descriptive statistics will be calculated for the serum concentrations of rilonacept by visit. Individual listings of serum concentrations will be provided.

Pharmacokinetic data may be used in a subsequent population PK evaluation that will be conducted outside of this study and described in a separate report.

7.7.8. Safety Analyses

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 the most recent version of MedDRA. TEAEs will be analyzed for all subjects combined and by treatment group in the RW period. Further analyses by severity and relationship to study drug as well as analyses of serious TEAEs will be presented.

Descriptive statistics will be used to summarize safety endpoints by visit for all subjects combined in the RI period and by treatment group in the RW period. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for clinical laboratory analyses (including safety laboratory measurements, ADAs, etc.), vital signs measurements, ECGs, and physical examination findings.

7.7.9. Interim Analyses

No interim analyses are planned for this study.

8. DATA QUALITY ASSURANCE

Assessment of subject compliance and adherence to study drug administration will be assessed by the site in collaboration with the visiting RN.

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be

implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management (ICH Q9).

8.1. Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, etc.

[redacted] will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant Standard Operating Procedures (SOPs) of [redacted]

Investigative site personnel will enter subject data into an EDC system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After the last study database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a Master DVD/CD-ROM copy of all of the site data from the study will be created and sent to Kiniksa for storage. [redacted] will maintain a duplicate Master DVD/CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to Kiniksa Pharmaceuticals.

9. ETHICS

9.1. Independent Ethics Committee or Institutional Review Board

Regulatory agencies and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, informed assent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by Kiniksa Pharmaceutical or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must promptly supply Kiniksa Pharmaceutical or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3. Subject Information and Consent

A written informed consent in compliance approved by an IRB/IEC, as appropriate, at each center/country shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent for (or assent form, as applicable) template may be provided by Kiniksa Pharmaceutical or its designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by Kiniksa Pharmaceutical or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before screening, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

It should be emphasized to the subjects that they may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

For potential subjects under the age of 18, a parent or legal guardian is required to sign and date the ICF and the potential subject is also required to sign and date an informed assent form. The informed assent form explains the trial, it’s purpose, procedures as well as risk and benefits in age-appropriate language. Both the ICF and informed assent form, as applicable, are required prior to participation in the trial. The Investigator shall retain the signed original ICF(s)/assent form(s), as applicable, and give a copy of the signed original form to the subject or legal guardian.

For this study, subjects will be required to sign and date the ICF (or assent form, if applicable) prior to entry to the study and prior to entry to LTE.

In addition, a separate ICF (assent, if applicable) will be needed for subjects participating in pharmacogenomic testing or the MRI sub-study.

10. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on local or country-specific industry and government standard operating procedures, working practice documents, or guidelines.

10.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by Kiniksa Pharmaceuticals, its designee, the regulatory agencies/authorities, or the IRB/IEC.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Kiniksa Pharmaceuticals or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2. Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow Kiniksa Pharmaceuticals or its designee to submit the complete and accurate certification or disclosure statements required under US Title 21 Code of Federal Regulations (CFR) Part 54. In addition, the Investigator must provide to Kiniksa Pharmaceuticals a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither Kiniksa Pharmaceuticals nor [redacted] is financially responsible for further treatment of the subject's disease.

10.3. Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original Investigator-signed Investigator agreement page of the protocol

- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 or local country-specific equivalent for outside the US
- Curriculum vitae for the Investigator and each sub-Investigator listed on Form FDA 1572 or local country-specific equivalent for outside the US
- Financial disclosure information
- IRB/IEC-approved ICFs/assent forms, as applicable, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

10.4. Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5. Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6. Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs to [redacted] and/or IRB/IEC according to the time line and method outlined in the protocol and as per local requirements. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7. Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB/IEC with a summary of the study's outcome and Kiniksa Pharmaceuticals and regulatory authority(ies) with any reports required.

10.8. Records Retention

It is the responsibility of the Investigator to ensure all essential trial documentation and source records (e.g., signed ICFs, study site/clinic files, subjects' hospital notes, copies of eCRFs) at their site are securely retained. The Sponsor will inform the Investigator of the time periods for retaining study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that

site for the study, as dictated by any institutional requirements or local laws or regulations; otherwise, the retention period by default will be 15 years.

10.9. Publications

[redacted]. Investigators are encouraged to participate in the study execution such that they may be invited to participate in the authorship of a potential publication in a manner commensurate with their participation in the study execution in accordance with International Committee of Medicinal Journal Editors standards. Any publication of the results will be subject to the terms and conditions provided in the study agreement.

11. STUDY MANAGEMENT

The administrative structure will include a Data Monitoring Committee (DMC) and a Clinical Endpoint Committee (CEC). Please refer to Section 6.7 for further details.

11.1. Monitoring

11.1.1. Monitoring of the Study

Data for each subject will be recorded in source records and in the eCRF. Data collection must be completed for each subject who signs an ICF.

For each subject enrolled, the Investigator or designee will document in the source records of the subject that the subject is enrolled in this study along with all safety and efficacy information. The Investigator is responsible for maintaining adequate case histories in the source records of each subject. Source data should be preserved for the maximum period of time permitted by the hospital/institution and made available by the Investigator in the cases described above.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

11.1.2. Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow Kiniksa Pharmaceuticals, representatives of Kiniksa Pharmaceuticals, or a regulatory agency(ies) access to all study records.

The Investigator should promptly notify Kiniksa Pharmaceuticals and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Kiniksa Pharmaceuticals and [redacted]

11.2. Management of Protocol Amendments and Deviations

11.2.1. Modification of the Protocol

Sponsor initiated amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC for approval and to the regulatory authorities, if required, before subjects can be enrolled into an amended protocol.

11.2.2. Protocol Deviations

A deviation from the protocol is any change, divergence, or departure from the study design or procedures defined in the protocol. No waivers will be granted for exemptions to inclusion/exclusion criteria. The Investigator will conduct the study in compliance with the protocol agreed to with the Sponsor and, if required, the regulatory authorities, and which was given approval/favorable opinion by the IRB/IEC. In the event of a protocol deviation, the Sponsor or a designee must be notified.

The Investigator, or person designated by the Investigator, must document and explain any deviation from the approved protocol. The Investigator will notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

11.3. Study Termination

The Sponsor has the right to terminate the study at any time due to the following reasons:

- New information leading to unfavorable risk-benefit judgment of the study drug, for example, due to occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or other unfavorable safety findings;
- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons;
- Discontinuation of the study drug development program by the Sponsor.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the termination of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

11.4. Final Report

Whether the study is completed or prematurely terminated, Kiniksa Pharmaceutical will ensure that the clinical study report(s) are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an Investigator signatory will be identified to approve the clinical study report. The Investigator will be provided reasonable

access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, Kiniksa Pharmaceutical will provide the Investigator(s) with the full summary of the study results. The Investigator(s) are encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers, as applicable.

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13. APPENDICES

13.1. Study Schedule of Activities

Table 2: 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									
Pericarditits 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								

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**
Pericardial pain (11-point NRS)	X[f]	DAILY[g]								X[g]
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			

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 Subject Status Update	X	X								X
IWRS Weight Input (pediatric only)		X								X
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 3: 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)[s]		X				X			X
ADA (Central)[s]						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 4: Study Schedule of Activities – Long Term Extension Treatment Period

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[aa]**
Visit Window[b] (days)	**+/- 2**	**+/- 2**	**+/- 2**	**+/- 45**
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)[s]		X		X
ADA (Central)[s]		X	X[bb]	
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.
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.
z The MRI to occur only if the previous MRI was done longer than 6 months ago.
aa Visit to occur 18 months from most recent documented recurrence.
bb Samples collected every 24 weeks.

Table 5: 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	

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**
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)[s]	X	X	X
ADA (Central)[s]	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		
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 and ADA samples will be collected prior to study drug administration. 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. Appendix: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Subjects will be asked to select the score that best describes their average level of pericarditis pain over the previous 24 hours using an 11-point NRS, where zero (0) indicates 'no pain' and ten (10) means indicates 'pain as bad as it could be'.

On this scale of 0-10, zero (0) indicates 'no pain' and ten (10) indicates 'pain as bad as it could be', please rate your pericarditis pain on average in the last 24 hours

13.3. Summary of Changes

This summary of changes document has been prepared to summarize changes to clinical protocol study KPL-914-C002 Amendment 2 (Version 3.0) when compared with the previous amendment (Version 2.0) dated 12 April 2019. The primary reason for this protocol amendment is to increase the ability to assess impact of length of treatment. A summary of the major protocol changes is described below including a rationale for change. In addition, the presentation of content was revised according to the Sponsor's template; no changes to the content of the study were altered as a result of this change unless otherwise specified below.

Section(s) Impacted	Protocol Change	Reason for Change
Global	Primary efficacy endpoint analysis triggered at 22 CEC events. Requirement for a full 24 weeks follow-up dropped for all subjects.	Study powered for time to event; increased enrolment ensures safety exposures are adequate.
Global	LTE extended to 24 months. Observation follow-up dropped.	Provide longer access to study drug for study participants.
Global	Other minor administrative and editorial changes were made throughout the protocol.	Provided for consistency and clarification purposes.