KPL-914-C001 Protocol and Amendments

CLINICAL STUDY PROTOCOL

An Open-Label Pilot Study of KPL-914 in Symptomatic Recurrent Idiopathic Pericarditis

Protocol Number:	KPL-914-C001
EudraCT Number:	Not Applicable
Investigational Medicinal Product:	KPL-914 (rilonacept)
Phase:	Phase 2
Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Medical Monitor:	[redacted]
Date of Protocol:	25 September 2017
Version of Protocol:	1.2

CONFIDENTIAL

1 Protocol Approval Signatures

1.1 Sponsor Signature

Protocol Title: An open-label pilot study of KPL-914 in symptomatic recurrent idiopathic pericarditis.

Protocol Number: KPL-914-C001

This study will be conducted in compliance with the clinical study protocol, ICH Good Clinical Practice and applicable regulatory requirements.

[redacted]

Signature

Date

2 Investigator and Administrative Structure

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Sponsor's Study Contact:	[redacted]
Sponsor's Medical Expert:	[redacted]
Drug safety/SAE-reporting:	[redacted]
Responsible CRO for Biostatistical Analysis:	[redacted]
CRO responsible for: Project Management, Monitoring, Quality Assurance, and Data Management:	[redacted]

3 Synopsis

Trial Number: KPL-914-C001
Trial Title: An open-label, pilot study of KPL-914 in symptomatic recurrent idiopathic pericarditis
Trial Centers: Approximately 15 sites in the United States
Development Phase: 2
Objective(s): Primary: To collect inter- and intra-subject variability data on C-reactive protein (CRP) measurements and the 11-point Numerical Rating Scale (NRS) instrument for assessment of pericardial pain in subjects with recurrent idiopathic pericarditis (RIP) both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in RIP. Secondary: To explore the time course to improvement of pericarditis parameters in symptomatic patients with RIP treated with KPL-914. To evaluate the safety of KPL-914 in symptomatic patients with RIP.
Methodology: This is an open-label single-active-arm pilot study to explore clinical and biochemical endpoints of improvement of pericarditis symptomatology and to collect inter- and intra-subject variability data on both at-baseline and on-treatment parameters in symptomatic patients with RIP who will be treated with once-weekly subcutaneously (SC)-administered injections of KPL-914. Patients identified for participation in this trial will present during a symptomatic episode of RIP, having previously experienced a first (index) episode of acute pericarditis followed by at least 1 recurrent episode before the current enrollment-qualifying episode, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference: - The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate [ESR], and white blood cell [WBC] count) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]). - *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having experienced a previous index episode of acute pericarditis followed by at least 1 recurrent episode of pericarditis prior to the presenting symptomatic episode of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Study subjects will be enrolled (Screening Visit 1 [SCV1]) at the time of a symptomatic episode. In addition to meeting the criteria for pericarditis in the judgement of the Investigator, all subjects must present with a CRP value ≥1 mg/dL at the time of study enrollment. Subjects included in the study may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for at least 3 days will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm the pre-treatment diagnostic workup. At the SCV1, baseline patient and disease characteristics will be determined and captured in the eCRF. Persistence of diagnostic criteria for pericarditis will be confirmed (Screening Visit 2 [SCV2]) within the 24 - 72 hour period before subjects advance to the Treatment Period of the study. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

Approximately 10 subjects will participate in the active Treatment Period of the study. Following review of the ongoing data by the Sponsor and the Investigators, the sample size may be increased to a total of up to 20 subjects. After having met all the entry criteria during the Screening Period, the subjects entering the Treatment Period will receive a loading dose of KPL-914 (2 x 160 mg SC) on Day 0, then 160 mg SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the patient as an outpatient SC administration. A visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be self-administered or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the patient, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study-related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.
Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF. Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF, and medication diary. At the discretion of the Investigator, "Treatment Responders" (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 administration can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks. Weekly Study Drug administrations during the EP are by self-administration, and study nurse visits to the patient's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis. During the EP, the Investigator may choose to wean concomitant NSAIDs, colchicine, and/or corticosteroids according to standard of care paradigms; all medication changes must be recorded in source records and the eCRF. Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after the Week 7 Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing patient management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each.

Given the following occurrences, dosing may be halted or reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg administered SC on Day 0, then 80 mg administered SC weekly for 5 additional weeks, in order to explore efficacy at a lower dose. Depending on treatment response observed with the 80 mg dose, the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject on a daily basis.

Number of Patients:

Approximately 10 symptomatic patients with RIP will be enrolled as study subjects. Following review of the available data, the Sponsor, in collaboration with the Investigators, may increase the sample size to up to 20 subjects to address additional hypotheses.

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

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

To be eligible to participate in the trial, a patient must meet all of the following criteria:

1. Has given consent and signed an Informed Consent Form (ICF).
2. Male or female, of any ethnic origin.
3. 18 to 70 years of age, inclusive.
4. Has had a prior *index episode* of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate, and white blood cell count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

5. Has had at least one prior *recurrent episode* of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
6. Has an ongoing symptomatic episode of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
7. Has an elevated CRP value (i.e., >1 mg/dL) at the time of study enrollment.
8. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days (although stable doses for at least 3 days will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.
9. If female, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
10. Is able to adequately maintain a daily medication diary.
11. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or changing exercise pattern) from the time of signature of the ICF to the End-of-Trial Visit (Week 7).

Exclusion Criteria

A patient who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific etiologies, including tuberculous, neoplastic, or purulent etiologies, post cardiac injury syndromes, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints within the 6-month period before dosing.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female patient who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A patient with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or physical exam. Have recent close contact with a person with active TB.
8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of

the study.

10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.
11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.
12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks of Study Drug administration, or has been treated with intravenous (IV) antibiotics for an infection within 2 months of first Study Drug administration.
15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a patient is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 30 days prior to Study Drug administration.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Patient who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Patient who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

Test Products, Dosage, and Mode of Administration:

KPL-914 (rilonacept) will be provided in its commercially-available formulation as a lyophilized powder to be reconstituted for SC administration.

KPL-914 will be administered as an initial loading dose of 2 x 160 mg SC on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks. After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg administered SC on Day 0, then 80 mg administered SC weekly for 5 additional weeks, in order to explore efficacy at a lower dose.

Subjects will receive a total of 6 doses of KPL-914 during the study active Treatment Period. Subjects who are considered to be "Treatment Responders" will be offered, at the discretion of the Investigator, participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued for a total duration of KPL-914 treatment of up to 24 weeks.

Concomitant Medication

- There is no wash-out of concomitant therapy (NSAIDs/colchicine/corticosteroids) during the Screening Period of the study.
- For the duration of the Treatment Period, concomitant pericarditis medications (e.g., NSAIDs, colchicine and corticosteroids), if used, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAIDs, colchicine, and/or corticosteroid dose is medically necessary, the NSAID, colchicine and/or corticosteroid dose can be down-titrated according to standard of care paradigms in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.
- Opioid analgesics, non-narcotic (non-NSAID) analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF.
- Medical management of pericarditis during the EP is based on Investigator discretion. For example, Investigators may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug, or change (increase or decrease) the dosing of NSAIDs/colchicine/ corticosteroids. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF.
- Prohibited concomitant medicines: Other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.

Duration of Treatment:

The Study Drug will be administered for 6 weeks in the base study Treatment Period.

"Treatment Responders" will be offered participation in an optional 18-week EP at the discretion of the Investigator.

Total subject participation is expected to last for up to 171 days for those that also participate in the 18-week EP.

Efficacy Measures:

- Clinical laboratory analyses (e.g., CRP).
- Pericarditis symptoms (i.e., pain) using a 11-point NRS (Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain)
- Echocardiogram (pericardial effusion)
- ECG (for pericarditis diagnostic findings)
- Pericarditis signs (e.g., fever, pericardial rub)
- Pericardial inflammation as determined by cardiac MRI (optional assessment)
- Quality of life (QoL) questionnaire (Appendix 3).

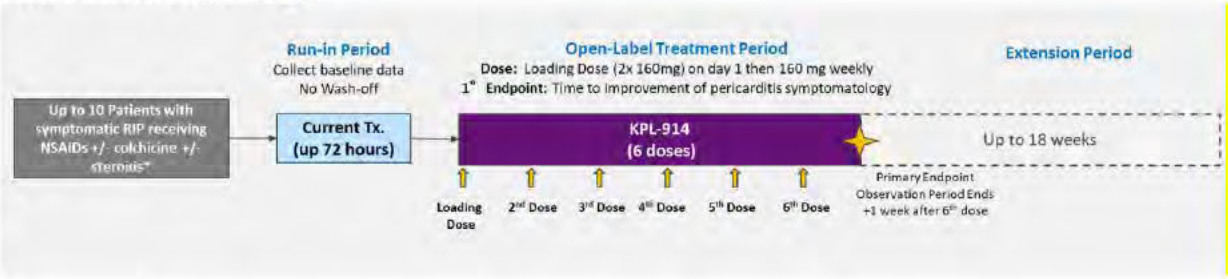
Safety Measure(s):

Safety endpoints for this study include frequency and severity of AEs and SAEs, clinical laboratory analyses (including safety laboratory measurements, anti-drug antibodies, etc.), vital sign measurements, ECGs, and physical examination findings.

Other Measure(s):

[redacted]

Overview of Trial Design



Trial Periods

1. Screening Period: The Screening Period starts with the signing of the ICF (SCV1) and may last for up to 3 days (72 hours) until SCV2. At SCV1, baseline patient and disease characteristics will be determined. Persistence of diagnostic criteria for pericarditis will be confirmed within ~24 to 72 hours at SCV2. Under special circumstances, the Investigator in consultation with the Sponsor can combine SCV1 and SCV2. The end of the Screening Period coincides with the start of the Treatment Period (Day 0 Visit).

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

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

2. Treatment Period: The first dose of Study Drug will be administered to subjects at the Study site/Clinic at Visit 1 on Day 0. During this visit, subjects will be trained for outpatient drug administration. Subsequent weekly Study Drug administrations from Weeks 2 to 5 will be self-administered by the patient as an outpatient SC administration. A visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End-of-Trial, Study Drug may be self-administered at home or administered at the Study site/clinic.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject.

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

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

3. Extension Period (EP): The EP is defined as the 18 weeks following the Treatment Period. Subjects who are considered to be "Treatment Responders" will be, at the discretion of the Investigator, offered participation in an optional 18-week EP, in which weekly administration of open-label KPL-914 may be continued for a total duration of 24 weeks. The weekly KPL-914 doses will be by self-administration, and study nurse visits to the patient's home as well as Investigator (or designee) telephone calls/virtual visits will continue on a monthly basis. During that EP, the Investigator may choose to change concomitant NSAID, colchicine, and/or corticosteroid treatment, recording all modifications in the source records and eCRF.

   Unscheduled clinic visits can be scheduled any time as determined by the Investigator/upon patient request. In addition, Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed.

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

Statistical Methods:

Analysis Populations

The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (e.g., NSAIDs, colchicine, corticosteroids) according to study protocol. The Safety Population will be the same as the mITT Population.

General Methods

Because of the small sample size no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or analysis group. For categorical endpoints, summary statistics will be calculated and presented for each treatment and/or analysis group.

Further details, including, for example, the process to be followed for reviewing individual pericarditis symptomatology endpoints to be used in the construction of a composite primary endpoint for subsequent trials, will be provided in the Statistical Analysis Plan (SAP).

Primary Endpoint

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

[redacted]

Table 1: Schedule of Evaluations

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

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

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

a. A second Screening visit (SCV2) should be performed within ~24h to 72h. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2. The last Screening and Day 0 procedures may be performed on the same day, but SCR procedures must be completed prior to Study Drug administration.

b. Subjects who do not complete the Treatment Period (withdraw consent or are discontinued before they have completed 6 weeks treatment), must be asked to complete the procedures specified at the EoT Visit.

c. Weekly intervals refer to 7 ± 1 days. The interval between Study Drug administrations must be at least 5 days.

d. Subjects should return for an optional Interval Evaluation Visit at the clinic between approximately Week 3 and 4, as determined by the Investigator.

e. Including age at first attack, number of previous attacks, and duration of attacks.

f. Drug administration training of subjects is performed at Visit 1. Study Drug will be administered in the Study Site/Clinic at Visit 1. Study Drug administrations are performed by the subjects (self-administration) on Visits (Outpatient) 2, 3, 4, 5, and 6. Participation in the Extension Phase (optional) is determined at the Week 6/EoT Visit 7 by the Investigator. Subjects who are eligible and who are willing to participate will be consented during EoT Visit 7 at the Study Site/Clinic. Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Study Site/Clinic (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7 relative to the timing of weekly dosing. Timing for dose administration is per direction of the Investigator based upon the prescribing information and study-specified dosing intervals. Continued weekly Study Drug treatment during the EP will be outpatient administration.

g. Full physical examination including assessment of pericardial rub.

h. Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.

i. Central 12-lead ECG and echocardiogram reading (including assessment of pericardial effusion). At SCV2 only the ECG will be obtained. The Study Site/Clinic reading of the ECG and the ECHO at the time of the examination will be used by the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.

j. Optional.

k. At the SCV1, information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured. During the Treatment Period, changes in concomitant medication since the last Study Site/Clinic visit will be documented. During the EP, changes in pericarditis/concomitant medication will be assessed at Study Site/Clinic Visits and in monthly outpatient phone calls/virtual visits.

l. Hematology, chemistry, and urinalysis will be performed at the Study Site/Clinic laboratories, and results when available will be entered into the eCRF with appropriate reference values. Serology (HCVAb, HBsAg, HBcAb, HBsAb and HIV) will be performed at SCV1 only. A Study Site/Clinic urine drug screen will be performed at SCV1 only. If SCV2 occurs at a different day than Visit 1 (Day 0), a sample for laboratory testing will also be taken at Visit 1, prior to Study Drug treatment. During each Visit at the Study Site/Clinic a sample for CRP will be obtained and sent to the central laboratory (or designated qualified laboratory) for analysis; at each Outpatient Visit; blood for central laboratory measurement of CRP will be obtained as described in the Laboratory Manual.

m. Biomarker and/or pharmacokinetics (PK) analysis samples will be drawn in all subjects and archived for future testing. If SCV2 occurs at a different day than Visit 1 (Day 0), a sample for biomarker/PK testing will also be taken at Visit 1, prior to Study Drug treatment. A blood sample to be archived for central laboratory measurement of biomarkers and PK will be obtained as described in the Laboratory Manual.

n. To be eligible to continue in the trial, a negative urine pregnancy test must be documented at the SCV1. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.

o. All AEs occurring after the subject receives the first dose of Study Drug will be captured in source records and eCRF.

p. At the SCV1, the Investigator or designee will instruct the subject about the use of the medication diary. The subject will be asked to complete an entry each evening into the medication diary during the Screening Period and Treatment Period. Only information on pain/rescue medication will be collected. Other concomitant treatments/medications are not required to be captured.

q. At the SCV2 and all subsequent visits at the Study Center, the Investigator or designee will review the Diary entry information to verify patient compliance. If the last screening visit occurs at a different day than Visit 1, the review will also be performed at Visit 1. Diary documentation will end at the End-of-Trial visit (Visit 7).

r. Subject assessment of pericardial pain using a validated 11-point Numerical Rating Scale. The assessment will be performed on-site during clinic visits and as part of a telephone call/virtual visit during outpatient treatment weeks. If the last screening visit occurs at a different day than Visit 1, the assessment will also be performed at Visit 1, prior to Study Drug treatment.

s. Subject global assessment of overall well-being will be assessed using a validated QoL Questionnaire (see Appendix 3). The assessment will be performed on-site during clinic visits. If SCV2 occurs at a different day than Visit 1 (Day 0), the global assessment will also be performed at Visit 1, prior to Study Drug administration.

t. Subjects may return for an optional EP Interval Evaluation Visit at the clinic between Week 15 and 20 (8 to 13 weeks after Visit 7), as determined by the Investigator.

u. Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a “Treatment Failure” may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

v. At weekly Investigator (or designee) phone calls/virtual visits during the Treatment Period, Study Drug compliance, medication diary compliance, and laboratory sample collection will be checked. The subjects will be asked using non-leading questions about any AEs occurring since the last contact (phone call/virtual visit or site visit), and NRS pain assessment will be performed. Investigator (or designee) phone calls/virtual visits will be performed monthly during the during the EP to perform NRS pain assessments, collect AE information, and review pericarditis/concomitant medications. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits.

w. During the Extension Period, Study Drug treatment is weekly by self-administration, and the study nurse visits to the home and Investigator (or designee) phone calls/virtual visits are monthly.

4 Table of Contents

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5 List of Abbreviations and Definition of Terms

AcP	accessory protein
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
b.p.m.	beats per minute
BUN	blood urea nitrogen
CAPS	Cryopyrin Associated Periodic Syndrome
CDC	Centers for Disease Control
CHO	Chinese hamster ovary
CI	confidence interval
CRO	contract research organization
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
CTAD	citrate, theophylline, adenosine, dipyridamole
EoT	End-of-Trial
EP	Extension Period
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IL-1	Interleukin-1
IL-1RA	IL-1 receptor antagonist
IL-1RI	IL-1 type I receptor
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	intravenous
kDa	kilo Dalton
KPL-914	Study Drug; nomenclature of rilonacept (ARCALYST®) in this protocol
LDH	lactate dehydrogenase
MCH	mean cell hemoglobin
MCHC	MCH concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mITT	modified intent to treat
MWS	Muckle-Wells Syndrome

NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drugs
PI	Prescribing Information
PP	per protocol
PPD	purified protein derivative
PRO	patient-reported outcome
PT	prothrombin
PTT	prothrombin time
QoL	quality of life
RBC	red blood cell
RIP	recurrent idiopathic pericarditis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCR	Safety Review Committee
SCV	screening visit
SD	standard deviation
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	serious and unexpected and related adverse reaction
TB	tuberculosis
[redacted]	[redacted]
TNF	tumor necrosis factor
US	United States of America
WBC	white blood cells
WHO	World Health Organization
WFI	water for injection

6 Introduction

Pericarditis accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction (Khandaker et al, 2010). 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). Diagnosis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic (ECG) changes, pericardial effusion, or elevated markers of inflammation (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Imazio et al, 2014). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define a pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-elevation or PR depression on ECG, and pericardial effusion (new or worsening). Elevations of 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 a common complication of acute pericarditis and affects 20–30% of patients (Imazio, 2014). It is characterized by the recurrence of signs and symptoms of pericarditis after a symptom-free interval of at least 4-6 weeks (Adler et al, 2015). The underlying pathogenesis of recurrent idiopathic pericarditis (RIP) remains unclear, although immune-mediated mechanisms are believed to play a key role in the pathogenesis (Imazio et al, 2005). A growing body of evidence suggests that these immune responses consist of both pathogenic autoimmune and auto-inflammatory processes (Cantarini et al, 2015; Doria et al, 2012). The presence of pro-inflammatory cytokines in the pericardial fluid of RIP patients lends direct support to both an autoimmune and/or auto-inflammatory etiopathogenesis (Pankuwait et al, 2000).

Currently available treatments for RIP include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids (Lilly, 2013). Aspirin and other NSAIDs are the first-line approach. Because high doses are often required, consideration should be given to gastric protection therapy. Colchicine is another mainstay therapy for RIP and is commonly used with NSAIDs, but a subset of patients has refractory symptoms and significant gastrointestinal side effects, including severe diarrhea, leading to discontinuation for intolerability. Glucocorticoids should be prescribed only to patients with idiopathic pericarditis who are refractory or intolerant to treatment with NSAIDs plus colchicine, because of the side effects associated with long-term corticosteroid therapy and because of a high rate of relapse when the corticosteroid is tapered or stopped (Maisch et al, 2004; Imazio, 2005; Lotrionte et al, 2010), particularly in the absence of colchicine treatment. Patients with refractory symptoms can be particularly challenging to manage, and multiple immunosuppressive medications have been used without consistent benefit (Baskar et al, 2016).

Interleukin-1 (IL-1) is a key cytokine that drives the pathophysiology of many inflammatory processes. It is implicated as a causative factor in various inflammatory human diseases. Although the pathogenic mechanism of auto-inflammatory disease is not completely understood, there is a growing body of evidence that IL-1 may be a primary driver of the symptomology and that targeting this cytokine may provide important benefits (Hoffman & Patel, 2004). [redacted]

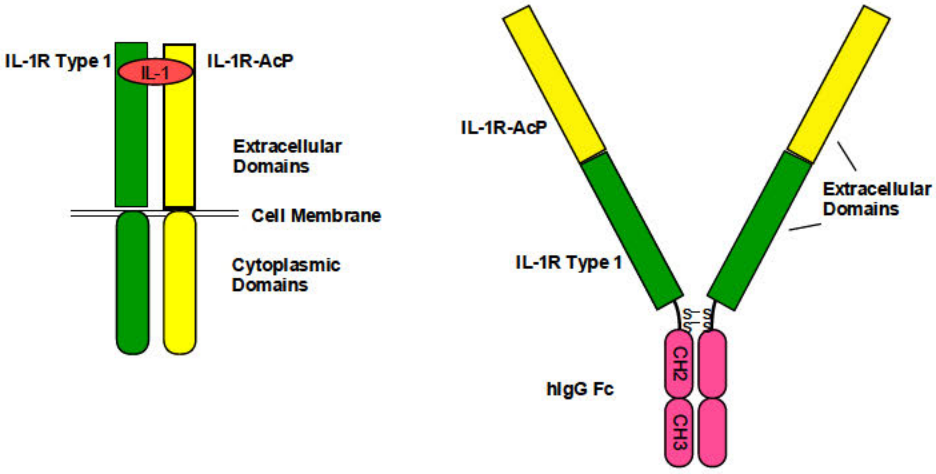
Rilonacept (marketed in the US under the trade name ARCALYST®; referred to as KPL-914 in this investigational study protocol) blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1α and IL-1β and prevents its interaction with IL-1 cell surface receptors. The equilibrium dissociation

constants for rilonacept binding to IL-1β, IL-1α and IL-1RA are 0.5 pM, 1.4 pM and 6.1 pM, respectively. By comparison, the IL-1 Type I receptor (IL-1RI) alone has approximately 1 nM affinity.

Rilonacept (KPL-914) is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human immunoglobulin G (IgG)1. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1RI and the IL-1 accessory protein (AcP) (Figure 1). Rilonacept was created by fusing the sequences encoding the extracellular domains of the AcP, IL-1RI, and the human Fc segment inline without any intervening linker sequences. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept is expressed in Chinese hamster ovary (CHO) cells and is purified with a series of chromatographic and filtration techniques.

The total molecular weight is ~251 kDa, of which 80% is protein (201 kDa) and 20% is carbohydrate (50 kDa).

Figure 1: Schematic of rilonacept (KPL-914)



Rilonacept was developed by Regeneron Pharmaceuticals, Inc. and is approved with the tradename ARCALYST® in the US for the treatment of Cryopyrin Associated Periodic Syndrome (CAPS), including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

Rilonacept is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. For subcutaneous (SC) administration, rilonacept is manufactured in a dosage form containing 160 mg per vial. The lyophilized powder is reconstituted with 2.3 mL of sterile Water for Injection (WFI) and drug is delivered in 2 mL at a concentration of 80 mg/mL. Clinical dosing (e.g., in CAPS) initiates with a loading dose of 320 mg SC followed by 160 mg administered SC weekly. A lower dose of 80 mg weekly (initiated with a 160 mg loading dose) was also tested in Phase 3 clinical trials in gout.

For a detailed review of the available rilonacept data, please refer to the Investigator Brochure and the ARCALYST® package insert.

Kiniksa Pharmaceuticals Ltd. (Kiniksa) is now developing rilonacept for the treatment of RIP (Rilonacept will be referred to as KPL-914 in this investigational study protocol). In this first pilot study in subjects with RIP, improvement of pericarditis symptomatology with KPL-914 administration as well as the safety

and dose relationships will be assessed. Commercially-available rilonacept (ARCALYST®) will be used in the study.

The nonclinical development program for rilonacept (ARCALYST®) demonstrated biological activity and adequate safety across toxicity studies (Appendix 2: ARCALYST® Prescribing Information).

The most common adverse reactions reported by patients with CAPS treated with ARCALYST® are injection-site reactions and upper respiratory tract infections. Hypersensitivity reactions associated with rilonacept administration have been rare.

Refer to the ARCALYST® PI for Important Safety Information regarding rilonacept (Appendix 2: ARCALYST® Prescribing Information).

Based on its IL-1-antagonistic properties, its weekly-dosing pharmacokinetics, and its well-understood safety profile as shown in patients with CAPS, rilonacept (KPL-914) is a promising candidate for the treatment of RIP.

7 Study Objectives

7.1 Primary Objective

To collect inter- and intra-subject variability data on C-reactive protein (CRP) measurements and the 11-point NRS instrument for assessment of pericardial pain in symptomatic subjects with recurrent idiopathic pericarditis (RIP) both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in RIP.

7.2 Secondary Objective(s)

To explore the time course to improvement of pericarditis parameters in symptomatic patients with RIP treated with KPL-914.

To evaluate the safety of KPL-914 in symptomatic patients with RIP.

8 Investigational Plan

8.1 Overall Study Design and Plan

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

Patients identified for participation in this trial will present during a symptomatic episode of RIP, having previously experienced a first (index) episode of acute pericarditis followed by at least 1 recurrent episode before the current enrollment-qualifying episode, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate [ESR], and white blood cell [WBC] count) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]).

- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having experienced a previous index episode of acute pericarditis followed by at least 1 recurrent episode of pericarditis prior to the presenting symptomatic episode of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Study subjects will be enrolled (Screening Visit 1 [SCV1]) at the time of a symptomatic episode. In addition to meeting the criteria for pericarditis in the judgement of the Investigator, all subjects must present with a CRP value ≥1 mg/dL at the time of study enrollment. Subjects included in the study may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for at least 3 days will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm the pre-treatment diagnostic workup. At the SCV1, baseline patient and disease characteristics will be determined and captured in the eCRF. Persistence of diagnostic criteria for pericarditis will be confirmed (Screening Visit 2 [SCV2]) within the 24 - 72 hour period before subjects advance to the Treatment Period of the study. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

Approximately 10 subjects will participate in the active Treatment Period of the study. Following review of the ongoing data by the Sponsor and the Investigators, the sample size may be increased to a total of up to 20 subjects. After having met all the entry criteria during the Screening Period, the subjects entering the

Treatment Period will receive a loading dose of KPL-914 (2 x 160 mg SC) on Day 0, then 160 mg SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the patient as an outpatient SC administration. A visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be self-administered or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the patient, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF and medication diary.

At the discretion of the Investigator, "Treatment Responders" (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks. Weekly

treatments during the EP are by self-administration, and study nurse visits to the patient's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis.

During the EP, the Investigator may choose to wean concomitant NSAIDs, colchicine, and/or corticosteroids according to standard of care paradigms; all medication changes must be recorded in source records and the eCRF. Investigators are encouraged to invite subjects to the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after the Week 7 Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing patient management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each.

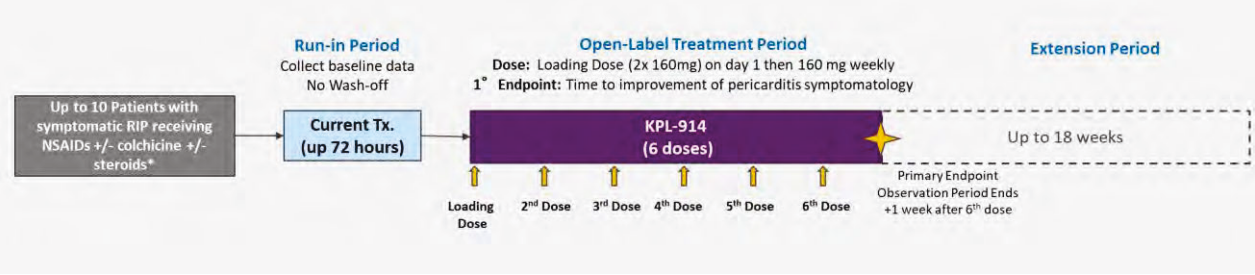
Given the following occurrences, dosing may be halted or reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg administered SC on Day 0, then 80 mg administered SC weekly for 5 additional weeks, in order to explore efficacy at a lower dose. Depending on treatment response observed with the 80 mg dose, the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject on a daily basis.

Figure 2: Overview of Trial Design



The study will be conducted in compliance with Good Clinical Practice regulations and other regulatory requirements.

8.2 Discussion of Study Design

Clinical information from the development of rilonacept in CAPS (ARCALYST®), the mode of action of rilonacept, as well as the inflammatory nature of RIP suggest that rilonacept (KPL-914) may safely and effectively resolve RIP. [redacted] The rationale for this pilot study is to collect time-course to pericarditis improvement data and safety information for up to 2 dose levels of KPL-914 (i.e., 160 mg and 80 mg) when administered to subjects with RIP. The study aims to provide data to support the design of future clinical studies with KPL-914 in RIP: in particular to inform inter-and intra-subject variability in CRP and NRS measurements, the time course of treatment response, and the dosage(s) of KPL-914 to be evaluated in a pivotal Phase 3 clinical trial.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

Approximately 10 symptomatic patients with RIP will be enrolled as study subjects. Following review of the available data, the Sponsor, in collaboration with the Investigators, may increase the sample size to up to 20 subjects to address additional hypotheses.

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

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and other research in this patient population.

8.3.2 Inclusion Criteria

To be eligible to participate in the trial, a subject must meet all of the following criteria:

1. Has given consent and signed an Informed Consent Form (ICF).
2. Male or female, of any ethnic origin.
3. 18 to 70 years of age, inclusive.
4. Has had a prior *index episode* of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate, and white blood cell count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
5. Has had at least one prior *recurrent episode* of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
6. Has an ongoing symptomatic episode of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.

7. Has an elevated CRP value (i.e., >1 mg/dL) at the time of study enrollment.
8. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days prior to Study Drug dosing (although stable doses for at least 3 days will be acceptable if, in the opinion of the Investigator in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.
9. If female, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
10. Is able to adequately maintain a daily medication diary.
11. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or change in exercise pattern) from the time of signature of the ICF to the End-of-Trial Visit (Week 7).

8.3.3 Exclusion Criteria

A subject who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific etiologies, including tuberculous, neoplastic, or purulent etiologies, post cardiac injury syndromes, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints within the 6-month period before dosing.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female patient who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A patient with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or physical exam. Have recent close contact with a person with active TB.
8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of the study.
10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.
11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.

12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks, or has been treated with IV antibiotics for an infection within 2 months of first Study Drug administration.
15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a patient is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 30 days (or 5 half-lives, whichever is longer) prior to Study Drug administration.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Patient who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Patient who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

8.3.4 Vaccination History and Immune status

IL-1 blockade may interfere with immune response to infections. Therefore, the Investigator should review with the subject the subject's vaccination history relative to the current medical guidelines for vaccine use. A recommended immunization schedule is available at the website of the Centers for Disease Control (CDC) (www.cdc.gov/vaccines/recs/scheduled/default.htm).

It is recommended that, prior to or shortly after initiation of therapy with KPL-914, subjects be brought up to date with all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In case a patient needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed (e.g., at the Study Site/Clinic) after the 6-week active Treatment Period. However, to minimize the potential confounding of KPL-914-related Adverse Experience reporting at initiation of KPL-914 dosing or measurements of CRP during the treatment period, vaccination should not be performed within the first 6 weeks after initiation of KPL-914 administration.

It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Administration of KPL-914 is prohibited within 12 weeks of having received a live (attenuated) vaccine. It is also possible that taking drugs that block IL-1 increases the risk of TB. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent TB infections before initiating therapy with KPL-914.

8.3.5 Removal of Subjects from Therapy or Assessments

Subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator on an ongoing basis as part of patient management. An SRC including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each.

Given the following occurrences, dosing may be halted or or the dose reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

In addition, subjects may stop study treatment or may be withdrawn from treatment for any of the following reasons:

- Subject request. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment
- Use of non-permitted concurrent therapy
- Non-compliance
- Investigator request.

Treatment Failures or subjects who are withdrawn from the study for safety reasons will be replaced at the discretion of the Sponsor. Similarly, subjects who do not comply with the protocol or who withdraw from the study for other reasons can be replaced. The reason(s) for withdrawal will be documented in the source records and the eCRF.

Subjects withdrawing from the study during the Treatment Period will be asked to complete the End-of-Trial evaluations to document the status of their pericarditis disease progression at the time of withdrawal from treatment. Subjects will continue to be followed for vital status for the duration of intended treatment to address informative censoring. Subjects withdrawing from the study during the EP will be asked to complete the Final Visit evaluations.

All reasonable efforts will be made to contact subjects who are lost to follow-up.

The Sponsor has the right to terminate the study at any time in case of safety concerns (e.g., SUSARs) or if special circumstances concerning the Investigational Medicinal Product (IMP) 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.

Pregnancy

Pregnant or lactating female subjects are excluded from study enrollment. While not explicitly stated in the rilonacept (ARCALYST®) PI (Appendix 2: ARCALYST® Prescribing Information), for the purposes of this experimental protocol, females of child-bearing potential (i.e., not postmenopausal and not sterilized) must use an active method of birth control during the course of the study, e.g., oral, implanted or injected contraceptive hormones, an intrauterine device, or a barrier method (e.g., diaphragm, condoms, spermicides).

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator without delay. If pregnancy is confirmed, the Investigator must notify the Sponsor within 24 hours and the subject must not receive (additional) Study Drug and must be discharged from the study. The subject must be asked regarding their willingness to complete the End-of-Trial Visit.

In the event that a subject is found to be pregnant after having received at least one Study Drug dose, the pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Instances of perinatal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment, will be reported to the Sponsor within 24 hours.

Full details will be recorded on the pregnancy form.

8.4 Investigational Medicinal Products

8.4.1 Investigational Medicinal Products Administered

During the Treatment Period, KPL-914 will be administered as an initial loading dose of 2 x 160 mg SC on Day 0, then 160 mg SC dosed once weekly for up to 5 subsequent weeks. At the discretion of the Investigator, subjects completing the Treatment Period may enter the 18-week Extension Period and receive up to 18 additional weekly doses of KPL-914.

At the discretion of the Sponsor in collaboration with the Investigators, the Study Drug dosing regimen may be decreased in a consecutive group of subjects to a loading dose of 2 x 80 mg SC on Day 0, then 80 mg SC dosed once weekly for 5 subsequent weeks to explore efficacy at a lower dose. Depending on treatment response observed with the 80 mg dose, the dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Sites for SC 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.

No placebo or active comparator drug will be used.

8.4.2 Identity of Investigational Medicinal Products

KPL-914 (rilonacept/ARCALYST®) is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. It 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 WFI is required prior to SC administration of the drug. The reconstituted drug product is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

After the addition of preservative-free sterile WFI, the vial contents should be reconstituted by gently shaking the vial for approximately 1 minute and then allowing it to sit for 1 minute. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for SC administration only.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®) as a lyophilized powder to be reconstituted for SC administration. The sites will receive Study Drug for on-site administration at Study Site/Clinic visits. Drug will be disseminated to the trial subjects for outpatient self-administration according to a supply chain described in the Pharmacy Manual.

The lyophilized Study Drug (KPL-914 also called rilonacept, US tradename: ARCALYST®) is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. After reconstitution, KPL-914 may be kept at room temperature, should be protected from light, and should be used within 3 hours of reconstitution. Unused portions of KPL-914 product must not be injected. All vials of used and unused Study Drug during the active Treatment Period must be returned to the clinical site for cataloguing and documentation of compliance.

The Sponsor through Regeneron Pharmaceuticals, Inc. will ensure that the Study Drug and certificates of analysis are available before the start of the study and at all times during the study.

ARCALYST® is a registered trademark of Regeneron Pharmaceuticals, Inc.

8.4.3 Method of Assigning Subjects to Treatment Groups

Patients who meet all of the inclusion criteria and none of the exclusion criteria will enter the Treatment Period at Visit 1 (Day 0).

Since this is an open-label, single-active-arm study, all subjects will receive KPL-914 active treatment. Assignment to treatment groups is not applicable.

8.4.4 Selection of Doses in the Study

This protocol is a pilot study intended to evaluate the safety, efficacy, and dose response of KPL-914 in the treatment of patients with RIP.

[redacted], treatment will be started with a loading dose of 320 mg delivered as two, 2-mL SC injections of 160 mg; dosing will continue with once-weekly injections of 160 mg administered as a single, 2-mL SC injection (Appendix 2: ARCALYST® Prescribing Information).

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if the majority of subjects achieve treatment response during the first half of the Treatment Period), the Sponsor, in collaboration with the Investigators, may elect

to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg SC on Day 0, then 80 mg SC weekly (the dose tested in the Phase 3 program for gout) for 5 additional weeks in order to explore efficacy at a lower dose. However, depending on treatment response observed with the 80 mg dose, the dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor.

8.4.5 Selection and Timing of Dose for Each Subject

The first administration of KPL-914 (and training for outpatient self-administration) will be performed under the supervision of a qualified healthcare professional at Visit 1 (Day 0). Afterwards, subjects will self-administer the Study Drug as an outpatient during the Treatment Period (and during the EP, as applicable). Study Drug administration will be performed once a week (every 7 ± 1 days). The interval between Study Drug administrations must be at least 5 days. Subjects will be instructed to not administer KPL-914 more often than once weekly and to administer only one syringe of Study Drug per week.

At Visit 1, subjects will be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously will be assessed to ensure proper administration of KPL-914, including rotation of injection sites. Patients will be instructed in proper vial, syringe, and needle disposal, and will be cautioned against reuse of these items. All used and unused Study Drug vials must be returned to the Study Site/Clinic for drug accountability assessment.

8.4.6 Blinding

Not applicable.

8.4.7 Prior and Concomitant Therapy

Subjects enrolled into the study may be using NSAIDs, colchicine, and/or corticosteroids in any combination at the time of study enrollment, but the dose levels must be stable for have been stable for at least 7 days, although stable doses for at least 3 days will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

For the duration of the Treatment Period, pericarditis medications (e.g., concomitant NSAIDs, colchicine and/or corticosteroids, if used) should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Subjects who received, within the 6-month period before dosing, immunomodulatory therapy other than, for example, corticosteroids or mycophenolate, which in the opinion of the Investigator (in consultation with the Sponsor) may interfere with the study endpoints, or subjects who used commercially-available rilonacept (ARCALYST®) within 90 days before the Screening Visit are excluded from participation.

Throughout the Treatment Period opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF. Other interleukin

(IL)-1 or IL-6 blockers, janus-activating kinase (JAK) and tumor necrosis factor (TNF) inhibitors are prohibited for the duration of the study.

Medical management of pericarditis during the EP is based on Investigator discretion. He/she may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug in consultation with the Sponsor, or change (increase or decrease) the dosing of NSAIDs/colchicine/corticosteroids. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a daily medication diary. Such information will be entered by the subject on a daily basis (evening).

8.4.8 Treatment Compliance

Study Drug will be administered to the patient by the Investigator or qualified study center staff at the Study Site/Clinic Visit 1 (Day 0). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the patient as an outpatient SC administration. A visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site. All medication use (for pericarditis and use of rescue [pain] medication) will be documented by the subject in the medication diary during the Treatment Period.

All vials of used and unused Study Drug during the active Treatment Period and the EP must be retained by the Study Site/Clinic and the subject to allow for cataloguing and documentation of compliance. Subjects must return all used and unused medication to the Study Site/Clinic. Drug accountability and documentation thereof is described in the Pharmacy Manual.

Study Drug compliance by the subject will be monitored during the Treatment Period by phone calls/virtual visits (made by qualified site staff). Subjects will be reminded of recording all medication information in the medication diary. The medication diary will be returned to the site by the subject and reviewed by the Investigator/qualified staff. During the EP, Study Drug use will be documented during monthly phone calls/virtual visits or Study Site/Clinic visits.

8.5 Study Procedures

All data of Study Site/Clinic visit assessments as well as Investigator (or designee) phone calls/virtual visits will be documented in source records and in the eCRF.

8.5.1 Screening Period

The Screening Period starts with the signature of the ICF and may last for up to 3 days. During this period, patient eligibility for entry into the Treatment Period will be determined. A rheumatology consultation during the Screening Period is optional.

At SCV1, baseline patient and disease characteristics will be determined. Persistence of diagnostic criteria for pericarditis will be confirmed within ~24 to 72 hours at SCV2. Under special circumstances, the Investigator in consultation with the Sponsor, can combine SCV1 and SCV2.

The end of the Screening Period may coincide with the start of the Treatment Period.

8.5.1.1 Screening Visit 1 (SCV1)

- At the SCV1, written informed consent will be obtained before any in-person assessments are made.
- All subjects will be assessed for eligibility against the inclusion and exclusion criteria.
- Demographic data, such as ethnic origin, date of birth and sex will be recorded.
- The subject's full medical history, including age at first attack, number of previous attacks, duration of attacks as well as concomitant illnesses/diseases will be documented.
- Information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured.
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
- A pregnancy test (urine dip-stick) will be done. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.
- 12-lead ECG and full echocardiogram (ECHO) will be performed. ECHO will include assessment of pericardial effusion. The Study Site/Clinic readings at the time of the examination will be available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- A cardiac MRI may be performed (optional). If done, the images will be assessed by a central reader. The Study Site/Clinic reading at the time of the examination may be used by the Investigator for clinical decision-making.
- Samples for Study Site/Clinic (safety and assessment) and central (CRP) clinical laboratory tests will be collected. Full hematology, chemistry, and urinalysis will be performed at laboratories of the Study Site only. A sample for CRP will be obtained and sent to the central laboratory for analysis. Serology (HCVAb, HBsAg, HBcAB, HBsAb and HIV) will be performed.
- Samples for archive biomarker and/or pharmacokinetics (PK) and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- A QuantiFERON® test for tuberculosis (TB) can be performed (optional).
- Screening for drugs of abuse and alcohol abuse will be performed on urine samples collected at this visit.
- A medication diary for documentation of pericarditis medication use and use of any rescue (pain) medication will be handed to the subject. The study Investigator or designated personnel will instruct the subject about the use of the medication diary. The subjects will be asked to complete an evening entry each day.
- The subjects will assess their pericardial pain based on a 11-point NRS.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.1.2 Screening Visit 2 (SCV2)

The end of the Screening Period (SCV2) coincides with the start of the Treatment Period (Day 0, Visit 1). All Screening assessments need to be completed prior to the first Study Drug administration.

- SCV2 should take place when the laboratory test results from SCV1 are available.
- Subjects will be reassessed for eligibility against the inclusion and exclusion criteria.
- Any changes in concomitant medications since SCV1 will be documented.
- A full physical examination will be performed, including re-assessment of pericardial rub.
- Vital signs will be measured.

- 12-lead ECG will be performed. The Study Site/Clinic reading at the time of the examination will be used by the Investigator for clinical decision-making. In addition, the ECG will be sent to a core laboratory for additional analysis.
- Samples for Study Site/Clinic (safety and assessment) and central (CRP) clinical laboratory tests will be collected.
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- The subjects will assess their pericardial pain based on the 11-point NRS (Figure 3).

When all screening procedures have been performed and the Investigator has confirmed the subject's eligibility for the study, the Study Drug will be administered to the subject (see Study Site/Clinic Visit 1).

8.5.2 Treatment Period

8.5.2.1 Visit 1 (Study Site/Clinic) - Day 0

- Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling, medication diary compliance verification and reminding, and subject NRS pericardial pain rating (see Figure 3) must be repeated prior to Study Drug dosing.
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected prior to Study Drug dosing, sent to the central laboratory, and stored for analysis.
- The subject's global overall well-being will be assessed prior to Study Drug dosing using a validated Quality of Life Questionnaire (Appendix 3).
- The initial dose of Study Drug will be administered at the Study Site/Clinic.
- Subjects will be trained for outpatient Study Drug self-administration and reminded of completion of the daily medication diary.
- Any AEs occurring during or after the subject receives the first dose of Study Drug will be captured.

When all Visit 1 procedures have been performed, an appointment for the first weekly phone call/virtual visit will be scheduled. Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

8.5.2.2 Visits 2 to 6 (Outpatient) - Weeks 2, 3, 4, 5, 6

- Visits 2, 3 4, 5, 6 will take place within intervals of 7 ± 1 days each after Visit 1.
- Subjects self-administer the Study Drug during Weeks 2 to 5. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site.
- Blood samples for CRP laboratory analysis will be collected (either by a visiting study nurse or at the Study Site or at a qualified local laboratory) and will be sent to the central laboratory for analysis.
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected (either by a visiting study nurse or at the Study Site or at a qualified local laboratory) and stored for analysis after shipment to the central laboratory.
- Any AEs that have occurred since the last contact will be assessed by non-leading questions as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Compliance with self-administration of drug, compliance with the medication diary, and compliance with laboratory blood sampling will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.

Subjects withdrawing from the study any time during study weeks 2 to 6 will be asked to return to the Study Site/Clinic for the Visit 7/End-of-Trial visit assessments.

8.5.2.3 Interval Evaluation Visit (Study Site/Clinic) - Week 3-4

An in-person Interval Evaluation Visit during approximately Weeks 3-4 of the Treatment Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator. The Interval Evaluation Visit may also be used to review the vaccination status of a study subject.

At the Interval Evaluation Visit, the following parameters will be assessed:

- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for Study Site/Clinic (safety and assessment) and central (CRP) clinical laboratory tests will be collected.
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.2.4 Unscheduled Visits (Study Site/Clinic) During the Treatment Period

Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. During the Unscheduled Visit, selected or comprehensive (see Interval Evaluation Visit) clinical and laboratory assessments may be performed.

Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a “Treatment Failure” may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

All study withdrawals must complete the Week 7/End-of-trial Visit either at the Unscheduled Visit or at a separate Week 7/End-of-trial Visit.

8.5.2.5 Visit 7/ End-of-Trial (Study Site/Clinic) - Week 6

At Visit 7, “Treatment Responders” (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week

EP, at the discretion of the Investigator. During the EP, weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

- Visit 7 will take place during Week 6 (or as soon as possible after study withdrawal if a subject has discontinued from Study Drug therapy).
- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since last Study Site visit will be documented.
- Samples for Study Site/Clinic (safety and assessment) and central (CRP) clinical laboratory tests will be collected.
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

When all of these procedures have been performed, the next Study Site/Clinic visit should be scheduled for those who continue KPL-914 treatment during the EP (Treatment Responders). Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Clinic/Site (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7. Continued weekly Study Drug treatment during the EP will be outpatient administration.

8.5.3 Extension Period

Subjects will self-administer the Study Drug on a weekly basis during the Extension Period, and study nurse visits to the patient's home will continue on a monthly basis. Investigator (or designee) phone calls/virtual visits will be performed monthly during the EP to perform NRS pain assessments, collect AE information, and document pericarditis/concomitant medication use. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits.

8.5.3.1 Unscheduled Visits (Study Site/Clinic) during the EP

Unscheduled Study Site/Clinic visits can take place during the Extension Period, as agreed upon by the Investigator and the subject or as needed.

- A physical examination will be performed.
- Vital signs will be measured.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for Study Site/Clinic (safety and assessment) and central (CRP) clinical laboratory tests will be collected.
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.

- A 12-lead ECG and a full ECHO will be performed as determined by the Investigator. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).

8.5.3.2 Interval Evaluation Visit During Extension Period (Study Site/Clinic) - Week 15-20

An in-person Interval Evaluation Visit during approximately Weeks 15-20 of the Extension Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator.

At the Extension Period Interval Evaluation Visit, the following parameters will be assessed:

- A physical examination will be performed.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for Study Site/Clinic (safety and assessment) and central (CRP) clinical laboratory tests will be collected.
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.3.3 Visit 8/Final Visit (Study Site/Clinic) - Week 25

- Visit 8 will take place 18 weeks after Visit 7 (or as soon as possible after study withdrawal during the EP).
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
- 12-lead ECG and ECHO will be performed. Echocardiogram will include assessment of pericardial effusion. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- An MRI can be performed (optional).
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for Study Site/Clinic (safety and assessment) and central (CRP) clinical laboratory tests will be collected.
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).

- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.4 Duration of Treatment

The overall study duration for subjects participating in the study until Visit 8 will be up to 171 days.

The test product will be administered weekly for 6 weeks in the base study Treatment Period. Treatment Responders will be offered participation in an optional 18-week EP at the discretion of the Investigator. During this EP the subject can receive 18 additional weekly doses of KPL-914.

8.6 Efficacy and Safety Variables

The Schedule of Evaluations in Table 1 shows the planned study assessments.

8.6.1 Individual Efficacy Assessments

8.6.1.1 C-Reactive Protein, Biomarker, and PK Assessments

CRP will be determined at Study Site/Clinic laboratory tests at Screening (SCV1 and SCV2) and during the Treatment Period (Visit 1 prior to dosing, if separate from SCV2, Interval Evaluation Visit [if applicable], and Visit 7/End-of-Trial). Results from the Study Site/Clinic CRP testing will inform the Investigator on the subject's pericarditis status for clinical decision-making and support decisions on classifications of subjects as Treatment Responders or Treatment Failures and on subsequent disease management during the Extension Period.

Central laboratory assessments of CRP will be performed at each Study Site/Clinic or outpatient study visit (samples collected by a visiting study nurse or at the Study Site/Clinic or a local laboratory). Centrally determined CRP values will be used for statistical evaluations and report writing but will not be used as basis of the Investigator's management the patient.

All subjects must present with elevated CRP values ≥1 mg/dL at the time of study enrollment. CRP changes and the time course to decrease and resolution of CRP to normal values ≤0.5 mg/dL will be assessed.

Samples from each study visit will be archived at the central laboratory for potential biomarker and/or PK analysis.

8.6.1.2 Echocardiogram (Pericardial Effusion)

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

Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart and is one of the common features of pericarditis. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening.

For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECHO images will be assessed by a central reader. The Study Site/Clinic reading of the ECHO at the time of the examination will be made available to the Investigator for clinical decision-making.

8.6.1.3 Electrocardiogram (Pericarditis Diagnostic Findings)

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

Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-elevation or PR depression. Changes in ECG findings will help determine the pericarditis status of a subject.

The Study Site/Clinic reading of the ECG at the time of the examination will be made available to the Investigator for clinical decision-making. For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECG tracings will be assessed by a central reader.

8.6.1.4 Pericarditis Signs (Fever, Pericardial Rub)

Common pericarditis signs include fever and pericardial rub. These pericarditis signs will be assessed via documentation of vital signs and physical examinations.

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

8.6.1.5 Pericarditis Pain (Chest Pain)

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011). The assessment will be performed at all study visits - on-site during Study Site/Clinic visits and as part of telephone calls/virtual visits during outpatient visits/treatment weeks (weekly during the Treatment Period and monthly during the EP).

Subjects will be asked to select the score that best describes their average level of pain over the previous 24 hours using a validated 11-point NRS instrument (Figure 3), 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 pain on average in the last 24 hours

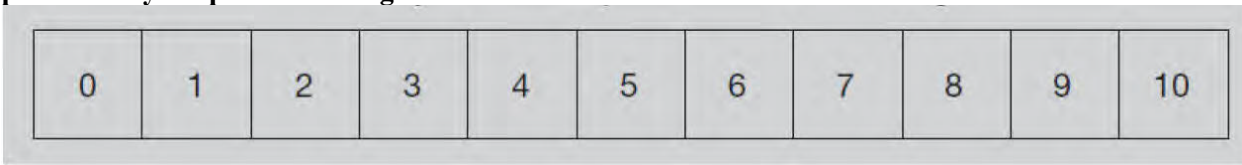


Figure 3: **11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain**

8.6.1.6 Magnetic Resonance Imaging

Cardiac MRI is an optional assessment and may be performed at study entry (SCV1) and at the final study visit (Visit 8) to assess any changes in pericardial inflammation.

For the purposes of the analysis of treatment response in all subjects at the end of the study, all cardiac MRI images will be assessed by a central reader. The Study Site/Clinic reading of the MRI at the time of the examination may be used by the Investigator for clinical decision-making.

8.6.1.7 Quality of Life Questionnaire

A validated Quality of Life Questionnaires will be used to assess changes in the subject's overall well-being (Hays et al 2009). The patient's global assessment will be performed at screening (SCV1), at Visit 1 (Day 0), at the Interval Evaluation Visit (Week 3-4), at the end of the Treatment Period (Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP, and at the Final Visit (Visit 8).

The Quality of Life Questionnaire to be used is presented in Appendix 3.

8.6.2 Safety Assessments

8.6.2.1 Adverse Events

Adverse Event Definition

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 and/or unintended 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.

In this study, individual elements of pericarditis symptomatology (including pain) are captured as an efficacy parameter. Pericarditis pain is not required to be reported as an AE. However, if, in the opinion of the Investigator, the subject experiences new symptoms that had not been previously reported in the constellation of symptoms recorded at baseline, these new symptoms should be reported as an AE.

The causal relationship between an AE and the Study Drug will be defined as below:

- **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 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 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 drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

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**: medically significant event; daily activities limited or completely halted; hospitalization or prolongation of hospitalization indicated.

Every reasonable effort will be made to follow subjects who have AEs. Any subject who has an ongoing AE at study end or early withdrawal will be followed, where possible, until resolution.

8.6.2.2 Serious Adverse Events

Serious Adverse Event Definition

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 Study Drug (e.g., car accident where 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 hospitalizations must be recorded on the medical history or physical examination page of the eCRF). Hospitalization is defined as an admission to the hospital ward or a short-stay-type unit longer than 24 hours. Prolongation of existing hospitalization is defined as 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 judgement 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 IMP.

Reporting of Serious Adverse Events

SAEs merit special concern and attention, and SAEs due to any cause, whether or not related to the Study Drug, must be reported by the Investigator to the Sponsor and designee within 24 hours of occurrence or when the Investigator becomes aware of the event. Report SAEs by fax or email using the designated SAE report to:

[redacted]

In addition, Investigator must report the SAE within 24 hours of learning of the event by telephone to:

[redacted]5

If the Investigator reports an SAE by telephone, then a written report must follow within 1 business day and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable.

Other Reasons for Immediate Reporting to [redacted]

- Overdose (accidental or intentional) of the investigational product or concomitant medication, regardless of whether it is considered an AE
- Any pregnancy diagnosed in a female subject or in a female partner of a male subject during treatment with an investigational product
- Hospitalization (including Emergency Room visits) which last for less than 24 hours. A determination will be made by the Sponsor in collaboration with [redacted] as to whether it is a SAE
- Any diagnosis of malignancy (excluding basal cell skin cancer) during the study should be reported to [redacted] within 24 hours.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 8.3.5.

All hospitalizations must be reported to [redacted] and Kiniksa within 24 hours; however, hospitalizations for elective medical/surgical procedures for preexisting illnesses that were planned prior to the subject's enrollment in the study may not be considered by the Investigator to be AEs. Complications resulting from planned procedures, however, require reporting to [redacted] and Kiniksa.

Whenever possible and practical, a blood sample (collected in a light blue top CTAD [citrate, theophylline, adenosine, dipyridamole] vacutainer tube) to potentially measure plasma drug levels should be obtained upon the development of any SAE or unusual AE that is judged to be related to study treatment.

Investigator Reporting Responsibilities to Institutional Review Board (IRB)

Unanticipated problems posing risks to study subjects will be reported to the IRB per their institutional policy. Copies of each report and documentation of IRB notification and acknowledgement of receipt will be kept in the Investigator's study file.

Sponsor Reporting Responsibilities to Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

8.6.2.3 Adverse Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; i.e., where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

Unexpected Adverse Reaction Definition

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with relevant product information for the IMP. The current version of the ARCALYST® PI should be used as the Single Source Safety Reference Document when determining if an event is unexpected. Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for a list of most frequent expected AEs. All suspected adverse reactions related to an investigational medicinal product (the tested investigational medicinal products and comparators, if involved) which occur in the concerned trial, and that are both unexpected and serious are subject to expedited reporting.

Warnings and Precautions

Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for Important Safety Information.

IL-1 blockade may interfere with immune response to infections. It is therefore recommended that prior to or shortly after initiation of therapy with KPL-914 patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In case a patient needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed during the active Treatment Period. However, to minimize the potential confounding of KPL-914-related AE reporting or CRP measurements during the KPL-914 Treatment Period, vaccination should not be performed during the Treatment Period (see Section 8.3.4). It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Taking KPL-914 with TNF inhibitors is not recommended because simultaneous inhibition of these two pathways may increase the risk of serious infections.

It is also possible that taking drugs 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 KPL-914.

8.6.2.4 Clinical Laboratory Variables

Clinical laboratory analyses will be performed at Study Site/Clinic or local laboratory near the patient and, for some parameters, at a central laboratory. Laboratory analyses will be used at Study Site/Clinic visits for the Investigator to assess disease status and to determine treatment response and study (drug) continuation

or withdrawal. Results for analyses performed by the Study Site/Clinic laboratory together with the laboratory reference ranges will be recorded in the eCRF and the Investigator must use clinical judgment to determine if any abnormal values are clinically significant or not.

Central laboratory samples for CRP analysis will be collected at both Study Site/Clinic and outpatient (by a visiting study nurse or at local contract laboratories) visits and the results will be used for statistical analyses and study reporting. Study Site/Clinic and local laboratory results will be used for clinical decision-making and will be available in the source documents and listed in the CSR).

The following analyses will be done at the **central laboratory**:

C-reactive protein (CRP)

The CRP analyzed by the central laboratory will not be the basis of the Investigator's clinical management of the patient. Results from the central laboratory will therefore not be transferred to the Investigator during the trial.

The following laboratory analyses will be performed at the **Study Site/Clinic laboratories** in accordance with local procedures and guidelines:

Hematology

Hemoglobin, hematocrit, coagulation parameters (prothrombin [PT], prothrombin time [PTT], D-dimer), ESR, fibrinogen, WBC count (total and differential), red blood cell (RBC) count, ESR, platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), MCH concentration (MCHC).

Clinical Chemistry

CRP, troponin, creatinine, creatine kinase, urea, (or blood urea nitrogen [BUN]), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol*, triglycerides*, calcium, phosphorus.

* Preferably fasting.

Urinalysis

pH, glucose, ketones, nitrites, leukocyte esterase, blood, protein and microscopy.

Serology

HCVAb, HBsAg, HBcAB, HBsAb and HIV tests (SCV 1 only)

8.6.2.5 Other Laboratory Variables

Samples for biomarkers, PK, and anti-rilonacept (anti-KPL-914) antibody testing will be drawn and archived at all visits. For PK and anti-rilonacept (anti-KPL-914) antibody testing, whole blood from subjects will be collected in 5-mL red-top vacutainer tubes (US B-D Cat #367814). For biomarker assessments, blood is collected in a 4.0-mL vacutainer K_2 EDTA tube.

Urine drug screen (alcohol, amphetamines, cocaine, or phencyclidine) at SCV1 only.

Screening for tuberculosis (QuantiFERON test) at SCV1 only (optional).

Screening for pregnancy (urine β-HCG) at SCV1 only.

The amount of blood to be taken during screening will be approximately 37 mL at SCV1 and approximately 17 mL at SCV2 (if done). The amount of blood to be taken at each Study Site/Clinic visit during the Treatment Period and EP will be approximately 31 mL. The amount of blood to be taken at each outpatient visit will be approximately 21 mL. At the optional unscheduled visit, approximately 61 mL are planned. The total amount of blood to be taken during the study will be up to approximately 320 mL.

8.6.2.6 Vital Signs

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

The following measurements will be taken: oral temperature, respiratory rate, blood pressure, and pulse. Oral temperature (fever) will also be assessed as efficacy parameter (see Section 8.6.1.4).

8.6.2.7 Physical Examination

At the Screening Visits 1 and 2, at the optional Evaluation Visit during the Treatment Period, at the End-of-Trial Visit (Visit 7), at Unscheduled and Evaluation Visits during the EP and at the Final Visit (Visit 8) a full physical examination including the assessment of pericardial rub (efficacy parameter) will be performed (see also Section 8.6.1.4).

8.6.2.8 Body Weight and Height

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

8.7 Statistical Methods

A full description of the statistical analyses to be performed together with the planned tables and figures will be given in a detailed document, the SAP, which will be developed and filed prior to data base lock. Any deviation(s) from the final SAP will be described and justified in the clinical study report.

8.7.1 Statistical and Analytical Plans

8.7.1.1 Datasets to be Analyzed

The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (NSAIDs, colchicine, and/or corticosteroids, if used during screening) according to study protocol. The Safety Population will be the same as the mITT Population.

8.7.1.2 General Statistical Methods

Because of the small sample size, no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or

analysis group. For categorical endpoints (e.g., responder vs. non-responder), summary statistics will be calculated and presented for each treatment and/or analysis group.

Further details will be provided in the SAP. Any deviation(s) from the original statistical plan will be described and justified in in the final study report.

8.7.1.3 Efficacy Endpoints

Primary Efficacy Endpoint

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

[redacted]

8.7.1.4 Safety Variables

AEs and SAEs, clinical laboratory evaluations, vital sign measurements, ECGs, and physical examination findings.

8.7.2 Determination of Sample Size

Approximately 10 symptomatic patients with RIP will be enrolled as study subjects. Following review of the available data, the Sponsor, in collaboration with the Investigators, may increase the sample size to up to 20 subjects to address additional hypotheses.

Subjects who discontinue the study (withdrawals and Treatment Early Failures) may be replaced at the Sponsor's discretion.

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and research in this patient population.

8.8 Quality Assurance and Quality Control

8.8.1 Audit and Inspection

The study may be selected for audit originating from the Sponsor or external organizations acting on behalf of the Sponsor. Audits will be followed by internal reports and corrective actions, if needed.

The Investigator agrees to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved. The anonymity of the patients must be safeguarded and data checked during audits remain confidential.

8.8.2 Monitoring

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.

The Investigator will permit study-related monitoring, audits, ethics committee review and regulatory inspection(s), providing direct access to source data and documents.

For each patient enrolled, the Investigator or designee will document in the source records of the patient that the patient 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 patient. 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 Good Clinical Practice (GCP) and International Conference on Harmonisation (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.

8.8.3 Data Management and Coding

The Sponsor or Clinical Research Organization (CRO) 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 the Sponsor or CRO.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and World Health Organization (WHO) Drug for therapies.

8.8.4 Record Keeping

It is the responsibility of the Investigator to ensure all essential trial documentation and source records (e.g., signed ICFs, Study Site/Clinic files, patients' hospital notes, copies of eCRFs, etc.) 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.

9 Records and Supplies

9.1 Drug Accountability

On receipt of the IMP (including rescue medication, if relevant), the Investigator (or deputy) will conduct an inventory of the supplies and verify that IMP supplies are received intact and in the correct amounts prior to completing a supplies receipt. The Investigator will retain a copy of this receipt at the study site and return the original receipt to the drug depot. The inventory of supplies at each study site will be reviewed by the study monitor.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®). All vials of used and unused Study Drug during the active Treatment Period 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.

10 Ethics

10.1 Institutional Review Board

Before initiation of the study at each investigational site, the protocol, all protocol amendments, the ICF, and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the IMP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB annually, or more frequently if requested by the IRB. On completion of the study, the Sponsor will notify the IRB that the study has ended.

10.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the Declaration of Helsinki and local regulations.

10.3 Subject Information and Consent

The Investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject and/or legal guardian has given written informed consent to participate in the study. The written consent must be given by the subject and/or the legal guardian of the subject, after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

Subjects and/or legal guardians will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IRB, Sponsor and/or CRO personnel.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

10.4 Subject Confidentiality (US Studies)

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA), applicable to national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the ethics committees approving this research, and the United States (US) FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

11 Reporting and Publication

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator(s) will be subject to mutual agreement between the Investigator and Kiniksa as outlined in the study agreement.

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13 Appendices

Appendix 1: Investigator Signature Page

Protocol Title: An open-label pilot study of KPL-914 in symptomatic Recurrent Idiopathic Pericarditis.

Protocol Number: KPL-914-C001

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and I will conduct the study as described in compliance with this protocol, GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Kiniksa Pharmaceuticals Ltd. (Kinksa) and of the IEC/IRB. I will submit the protocol modifications and/or any ICF modifications to Kiniksa and IEC/IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all Case Report Forms, laboratory samples or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Kiniksa, to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

Appendix 2: ARCALYST® Prescribing Information

ARCALYST- rilonacept injection, powder, lyophilized, for solution
Regeneron Pharmaceuticals, Inc.

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: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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			Endpoint		

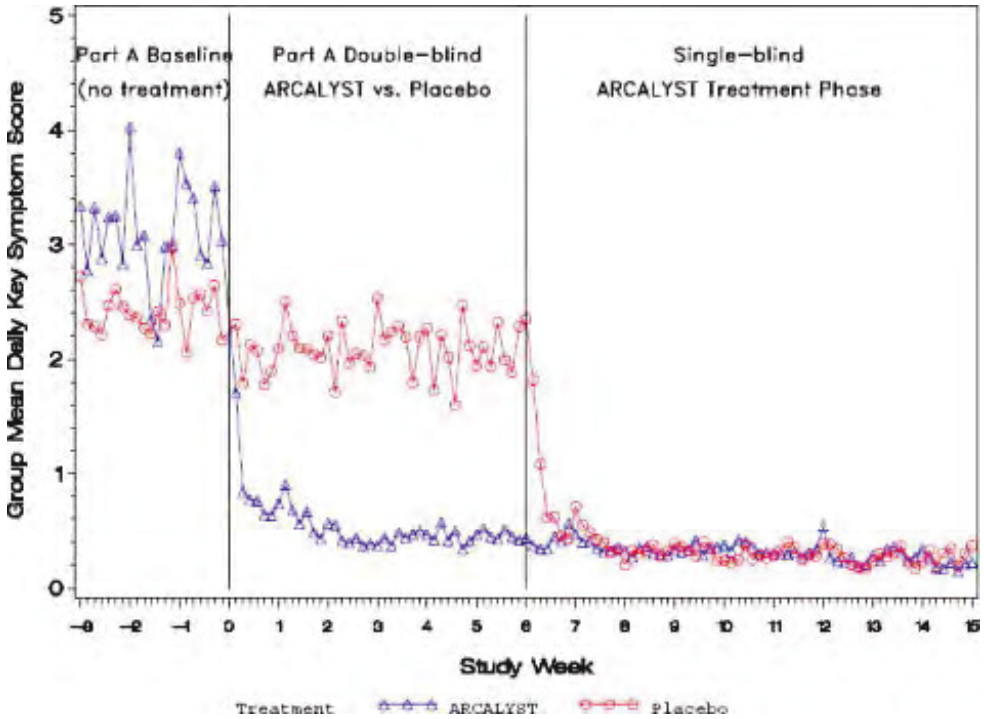
Period (Weeks 4 to 6)	2.1	0.5	Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment 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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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):

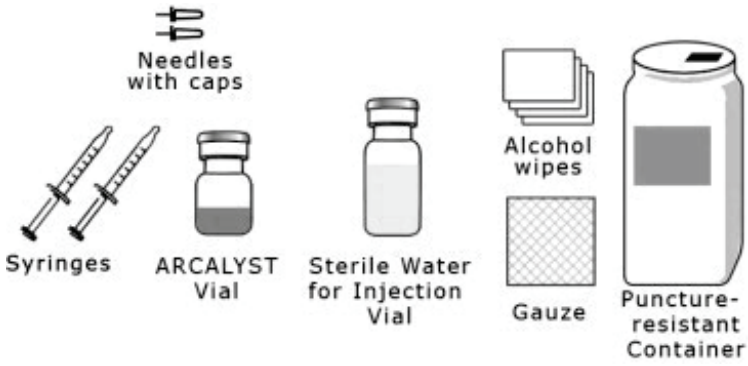


Figure 1

- 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

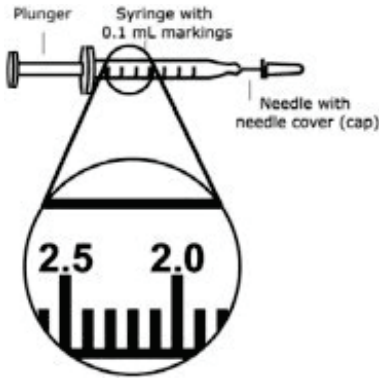


Figure 2

- 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).

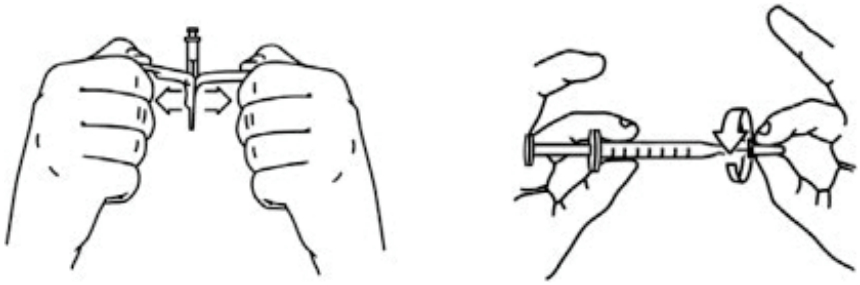


Figure 4

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).

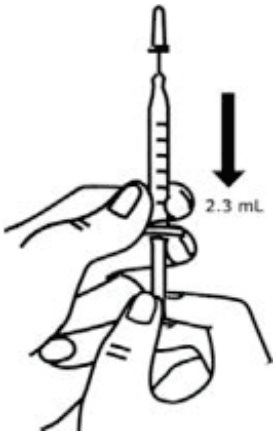


Figure 5

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).

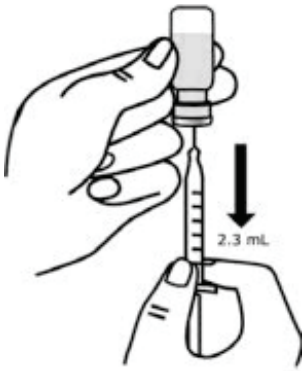


Figure 7

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).

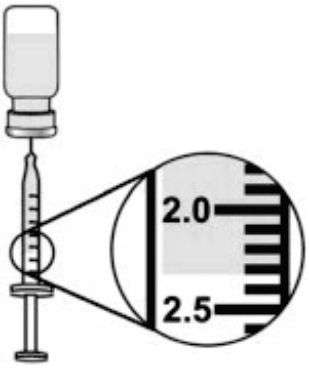


Figure 8

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).

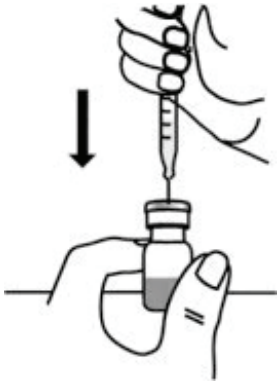


Figure 9

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.

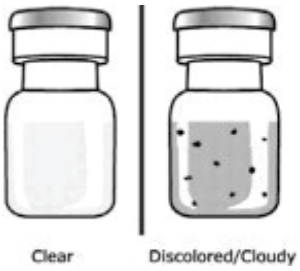


Figure 11

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).

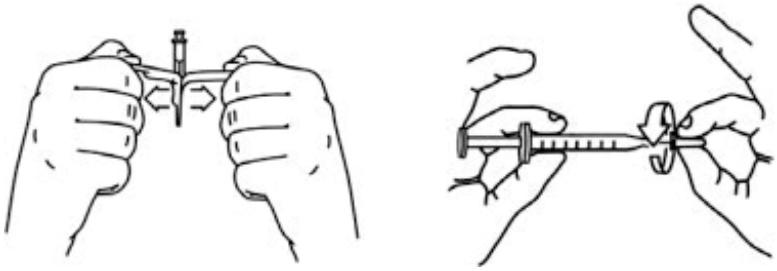


Figure 13

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).

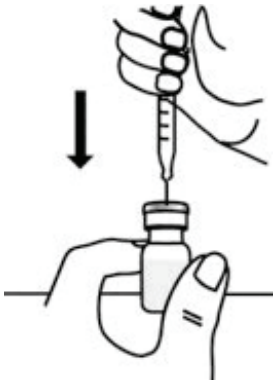


Figure 15

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).

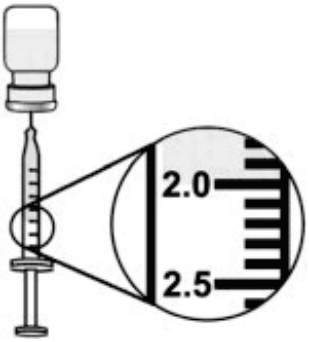


Figure 16

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.

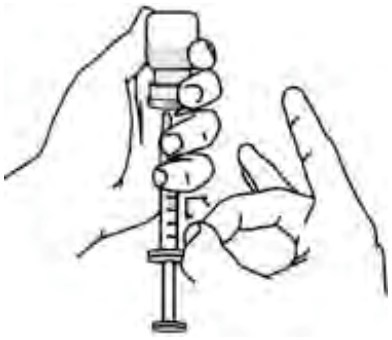


Figure 17

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)

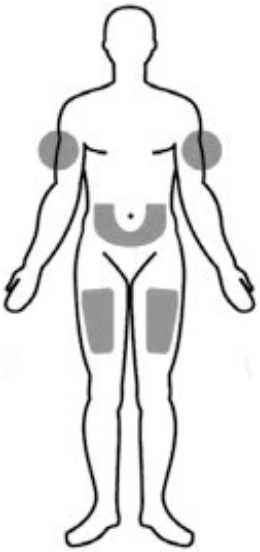


Figure 19

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).

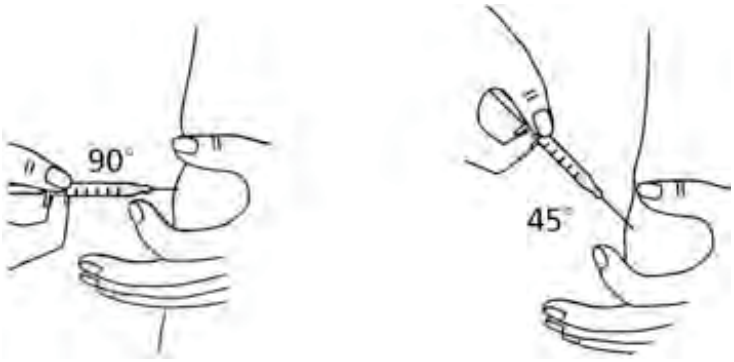


Figure 21

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).

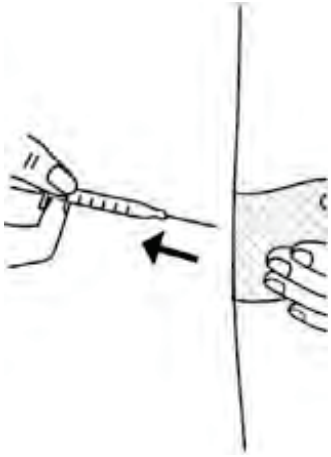


Figure 22

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:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
U.S. License Number 1760
NDC 61755-001-01

V 4.0

Principal Display Panel - Vial Carton

NDC 61755-001-01

Arcalyst®

(rilonacept)

Injection for Subcutaneous Use

220 mg sterile powder for reconstitution

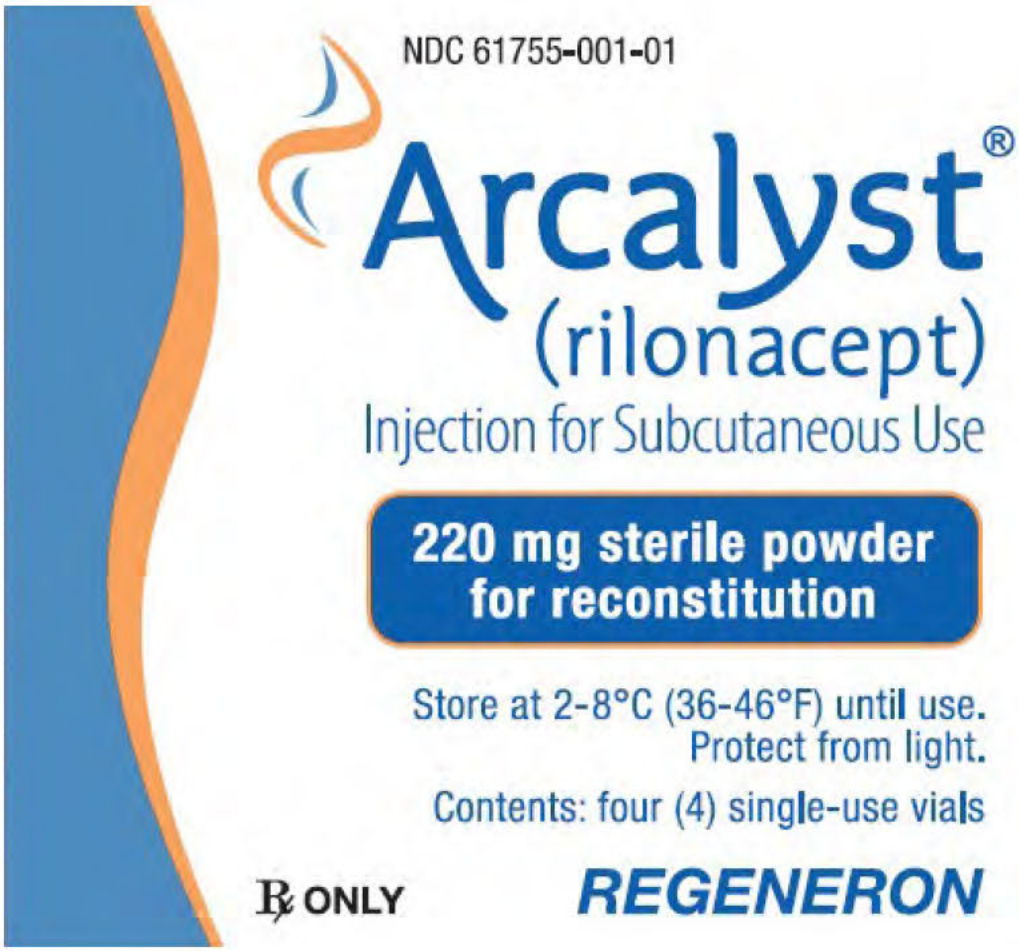
Store at 2-8°C (36-46°F) until use.

Protect from light.

Contents: four (4) single-use vials

Rx ONLY

REGENERON



ARCALYST

rilonacept injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61755 001

Route of Administration	SUBCUTANEOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
rilonacept (UNII: 8K80YB5GMG) (rilonacep UNII:8K80YB5GMG)	rilonacep	160 mg in 2 mL

Inactive Ingredients

Ingredient Name	Strength
Histidine (UNII: 4QD397987E)	
Arginine (UNII: 94ZLA3W45F)	
Polyethylene glycol 3350 (UNII: G2M7P15E5P)	
Sucrose (UNII: C151H8M554)	
Glycine (UNII: TE7660XO1C)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61755 001 01	4 in 1 CARTON	03/24/2008	
1		2 mL in 1 VIAL, SINGLE USE; Type 0: No a Combina ion Produc		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125249	02/27/2008	

Labeler - Regeneron Pharmaceuticals, Inc. (194873139)

Establishment

Name	Address	ID/FEI	Business Operations
Regeneron Pharmaceu icals, Inc.		945589711	ANALYSIS(61755 001) , API MANUFACTURE(61755 001) , LABEL(61755 001)

Appendix 3: Quality of Life Instrument

PROMIS Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global06	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Scale v1.2 – Global Health

	In the past 7 days…					
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
Global10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
Global08r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

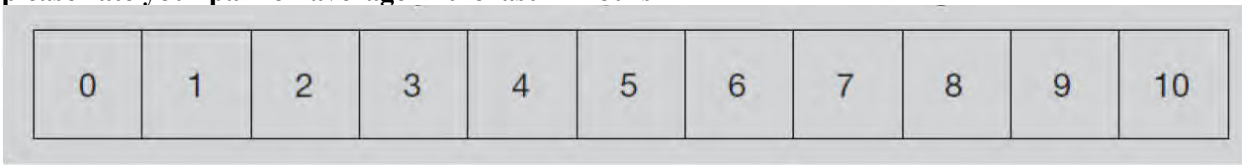
Global07r	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011).

Subjects will be asked to select the score that best describes their average level of 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 pain on average in the last 24 hours



CLINICAL STUDY PROTOCOL

An Open-Label Pilot Study of KPL-914 in Symptomatic Recurrent Idiopathic Pericarditis

Protocol Number:	KPL-914-C001
EudraCT Number:	Not Applicable
Investigational Medicinal Product:	KPL-914 (rilonacept)
Phase:	Phase 2
Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Medical Monitor:	[redacted]
Date of Protocol:	17 January 2018
Version of Protocol:	2.0 (Supersedes Version 1.2 dated 25 September 2017)

1 Protocol Approval Signatures

1.1 Sponsor Signature

Protocol Title: An open-label pilot study of KPL-914 in symptomatic recurrent idiopathic pericarditis.

Protocol Number: KPL-914-C001

This study will be conducted in compliance with the clinical study protocol, ICH Good Clinical Practice and applicable regulatory requirements.

[redacted]

[redacted]

2 Investigator and Administrative Structure

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Sponsor's Study Contact:	[redacted]
Sponsor's Medical Expert:	[redacted]
Drug safety/SAE-reporting:	[redacted]
Responsible CRO for Biostatistical Analysis:	[redacted]
CRO responsible for: Project Management, Monitoring, Quality Assurance, and Data Management:	[redacted]

3 Synopsis

Trial Number: KPL-914-C001
Trial Title: An open-label, pilot study of KPL-914 in symptomatic recurrent idiopathic pericarditis
Trial Centers: Approximately 15 sites in the United States
Development Phase: 2
Objective(s): Primary: To collect inter- and intra-subject variability data on C-reactive protein (CRP) measurements and the 11-point Numerical Rating Scale (NRS) instrument for assessment of pericardial pain in subjects with recurrent idiopathic pericarditis (RIP) both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in RIP. Secondary: To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914. To evaluate the safety of KPL-914 in symptomatic subjects with RIP.
Methodology: This is an open-label single-active-arm pilot study to explore clinical and biochemical endpoints of improvement of pericarditis symptomatology and to collect inter- and intra-subject variability data on both at-baseline and on-treatment parameters in symptomatic subjects with RIP who will be treated with once-weekly subcutaneously (SC)-administered injections of KPL-914. Subjects identified for participation in this trial will present during a symptomatic episode of RIP, having previously experienced a first (index) episode of acute pericarditis followed by at least 1 recurrent episode before the current enrollment-qualifying episode, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference: - The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate [ESR], and white blood cell [WBC] count) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]). - *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having experienced a previous index episode of acute pericarditis followed by at least 1 recurrent episode of pericarditis prior to the presenting symptomatic episode of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Prior to enrollment, potential subjects may enter an optional Prescreening Period after signing a Prescreening ICFto allow monitoring for symptoms and inflammatory markers (CRP, ESR, etc) while existing medications for recurrent idiopathic pericarditis may be managed by the Investigator or their clinician according to standard of care.

Study subjects will be enrolled (Screening Visit 1 [SCV1]) at the time of a symptomatic episode. In addition to meeting the criteria for pericarditis in the judgement of the Investigator, all subjects must present with a CRP value ≥1 mg/dL at the time of study enrollment. Subjects included in the study may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm the pre-treatment diagnostic workup. At the SCV1, baseline subject and disease characteristics will be determined and captured in the eCRF. Persistence of diagnostic criteria for pericarditis will be confirmed (Screening Visit 2 [SCV2]) within the 24 - 72 hour period before subjects advance to the Treatment Period of the study. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

Approximately 10 subjects will participate in the active Treatment Period of the study. Following review of the ongoing data by the Sponsor and the Investigators, the sample size may be increased to a total of up to 20 subjects. After having met all the entry criteria during the Screening Period, the subjects entering the Treatment Period will receive a loading dose of KPL-914 (2 x 160 mg SC) on Day 0, then 160 mg SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject as an outpatient SC administration. A visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be self-administered or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the subject, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study-related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.
Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF. Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF, and medication diary. At the discretion of the Investigator, "Treatment Responders" (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 administration can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks. Weekly Study Drug administrations during the EP are by self-administration, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis. During the EP, the Investigator may choose to wean concomitant NSAIDs, colchicine, and/or corticosteroids according to standard of care paradigms; all medication changes must be recorded in source records and the eCRF. Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7/End of Trial Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing subject management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each.

Given the following occurrences, dosing may be halted or reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg administered SC on Day 0, then 80 mg administered SC weekly for 5 additional weeks, in order to explore efficacy at a lower dose. Depending on treatment response observed with the 80 mg dose, the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject on a daily basis.

Number of Subjects:

Approximately 10 symptomatic subjects with RIP will be enrolled as study subjects. Following review of the available data, the Sponsor, in collaboration with the Investigators, may increase the sample size to up to 20 subjects to address additional hypotheses.

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

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

To be eligible to participate in the trial, a subject must meet all of the following criteria:

1. Has given consent and signed an Informed Consent Form (ICF).
2. Male or female, of any ethnic origin.
3. 18 to 70 years of age, inclusive.
4. Has had a prior *index episode* of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate, and white blood cell count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

5. Has had at least one prior *recurrent episode* of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
6. Has an ongoing symptomatic episode of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
7. Has an elevated CRP value (i.e., >1 mg/dL) at the time of study enrollment.
8. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days (although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.
9. If female, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
10. Is able to adequately maintain a daily medication diary.
11. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or changing exercise pattern) from the time of signature of the ICF to the End-of-Trial Visit (Week 6).

Exclusion Criteria

A subject who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific etiologies, including tuberculous, neoplastic, or purulent etiologies, post cardiac injury syndromes, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints within the 6-month period before dosing.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female subject who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A subject with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or physical exam. Have recent close contact with a person with active TB.
8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of

the study.

10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.
11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.
12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks of Study Drug administration, or has been treated with intravenous (IV) antibiotics for an infection within 2 months of first Study Drug administration.
15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a subject is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 30 days prior to Study Drug administration.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Subject who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Subject who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

Test Products, Dosage, and Mode of Administration:

KPL-914 (rilonacept) will be provided in its commercially-available formulation as a lyophilized powder to be reconstituted for SC administration.

KPL-914 will be administered as an initial loading dose of 2 x 160 mg SC on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks. After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg administered SC on Day 0, then 80 mg administered SC weekly for 5 additional weeks, in order to explore efficacy at a lower dose.

Subjects will receive a total of 6 doses of KPL-914 during the study active Treatment Period. Subjects who are considered to be "Treatment Responders" will be offered, at the discretion of the Investigator, participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued for a total duration of KPL-914 treatment of up to 24 weeks.

Concomitant Medication

- There is no wash-out of concomitant therapy (NSAIDs/colchicine/corticosteroids) during the Screening Period of the study.
- For the duration of the Treatment Period, concomitant pericarditis medications (e.g., NSAIDs, colchicine and corticosteroids), if used, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAIDs, colchicine, and/or corticosteroid dose is medically necessary, the NSAID, colchicine and/or corticosteroid dose can be down-titrated according to standard of care paradigms in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.
- Opioid analgesics, non-narcotic (non-NSAID) analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF.
- Medical management of pericarditis during the EP is based on Investigator discretion. For example, Investigators may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug, or change (increase or decrease) the dosing of NSAIDs/colchicine/ corticosteroids. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF.
- Prohibited concomitant medicines: Other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.

Duration of Treatment:

The Study Drug will be administered for 6 weeks in the base study Treatment Period.

"Treatment Responders" will be offered participation in an optional 18-week EP at the discretion of the Investigator.

Total subject participation is expected to last for up to 171 days for those that also participate in the 18-week EP.

Efficacy Measures:

- Clinical laboratory analyses (e.g., CRP).
- Pericarditis symptoms (i.e., pain) using a 11-point NRS (Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain)
- Echocardiogram (pericardial effusion)
- ECG (for pericarditis diagnostic findings)
- Pericarditis signs (e.g., fever, pericardial rub)
- Pericardial inflammation as determined by cardiac MRI (optional assessment)
- Quality of life (QoL) questionnaire (Appendix 3).

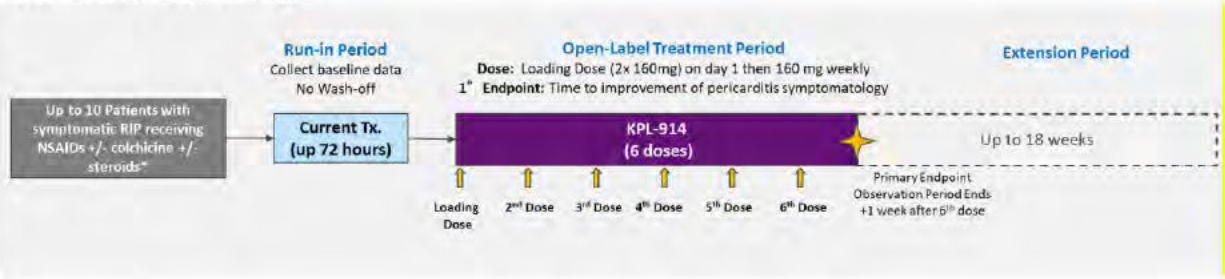
Safety Measure(s):

Safety endpoints for this study include frequency and severity of AEs and SAEs, clinical laboratory analyses (including safety laboratory measurements, anti-drug antibodies, etc.), vital sign measurements, ECGs, and physical examination findings.

Other Measure(s):

[redacted]

Overview of Trial Design



Trial Periods

1. Prescreening Period: Prior to enrollment, potential subjects may enter an optional prescreening period after signing a Prescreening ICF to allow monitoring for symptoms and inflammatory markers (CRP, ESR, etc) while existing medications for recurrent idiopathic pericarditis may be managed by the Investigator or their clinician according to standard of care.
2. Screening Period: The Screening Period starts with the signing of the full study ICF (SCV1) and may last for up to 3 days (72 hours) until SCV2. At SCV1, baseline subject and disease characteristics will be determined. Persistence of diagnostic criteria for pericarditis will be confirmed within ~24 to 72 hours at SCV2. Under special circumstances, the Investigator in consultation with the Sponsor can combine SCV1 and SCV2. The end of the Screening Period coincides with the start of the Treatment Period (Day 0 Visit).

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

   Patient-reported pericardial pain evaluations will be performed on-site at SCV1 and SCV2 using a validated 11-point NRS instrument. A patient-reported QoL questionnaire will be administered as well.
3. Treatment Period: The first dose of Study Drug will be administered to subjects at the Study site/Clinic at Visit 1 on Day 0. During this visit, subjects will be trained for outpatient drug administration. Subsequent weekly Study Drug administrations from Weeks 2 to 5 will be self-administered by the subject as an outpatient SC administration. A visiting study nurse will

assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End-of-Trial, Study Drug may be self-administered at home or administered at the Study site/clinic.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject.

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

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

4. Extension Period (EP): The EP is defined as the 18 weeks following the Treatment Period. Subjects who are considered to be "Treatment Responders" will be, at the discretion of the Investigator, offered participation in an optional 18-week EP, in which weekly administration of open-label KPL-914 may be continued for a total duration of 24 weeks. The weekly KPL-914 doses will be by self-administration, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits will continue on a monthly basis. During that EP, the Investigator may choose to change concomitant NSAID, colchicine, and/or corticosteroid treatment, recording all modifications in the source records and eCRF.

   Unscheduled clinic visits can be scheduled any time as determined by the Investigator/upon subject request. In addition, Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed.

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

Statistical Methods:

Analysis Populations

The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (e.g., NSAIDs, colchicine, corticosteroids) according to study protocol without a major protocol violation. The Safety Population will be the same as the mITT Population.

General Methods

Because of the small sample size no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or analysis group. For categorical endpoints, summary statistics will be calculated and presented for each treatment and/or analysis group.

Further details, including, for example, the process to be followed for reviewing individual pericarditis symptomatology endpoints to be used in the construction of a composite primary endpoint for subsequent trials, will be provided in the Statistical Analysis Plan (SAP).

Primary Endpoint

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

Table 1: Schedule of Evaluations

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

Trial Period →		**Run-In Period (Up to 3 days)**		**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →	**Pre-screening Period**	**Day -3 to Day 0[a]**		**Day 0[b]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial[c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 Clinic**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓					**Unscheduled Visits[u]**										
Clinical laboratory tests (incl CRP)– Central laboratory [l]		X	X	(X)[x]	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (lipid panel) – Central Laboratory				X							X				X
Clinical laboratory tests (incl CRP) – Study Site/Clinic laboratory [m]	X[y]	X	X	(X)[x]			X				X		X	X	X
Biomarker testing, PK, and anti-rilonacept antibody – Central Laboratory [l]		X		(X)	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [n]		X													
AE evaluations [o]				X	X	X	X	X	X	X	X	X	X	X	X
Medication diary dispensing [p]		X													
Medication diary compliance verification and reminder [q]			X	(X)[x]			X				X				X
Pericardial pain (11-pt Numerical Rating Scale)[r]	X	X	X	(X)[x]	X	X	X	X	X	X	X	X	X	X	X

Trial Period →		**Run-In Period (Up to 3 days)**		**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →	**Pre-screening Period**	**Day -3 to Day 0[a]**		**Day 0[b]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial[c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 Clinic**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓					**Unscheduled Visits[u]**										
PGA (QoL questionnaire) [s]		X		X			X				X			X	X
Dosing Procedure Questionnaire [z]						X				X				X	
Investigator (or designee) phone call/virtual visit [v]					X	X		X	X	X		X (monthly)			

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

a. A second Screening visit (SCV2) should be performed within ~24h to 72h. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2. The last Screening and Day 0 procedures may be performed on the same day, but SCR procedures must be completed prior to Study Drug administration.

b. Subjects who do not complete the Treatment Period (withdraw consent or are discontinued before they have completed 6 weeks treatment), must be asked to complete the procedures specified at the EoT Visit.

c. Weekly intervals refer to 7 ± 1 days. The interval between Study Drug administrations must be at least 5 days.

d. Subjects should return for an optional Interval Evaluation Visit at the clinic between approximately Week 3 and 4, as determined by the Investigator.

e. Including age at first attack, number of previous attacks, and duration of attacks.

f. Drug administration training of subjects is performed at Visit 1. Study Drug will be administered in the Study Site/Clinic at Visit 1. Study Drug administrations are performed by the subjects (self-administration) on Visits (Outpatient) 2, 3, 4, 5, and 6. Participation in the Extension Phase (optional) is determined at the Week 6/EoT Visit 7 by the Investigator. Subjects who are eligible and who are willing to participate will be consented during EoT Visit 7 at the Study Site/Clinic. Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Study Site/Clinic (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7 relative to the timing of

weekly dosing. Timing for dose administration is per direction of the Investigator based upon the prescribing information and study-specified dosing intervals. Continued weekly Study Drug treatment during the EP will be outpatient administration.

g. Full physical examination including assessment of pericardial rub.

h. Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.

i. Central 12-lead ECG and echocardiogram reading (including assessment of pericardial effusion). At SCV2 only the ECG will be obtained. The Study Site/Clinic reading of the ECG and the ECHO at the time of the examination will be used by the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.

j. Optional.

k. At the SCV1, information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured. During the Treatment Period, changes in concomitant medication since the last Study Site/Clinic visit will be documented. During the EP, changes in pericarditis/concomitant medication will be assessed at Study Site/Clinic Visits and in monthly outpatient phone calls/virtual visits.

l. Biomarker, pharmacokinetics (PK) and anti-rilonacept antibody analysis samples will be drawn in all subjects and archived for future testing. . During each Visit at the Study Site/Clinic a sample for CRP will be obtained and sent to the central laboratory (or designated qualified laboratory) for analysis; at each Outpatient Visit; blood for central laboratory measurement of CRP will be obtained as described in the Laboratory Manual.

m. Hematology, chemistry, and urinalysis will be performed at the Study Site/Clinic laboratories, and results when available will be entered into the eCRF with appropriate reference values. Serology (HCVAb, HBsAg, HBcAb, HBsAb and HIV) and urine drug screen will be performed at SCV1 only.

n. To be eligible to continue in the trial, a negative urine pregnancy test must be documented at the SCV1. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.

o. All AEs occurring after the subject receives the first dose of Study Drug will be captured in source records and eCRF.

p. At the SCV1, the Investigator or designee will instruct the subject about the use of the medication diary. The subject will be asked to complete a entries into the medication diary during the Screening Period and Treatment Period. Only information on pain/rescue medication will be collected. Other concomitant treatments/medications are not required to be captured.

q. At the SCV2 and all subsequent visits at the Study Center, the Investigator or designee will review the Diary entry information to verify subject compliance. If the last screening visit occurs at a different day than Visit 1, the review will also be performed at Visit 1. Diary documentation will end at the End-of-Trial visit (Visit 7).

r. Subject assessment of pericardial pain using a validated 11-point Numerical Rating Scale. The assessment will be performed on-site during clinic visits and as part of a telephone call/virtual visit during outpatient treatment weeks. If the last screening visit occurs at a different day than Visit 1, the assessment will also be performed at Visit 1, prior to Study Drug treatment.

s. Subject global assessment of overall well-being will be assessed using a validated QoL Questionnaire (see Appendix 3). The assessment will be performed on-site during clinic visits. If SCV2 occurs at a different day than Visit 1 (Day 0), the global assessment will also be performed at Visit 1, prior to Study Drug administration.

t. Subjects may return for an optional EP Interval Evaluation Visit at the clinic between Week 15 and 20 (8 to 13 weeks after Visit 7), as determined by the Investigator.

u. Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a “Treatment Failure” may be withdrawn from further Study Drug treatment at the

discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

v. At weekly Investigator (or designee) phone calls/virtual visits during the Treatment Period, Study Drug compliance, medication diary compliance, and laboratory sample collection will be checked. The subjects will be asked using non-leading questions about any AEs occurring since the last contact (phone call/virtual visit or site visit), and NRS pain assessment will be performed. Investigator (or designee) phone calls/virtual visits will be performed monthly during the during the EP to perform NRS pain assessments, collect AE information, and review pericarditis/concomitant medications. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits.
w. During the Extension Period, Study Drug treatment is weekly by self-administration, and the study nurse visits to the home and Investigator (or designee) phone calls/virtual visits are monthly.
x. Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling and subject NRS pericardial pain rating must be repeated prior to Study Drug dosing.
y. Per Standard of Care.
z. The dosing preparation and administration questionnaire must be completed in the presence of Study Staff (via virtual visit) or visiting nurse.

4 Table of Contents

List of In-text Tables

List of In-text Figures

5 List of Abbreviations and Definition of Terms

AcP	accessory protein
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
b.p.m.	beats per minute
BUN	blood urea nitrogen
CAPS	Cryopyrin Associated Periodic Syndrome
CDC	Centers for Disease Control
CHO	Chinese hamster ovary
CI	confidence interval
CRO	contract research organization
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
CTAD	citrate, theophylline, adenosine, dipyridamole
EoT	End-of-Trial
EP	Extension Period
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IL-1	Interleukin-1
IL-1RA	IL-1 receptor antagonist
IL-1RI	IL-1 type I receptor
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	intravenous
kDa	kilo Dalton
KPL-914	Study Drug; nomenclature of rilonacept (ARCALYST®) in this protocol
LDH	lactate dehydrogenase
MCH	mean cell hemoglobin
MCHC	MCH concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mITT	modified intent to treat
MWS	Muckle-Wells Syndrome

NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drugs
PI	Prescribing Information
PP	per protocol
PPD	purified protein derivative
PRO	patient-reported outcome
PT	prothrombin
PTT	prothrombin time
QoL	quality of life
RBC	red blood cell
RIP	recurrent idiopathic pericarditis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCR	Safety Review Committee
SCV	screening visit
SD	standard deviation
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	serious and unexpected and related adverse reaction
TB	tuberculosis
[redacted]	[redacted]
TNF	tumor necrosis factor
US	United States of America
WBC	white blood cells
WHO	World Health Organization
WFI	water for injection

6 Introduction

Pericarditis accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction (Khandaker et al, 2010). 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). Diagnosis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic (ECG) changes, pericardial effusion, or elevated markers of inflammation (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Imazio et al, 2014). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define a pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-elevation or PR depression on ECG, and pericardial effusion (new or worsening). Elevations of 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 a common complication of acute pericarditis and affects 20–30% of patients (Imazio, 2014). It is characterized by the recurrence of signs and symptoms of pericarditis after a symptom-free interval of at least 4-6 weeks (Adler et al, 2015). The underlying pathogenesis of recurrent idiopathic pericarditis (RIP) remains unclear, although immune-mediated mechanisms are believed to play a key role in the pathogenesis (Imazio et al, 2005). A growing body of evidence suggests that these immune responses consist of both pathogenic autoimmune and auto-inflammatory processes (Cantarini et al, 2015; Doria et al, 2012). The presence of pro-inflammatory cytokines in the pericardial fluid of RIP patients lends direct support to both an autoimmune and/or auto-inflammatory etiopathogenesis (Pankuwait et al, 2000).

Currently available treatments for RIP include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids (Lilly, 2013). Aspirin and other NSAIDs are the first-line approach. Because high doses are often required, consideration should be given to gastric protection therapy. Colchicine is another mainstay therapy for RIP and is commonly used with NSAIDs, but a subset of patients has refractory symptoms and significant gastrointestinal side effects, including severe diarrhea, leading to discontinuation for intolerability. Glucocorticoids should be prescribed only to patients with idiopathic pericarditis who are refractory or intolerant to treatment with NSAIDs plus colchicine, because of the side effects associated with long-term corticosteroid therapy and because of a high rate of relapse when the corticosteroid is tapered or stopped (Maisch et al, 2004; Imazio, 2005; Lotrionte et al, 2010), particularly in the absence of colchicine treatment. Patients with refractory symptoms can be particularly challenging to manage, and multiple immunosuppressive medications have been used without consistent benefit (Baskar et al, 2016).

Interleukin-1 (IL-1) is a key cytokine that drives the pathophysiology of many inflammatory processes. It is implicated as a causative factor in various inflammatory human diseases. Although the pathogenic mechanism of auto-inflammatory disease is not completely understood, there is a growing body of evidence that IL-1 may be a primary driver of the symptomology and that targeting this cytokine may provide important benefits (Hoffman & Patel, 2004). [redacted]

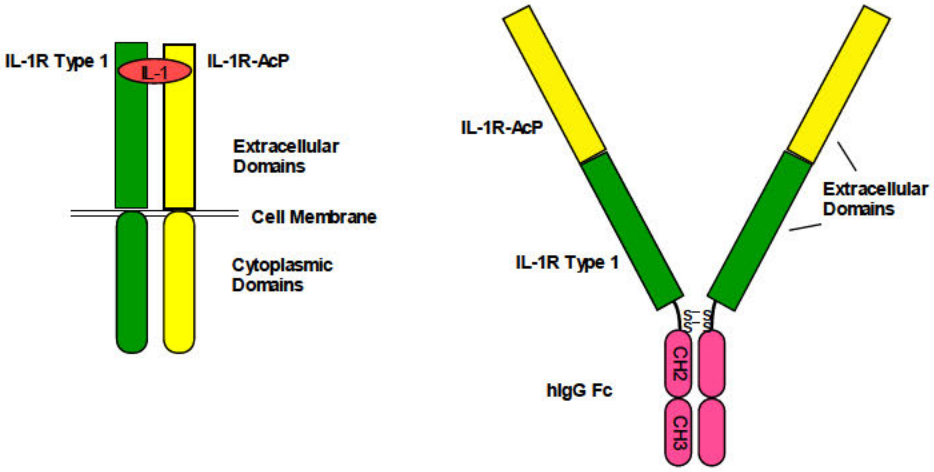
Rilonacept (marketed in the US under the trade name ARCALYST®; referred to as KPL-914 in this investigational study protocol) blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1α and IL-1β and prevents its interaction with IL-1 cell surface receptors. The equilibrium dissociation

constants for rilonacept binding to IL-1β, IL-1α and IL-1RA are 0.5 pM, 1.4 pM and 6.1 pM, respectively. By comparison, the IL-1 Type I receptor (IL-1RI) alone has approximately 1 nM affinity.

Rilonacept (KPL-914) is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human immunoglobulin G (IgG)1. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1RI and the IL-1 accessory protein (AcP) (Figure 1). Rilonacept was created by fusing the sequences encoding the extracellular domains of the AcP, IL-1RI, and the human Fc segment inline without any intervening linker sequences. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept is expressed in Chinese hamster ovary (CHO) cells and is purified with a series of chromatographic and filtration techniques.

The total molecular weight is ~251 kDa, of which 80% is protein (201 kDa) and 20% is carbohydrate (50 kDa).

Figure 1: Schematic of rilonacept (KPL-914)



Rilonacept was developed by Regeneron Pharmaceuticals, Inc. and is approved with the tradename ARCALYST® in the US for the treatment of Cryopyrin Associated Periodic Syndrome (CAPS), including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

Rilonacept is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. For subcutaneous (SC) administration, rilonacept is manufactured in a dosage form containing 160 mg per vial. The lyophilized powder is reconstituted with 2.3 mL of sterile Water for Injection (WFI) and drug is delivered in 2 mL at a concentration of 80 mg/mL. Clinical dosing (e.g., in CAPS) initiates with a loading dose of 320 mg SC followed by 160 mg administered SC weekly. A lower dose of 80 mg weekly (initiated with a 160 mg loading dose) was also tested in Phase 3 clinical trials in gout.

For a detailed review of the available rilonacept data, please refer to the Investigator Brochure and the ARCALYST® package insert.

Kiniksa Pharmaceuticals Ltd. (Kiniksa) is now developing rilonacept for the treatment of RIP (Rilonacept will be referred to as KPL-914 in this investigational study protocol). In this first pilot study in subjects with RIP, improvement of pericarditis symptomatology with KPL-914 administration as well as the safety

and dose relationships will be assessed. Commercially-available rilonacept (ARCALYST®) will be used in the study.

The nonclinical development program for rilonacept (ARCALYST®) demonstrated biological activity and adequate safety across toxicity studies (Appendix 2: ARCALYST® Prescribing Information).

The most common adverse reactions reported by patients with CAPS treated with ARCALYST® are injection-site reactions and upper respiratory tract infections. Hypersensitivity reactions associated with rilonacept administration have been rare.

Refer to the ARCALYST® PI for Important Safety Information regarding rilonacept (Appendix 2: ARCALYST® Prescribing Information).

Based on its IL-1-antagonistic properties, its weekly-dosing pharmacokinetics, and its well-understood safety profile as shown in patients with CAPS, rilonacept (KPL-914) is a promising candidate for the treatment of RIP.

7 Study Objectives

7.1 Primary Objective

To collect inter- and intra-subject variability data on C-reactive protein (CRP) measurements and the 11-point NRS instrument for assessment of pericardial pain in symptomatic subjects with recurrent idiopathic pericarditis (RIP) both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in RIP.

7.2 Secondary Objective(s)

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

8 Investigational Plan

8.1 Overall Study Design and Plan

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

Subjects identified for participation in this trial will present during a symptomatic episode of RIP, having previously experienced a first (index) episode of acute pericarditis followed by at least 1 recurrent episode before the current enrollment-qualifying episode, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate [ESR], and white blood cell [WBC] count) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]).

- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having experienced a previous index episode of acute pericarditis followed by at least 1 recurrent episode of pericarditis prior to the presenting symptomatic episode of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Prior to enrolment, potential subjects may enter an optional Prescreening Period, after signing a Prescreening ICFto allow monitoring for symptoms and inflammatory markers (CRP, ESR, etc) while existing medications for recurrent idiopathic pericarditis may be managed by the Investigator or their clinician according to standard of care.

Study subjects will be enrolled (Screening Visit 1 [SCV1]) at the time of a symptomatic episode. In addition to meeting the criteria for pericarditis in the judgement of the Investigator, all subjects must present with a CRP value ≥1 mg/dL at the time of study enrollment. Subjects included in the study may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm the pre-treatment diagnostic workup. At the SCV1, baseline subject and disease characteristics will be determined and captured in the eCRF. Persistence of diagnostic criteria for pericarditis will be confirmed (Screening Visit 2 [SCV2]) within the 24 - 72 hour period before subjects advance to the Treatment Period of the study. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

Approximately 10 subjects will participate in the active Treatment Period of the study. Following review of the ongoing data by the Sponsor and the Investigators, the sample size may be increased to a total of up to 20 subjects. After having met all the entry criteria during the Screening Period, the subjects entering the Treatment Period will receive a loading dose of KPL-914 (2 x 160 mg SC) on Day 0, then 160 mg SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject as an outpatient SC administration. A visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be self-administered or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the subject, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF and medication diary.

At the discretion of the Investigator, "Treatment Responders" (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and/or

absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks. Weekly treatments during the EP are by self-administration, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis.

During the EP, the Investigator may choose to wean concomitant NSAIDs, colchicine, and/or corticosteroids according to standard of care paradigms; all medication changes must be recorded in source records and the eCRF. Investigators are encouraged to invite subjects to the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after the Visit 7/End of Trial Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing subject management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each.

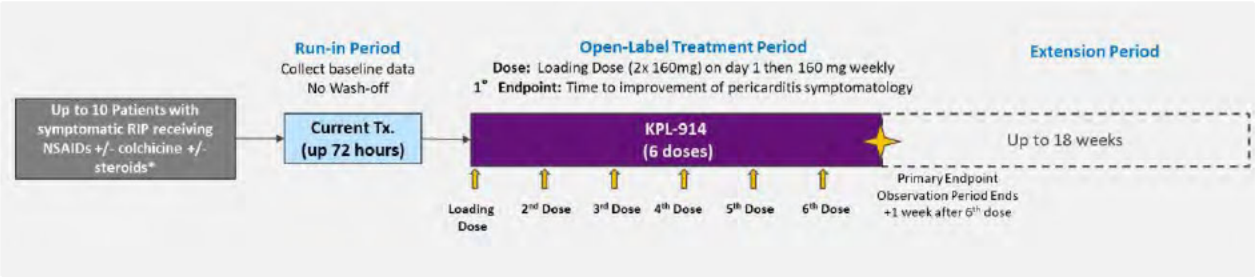
Given the following occurrences, dosing may be halted or reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg administered SC on Day 0, then 80 mg administered SC weekly for 5 additional weeks, in order to explore efficacy at a lower dose. Depending on treatment response observed with the 80 mg dose, the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject on a daily basis.

Figure 2: Overview of Trial Design



The study will be conducted in compliance with Good Clinical Practice regulations and other regulatory requirements.

8.2 Discussion of Study Design

Clinical information from the development of rilonacept in CAPS (ARCALYST®), the mode of action of rilonacept, as well as the inflammatory nature of RIP suggest that rilonacept (KPL-914) may safely and effectively resolve RIP. [redacted] The rationale for this pilot study is to collect time-course to pericarditis improvement data and safety information for up to 2 dose levels of KPL-914 (i.e., 160 mg and 80 mg) when administered to subjects with RIP. The study aims to provide data to support the design of future clinical studies with KPL-914 in RIP: in particular to inform inter-and intra-subject variability in CRP and NRS measurements, the time course of treatment response, and the dosage(s) of KPL-914 to be evaluated in a pivotal Phase 3 clinical trial.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

Approximately 10 symptomatic subjects with RIP will be enrolled as study subjects. Following review of the available data, the Sponsor, in collaboration with the Investigators, may increase the sample size to up to 20 subjects to address additional hypotheses.

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

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and other research in this patient population.

8.3.2 Inclusion Criteria

To be eligible to participate in the trial, a subject must meet all of the following criteria:

1. Has given consent and signed an Informed Consent Form (ICF).
2. Male or female, of any ethnic origin.
3. 18 to 70 years of age, inclusive.
4. Has had a prior *index episode* of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the

Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate, and white blood cell count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

5. Has had at least one prior *recurrent episode* of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
6. Has an ongoing symptomatic episode of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
7. Has an elevated CRP value (i.e., >1 mg/dL) at the time of study enrollment.
8. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days prior to Study Drug dosing (although stable doses for a shorter period will be acceptable if, in the opinion of the Investigator in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.
9. If female, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
10. Is able to adequately maintain a daily medication diary.
11. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or change in exercise pattern) from the time of signature of the ICF to the End-of-Trial Visit (Week 6).

8.3.3 Exclusion Criteria

A subject who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific etiologies, including tuberculous, neoplastic, or purulent etiologies, post cardiac injury syndromes, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints within the 6-month period before dosing.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female subject who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A subject with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or

physical exam. Have recent close contact with a person with active TB.

8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of the study.
10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.
11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.
12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks, or has been treated with IV antibiotics for an infection within 2 months of first Study Drug administration.
15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a subject is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 30 days (or 5 half-lives, whichever is longer) prior to Study Drug administration.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Subject who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Subject who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

8.3.4 Vaccination History and Immune status

IL-1 blockade may interfere with immune response to infections. Therefore, the Investigator should review with the subject the subject's vaccination history relative to the current medical guidelines for vaccine use. A recommended immunization schedule is available at the website of the Centers for Disease Control (CDC) (www.cdc.gov/vaccines/recs/scheduled/default.htm).

It is recommended that, prior to or shortly after initiation of therapy with KPL-914, subjects be brought up to date with all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza

vaccine. In case a subject needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed (e.g., at the Study Site/Clinic) after the 6-week active Treatment Period. However, to minimize the potential confounding of KPL-914-related Adverse Experience reporting at initiation of KPL-914 dosing or measurements of CRP during the treatment period, vaccination should not be performed within the first 6 weeks after initiation of KPL-914 administration.

It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Administration of KPL-914 is prohibited within 12 weeks of having received a live (attenuated) vaccine. It is also possible that taking drugs that block IL-1 increases the risk of TB. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent TB infections before initiating therapy with KPL-914.

8.3.5 Removal of Subjects from Therapy or Assessments

Subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator on an ongoing basis as part of subject management. An SRC including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each.

Given the following occurrences, dosing may be halted or the dose reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

In addition, subjects may stop study treatment or may be withdrawn from treatment for any of the following reasons:

- Subject request. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment
- Use of non-permitted concurrent therapy
- Non-compliance
- Investigator request.

Treatment Failures or subjects who are withdrawn from the study for safety reasons will be replaced at the discretion of the Sponsor. Similarly, subjects who do not comply with the protocol or who withdraw from

the study for other reasons can be replaced. The reason(s) for withdrawal will be documented in the source records and the eCRF.

Subjects withdrawing from the study during the Treatment Period will be asked to complete the End-of-Trial evaluations to document the status of their pericarditis disease progression at the time of withdrawal from treatment. Subjects will continue to be followed for vital status for the duration of intended treatment to address informative censoring. Subjects withdrawing from the study during the EP will be asked to complete the Final Visit evaluations.

All reasonable efforts will be made to contact subjects who are lost to follow-up.

The Sponsor has the right to terminate the study at any time in case of safety concerns (e.g., SUSARs) or if special circumstances concerning the Investigational Medicinal Product (IMP) 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.

Pregnancy

Pregnant or lactating female subjects are excluded from study enrollment. While not explicitly stated in the rilonacept (ARCALYST®) PI (Appendix 2: ARCALYST® Prescribing Information), for the purposes of this experimental protocol, females of child-bearing potential (i.e., not postmenopausal and not sterilized) must use an active method of birth control during the course of the study, e.g., oral, implanted or injected contraceptive hormones, an intrauterine device, or a barrier method (e.g., diaphragm, condoms, spermicides).

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator without delay. If pregnancy is confirmed, the Investigator must notify the Sponsor within 24 hours and the subject must not receive (additional) Study Drug and must be discharged from the study. The subject must be asked regarding their willingness to complete the End-of-Trial Visit.

In the event that a subject is found to be pregnant after having received at least one Study Drug dose, the pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Instances of perinatal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment, will be reported to the Sponsor within 24 hours.

Full details will be recorded on the pregnancy form.

8.4 Investigational Medicinal Products

8.4.1 Investigational Medicinal Products Administered

During the Treatment Period, KPL-914 will be administered as an initial loading dose of 2 x 160 mg SC on Day 0, then 160 mg SC dosed once weekly for up to 5 subsequent weeks. At the discretion of the Investigator, subjects completing the Treatment Period may enter the 18-week Extension Period and receive up to 18 additional weekly doses of KPL-914.

At the discretion of the Sponsor in collaboration with the Investigators, the Study Drug dosing regimen may be decreased in a consecutive group of subjects to a loading dose of 2 x 80 mg SC on Day 0, then 80 mg SC dosed once weekly for 5 subsequent weeks to explore efficacy at a lower dose. Depending on treatment

response observed with the 80 mg dose, the dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Sites for SC 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.

No placebo or active comparator drug will be used.

8.4.2 Identity of Investigational Medicinal Products

KPL-914 (rilonacept/ARCALYST®) is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. It 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 WFI is required prior to SC administration of the drug. The reconstituted drug product is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

After the addition of preservative-free sterile WFI, the vial contents should be reconstituted by gently shaking the vial for approximately 1 minute and then allowing it to sit for 1 minute. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for SC administration only.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®) as a lyophilized powder to be reconstituted for SC administration. The sites will receive Study Drug for on-site administration at Study Site/Clinic visits. Drug will be disseminated to the trial subjects for outpatient self-administration according to a supply chain described in the Pharmacy Manual.

The lyophilized Study Drug (KPL-914 also called rilonacept, US tradename: ARCALYST®) is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. After reconstitution, KPL-914 may be kept at room temperature, should be protected from light, and should be used within 3 hours of reconstitution. Unused portions of KPL-914 product must not be injected. All vials of used and unused Study Drug during the active Treatment Period must be returned to the clinical site for cataloguing and documentation of compliance.

The Sponsor through Regeneron Pharmaceuticals, Inc. will ensure that the Study Drug and certificates of analysis are available before the start of the study and at all times during the study.

ARCALYST® is a registered trademark of Regeneron Pharmaceuticals, Inc.

8.4.3 Method of Assigning Subjects to Treatment Groups

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will enter the Treatment Period at Visit 1 (Day 0).

Since this is an open-label, single-active-arm study, all subjects will receive KPL-914 active treatment. Assignment to treatment groups is not applicable.

8.4.4 Selection of Doses in the Study

This protocol is a pilot study intended to evaluate the safety, efficacy, and dose response of KPL-914 in the treatment of patients with RIP.

[redacted] treatment will be started with a loading dose of 320 mg delivered as two, 2-mL SC injections of 160 mg; dosing will continue with once-weekly injections of 160 mg administered as a single, 2-mL SC injection (Appendix 2: ARCALYST® Prescribing Information).

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if the majority of subjects achieve treatment response during the first half of the Treatment Period), the Sponsor, in collaboration with the Investigators, may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects to a loading dose of 2 x 80 mg SC on Day 0, then 80 mg SC weekly (the dose tested in the Phase 3 program for gout) for 5 additional weeks in order to explore efficacy at a lower dose. However, depending on treatment response observed with the 80 mg dose, the dose administered to either these subjects or subsequent subjects may be changed back to 160 mg by the Investigator in collaboration with the Sponsor.

8.4.5 Selection and Timing of Dose for Each Subject

The first administration of KPL-914 (and training for outpatient self-administration) will be performed under the supervision of a qualified healthcare professional at Visit 1 (Day 0). Afterwards, subjects will self-administer the Study Drug as an outpatient during the Treatment Period (and during the EP, as applicable). Study Drug administration will be performed once a week (every 7 ± 1 days). The interval between Study Drug administrations must be at least 5 days. Subjects will be instructed to not administer KPL-914 more often than once weekly and to administer only one syringe of Study Drug per week.

At Visit 1, subjects will be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously will be assessed to ensure proper administration of KPL-914, including rotation of injection sites. Subjects will be instructed in proper vial, syringe, and needle disposal, and will be cautioned against reuse of these items. All used and unused Study Drug vials must be returned to the Study Site/Clinic for drug accountability assessment.

8.4.6 Blinding

Not applicable.

8.4.7 Prior and Concomitant Therapy

Subjects enrolled into the study may be using NSAIDs, colchicine, and/or corticosteroids in any combination at the time of study enrollment, but the dose levels must be stable for have been stable for at least 7 days, although stable doses for shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

For the duration of the Treatment Period, pericarditis medications (e.g., concomitant NSAIDs, colchicine and/or corticosteroids, if used) should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine and/or

corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Subjects who received, within the 6-month period before dosing, immunomodulatory therapy other than, for example, corticosteroids or mycophenolate, which in the opinion of the Investigator (in consultation with the Sponsor) may interfere with the study endpoints, or subjects who used commercially-available rilonacept (ARCALYST®) within 90 days before the Screening Visit are excluded from participation.

Throughout the Treatment Period opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF. Other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) and tumor necrosis factor (TNF) inhibitors are prohibited for the duration of the study.

Medical management of pericarditis during the EP is based on Investigator discretion. He/she may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug in consultation with the Sponsor, or change (increase or decrease) the dosing of NSAIDs/colchicine/corticosteroids. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a daily medication diary. Such information will be entered by the subject on a real-time basis.

8.4.8 Treatment Compliance

Study Drug will be administered to the subject by the Investigator or qualified study center staff at the Study Site/Clinic Visit 1 (Day 0). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject as an outpatient SC administration. The study center staff or a visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site. All medication use (for pericarditis and use of rescue [pain] medication) will be documented by the subject in the medication diary during the Treatment Period.

All vials of used and unused Study Drug during the active Treatment Period and the EP must be retained by the Study Site/Clinic and the subject to allow for cataloguing and documentation of compliance. Subjects must return all used and unused medication to the Study Site/Clinic. Drug accountability and documentation thereof is described in the Pharmacy Manual.

Study Drug compliance by the subject will be monitored during the Treatment Period by phone calls/virtual visits (made by qualified site staff). Subjects will be reminded of recording all pericarditis and rescue pain medication information in the medication diary. The medication diary will be returned to the site by the subject and reviewed by the Investigator/qualified staff. During the EP, Study Drug use will be documented during monthly phone calls/virtual visits or Study Site/Clinic visits.

8.5 Study Procedures

All data of Study Site/Clinic visit assessments as well as Investigator (or designee) phone calls/virtual visits will be documented in source records and in the eCRF.

8.5.1 Prescreening Period

Prior to enrollment, potential subjects may enter an optional Prescreening Period, after signing of a Prescreening ICF, to allow monitoring for symptoms, inflammatory markers (CRP, ESR, etc) while existing medications for recurrent idiopathic pericarditis may be managed by the Investigator or their clinician per standard of care.

The Prescreening Period starts with the signing of the Prescreening ICF and lasts until the subject enters the Screening Period by signing the ICF for the full study or is withdrawn (see section 8.3.5).

8.5.2 Screening Period

The Screening Period starts with the signature of the ICF and may last for up to 3 days. During this period, subject eligibility for entry into the Treatment Period will be determined. A rheumatology consultation during the Screening Period is optional.

At SCV1, baseline subject and disease characteristics will be determined. Persistence of diagnostic criteria for pericarditis will be confirmed within ~24 to 72 hours at SCV2. Under special circumstances, the Investigator in consultation with the Sponsor, can combine SCV1 and SCV2.

The end of the Screening Period may coincide with the start of the Treatment Period.

8.5.2.1 Screening Visit 1 (SCV1)

- At the SCV1, written informed consent will be obtained before any protocol-specific assessments are made.
- All subjects will be assessed for eligibility against the inclusion and exclusion criteria.
- Demographic data, such as ethnic origin, date of birth and sex will be recorded.
- The subject's full medical history, including age at first attack, number of previous attacks, duration of attacks as well as concomitant illnesses/diseases will be documented.
- Information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured.
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
- A pregnancy test (urine dip-stick) will be done. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.
- 12-lead ECG and full echocardiogram (ECHO) will be performed. ECHO will include assessment of pericardial effusion. The Study Site/Clinic readings at the time of the examination will be available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- A cardiac MRI may be performed (optional). If done, the images will be assessed by a central reader. The Study Site/Clinic reading at the time of the examination may be used by the Investigator for clinical decision-making.
- Samples for laboratory tests will be collected.

- Local Lab Assessments:
  - Full hematology (including ESR), chemistry (including CRP), and urinalysis
  - Serology (HCVAb, HBsAg, HBcAB, HBsAb and HIV)
  - A QuantiFERON® test for tuberculosis (TB) can be performed (optional).

Screening for drugs of abuse and alcohol abuse will be performed on urine samples collected at this visit.

- Central Laboratory Assessments:
  - CRP/hsCRP

- Samples for archive biomarker, pharmacokinetics (PK), and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.A medication diary for documentation of pericarditis medication use and use of any rescue (pain) medication will be handed to the subject. The study Investigator or designated personnel will instruct the subject about the use of the medication diary. The subjects will be asked to complete entries immediately following administration .
- The subjects will assess their pericardial pain based on a 11-point NRS.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.2.2 Screening Visit 2 (SCV2)

The end of the Screening Period (SCV2) coincides with the start of the Treatment Period (Day 0, Visit 1). All Screening assessments need to be completed prior to the first Study Drug administration.

- SCV2 should take place when the laboratory test results from SCV1 are available.
- Subjects will be reassessed for eligibility against the inclusion and exclusion criteria.
- Any changes in concomitant medications since SCV1 will be documented.
- A full physical examination will be performed, including re-assessment of pericardial rub.
- Vital signs will be measured.
- 12-lead ECG will be performed. The Study Site/Clinic reading at the time of the examination will be used by the Investigator for clinical decision-making. In addition, the ECG will be sent to a core laboratory for additional analysis.
- Samples for laboratory tests will be collected.
  - Local Lab Assessments:
    - Full hematology (including ESR), chemistry (including CRP), and urinalysis
  - Central Laboratory Assessments:
    - CRP/hsCRP
    -
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- The subjects will assess their pericardial pain based on the 11-point NRS (Figure 3).

When all screening procedures have been performed and the Investigator has confirmed the subject's eligibility for the study, the Study Drug will be administered to the subject (see Study Site/Clinic Visit 1).

8.5.3 Treatment Period

8.5.3.1 Visit 1 (Study Site/Clinic) - Day 0

Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling (including CRP), medication diary compliance verification and reminding, and subject NRS pericardial pain rating (see Figure 3) must be repeated prior to Study Drug dosing.

- Sample for lipid panel to be sent to the Central Laboratory for analysis
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected prior to Study Drug dosing, sent to the central laboratory, and stored for analysis.
- The subject's global overall well-being will be assessed prior to Study Drug dosing using a validated Quality of Life Questionnaire (Appendix 3).
- The initial dose of Study Drug will be administered at the Study Site/Clinic.
- Subjects will be trained for outpatient Study Drug self-administration and reminded of completion of the daily medication diary.
- Any AEs occurring during or after the subject receives the first dose of Study Drug will be captured.

When all Visit 1 procedures have been performed, an appointment for the first weekly phone call/virtual visit will be scheduled. Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

8.5.3.2 Visits 2 to 6 (Outpatient) - Weeks 2, 3, 4, 5, 6

- Visits 2, 3, 4, 5, 6 will take place within intervals of 7 ± 1 days each after Visit 1.
- Subjects self-administer the Study Drug during Weeks 2 to 5. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site.
- Samples for laboratory tests will be collected.
    - Central Laboratory Assessments:
        - CRP/hsCRP
        -
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected (either by a visiting study nurse or at the Study Site or at a qualified local laboratory) and stored for analysis after shipment to the central laboratory.
- After dosing at Week 3 and Week 6, a questionnaire to assess the dosing system will be completed by the subject and by the study center staff or visiting nurse observing the dosing
- Any AEs that have occurred since the last contact will be assessed by non-leading questions as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Compliance with self-administration of drug, compliance with the medication diary, and compliance with laboratory blood sampling will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.

Subjects withdrawing from the study any time during study weeks 2 to 6 will be asked to return to the Study Site/Clinic for the Visit 7/End-of-Trial visit assessments.

8.5.3.3 Interval Evaluation Visit (Study Site/Clinic) - Week 3-4

An in-person Interval Evaluation Visit during approximately Weeks 3-4 of the Treatment Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator. The Interval Evaluation Visit may also be used to review the vaccination status of a study subject.

At the Interval Evaluation Visit, the following parameters will be assessed:

- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.3.4 Unscheduled Visits (Study Site/Clinic) During the Treatment Period

Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. During the Unscheduled Visit, selected or comprehensive (see Interval Evaluation Visit) clinical and laboratory assessments may be performed.

Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a “Treatment Failure” may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

All study withdrawals must complete the Visit 7/End-of-trial Visit either at the Unscheduled Visit or at a separate Visit 7/End-of-trial Visit.

8.5.3.5 Visit 7/ End-of-Trial (Study Site/Clinic) - Week 6

At Visit 7, “Treatment Responders” (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week

EP, at the discretion of the Investigator. During the EP, weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

- Visit 7 will take place during Week 6 (or as soon as possible after study withdrawal if a subject has discontinued from Study Drug therapy).
- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since last Study Site visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Lipid panel
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

When all of these procedures have been performed, the next Study Site/Clinic visit should be scheduled for those who continue KPL-914 treatment during the EP (Treatment Responders). Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Clinic/Site (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7. Continued weekly Study Drug treatment during the EP will be outpatient administration.

8.5.4 Extension Period

Subjects will self-administer the Study Drug on a weekly basis and complete the medication diary during the Extension Period. Study nurse visits to the subject's home will continue on a monthly basis. Investigator (or designee) phone calls/virtual visits will be performed monthly during the EP to perform NRS pain assessments, collect AE information, and document pericarditis/concomitant medication use. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits.

8.5.4.1 Unscheduled Visits (Study Site/Clinic) during the EP

Unscheduled Study Site/Clinic visits can take place during the Extension Period, as agreed upon by the Investigator and the subject or as needed.

- A physical examination will be performed.
- Vital signs will be measured.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.

- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- A 12-lead ECG and a full ECHO will be performed as determined by the Investigator. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).

8.5.4.2 Interval Evaluation Visit During Extension Period (Study Site/Clinic) - Week 15-20

An in-person Interval Evaluation Visit during approximately Weeks 15-20 of the Extension Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator.

At the Extension Period Interval Evaluation Visit, the following parameters will be assessed:

- A physical examination will be performed.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.4.3 Visit 8/Final Visit (Study Site/Clinic) - Week 25

- Visit 8 will take place 18 weeks after Visit 7 (or as soon as possible after study withdrawal during the EP).
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.

- 12-lead ECG and ECHO will be performed. Echocardiogram will include assessment of pericardial effusion. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- An MRI can be performed (optional).
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Lipid panel
    - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.5 Duration of Treatment

The overall study duration for subjects participating in the study until Visit 8 will be up to 171 days.

The test product will be administered weekly for 6 weeks in the base study Treatment Period. Treatment Responders will be offered participation in an optional 18-week EP at the discretion of the Investigator. During this EP the subject can receive 18 additional weekly doses of KPL-914.

8.6 Efficacy and Safety Variables

The Schedule of Evaluations in Table 1 shows the planned study assessments.

8.6.1 Individual Efficacy Assessments

8.6.1.1 C-Reactive Protein, Biomarker, and PK Assessments

CRP will be determined at Study Site/Clinic laboratory tests at Screening (SCV1 and SCV2) and during the Treatment Period (Visit 1 prior to dosing, if separate from SCV2, Interval Evaluation Visit [if applicable], and Visit 7/End-of-Trial). Results from the Study Site/Clinic CRP testing will inform the Investigator on the subject's pericarditis status for clinical decision-making and support decisions on classifications of subjects as Treatment Responders or Treatment Failures and on subsequent disease management during the Extension Period.

Central laboratory assessments of CRP will be performed at each Study Site/Clinic or outpatient study visit (samples collected by a visiting study nurse or at the Study Site/Clinic or a local laboratory). Centrally determined CRP values will be used for statistical evaluations and report writing but will not be used as basis of the Investigator's management of the subject.

All subjects must present with elevated CRP values ≥1 mg/dL at the time of study enrollment. CRP changes and the time course to decrease and resolution of CRP to normal values ≤0.5 mg/dL will be assessed.

Samples from each study visit will be archived at the central laboratory for potential biomarker and/or PK analysis.

8.6.1.2 Echocardiogram (Pericardial Effusion)

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

Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart and is one of the common features of pericarditis. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening.

For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECHO images will be assessed by a central reader. The Study Site/Clinic reading of the ECHO at the time of the examination will be made available to the Investigator for clinical decision-making.

8.6.1.3 Electrocardiogram (Pericarditis Diagnostic Findings)

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

Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-elevation or PR depression. Changes in ECG findings will help determine the pericarditis status of a subject.

The Study Site/Clinic reading of the ECG at the time of the examination will be made available to the Investigator for clinical decision-making. For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECG tracings will be assessed by a central reader.

8.6.1.4 Pericarditis Signs (Fever, Pericardial Rub)

Common pericarditis signs include fever and pericardial rub. These pericarditis signs will be assessed via documentation of vital signs and physical examinations.

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

8.6.1.5 Pericarditis Pain (Chest Pain)

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011). The assessment will be performed at all study visits - on-site during Study Site/Clinic visits and as part of telephone calls/virtual visits during outpatient visits/treatment weeks (weekly during the Treatment Period and monthly during the EP).

Subjects will be asked to select the score that best describes their average level of pain over the previous 24 hours using a validated 11-point NRS instrument (Figure 3), 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 pain on average in the last 24 hours

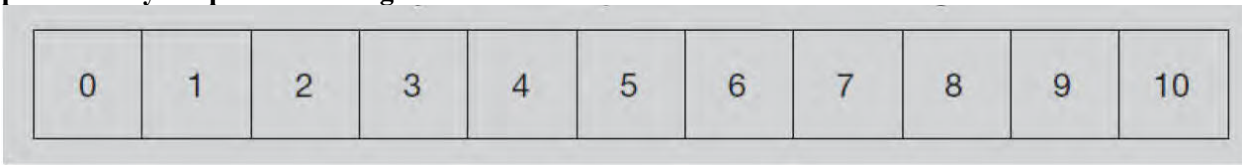


Figure 3: **11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain**

8.6.1.6 Magnetic Resonance Imaging

Cardiac MRI is an optional assessment and may be performed at study entry (SCV1) and at the final study visit (Visit 8) to assess any changes in pericardial inflammation.

For the purposes of the analysis of treatment response in all subjects at the end of the study, all cardiac MRI images will be assessed by a central reader. The Study Site/Clinic reading of the MRI at the time of the examination may be used by the Investigator for clinical decision-making.

8.6.1.7 Quality of Life Questionnaire

A validated Quality of Life Questionnaires will be used to assess changes in the subject's overall well-being (Hays et al 2009). The subject's global assessment will be performed at screening (SCV1), at Visit 1 (Day 0), at the Interval Evaluation Visit (Week 3-4), at the end of the Treatment Period (Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP, and at the Final Visit (Visit 8).

The Quality of Life Questionnaire to be used is presented in Appendix 3.

8.6.1.8 Dosing Procedure Questionnaire

A questionnaire will be used to assess the dose preparation and administration procedure immediately after self-injecting the Study Drug in the presence of the Study Staff (either in person or via virtual visit) or of the visiting nurse. Each subject will complete a questionnaire after the third self-injection (third dose, Week 3) and the sixth self-injection (sixth dose, Week 6), and once during the extension period. The Study Staff/visiting nurse observing the injection will also complete an observation checklist for observing subjects interacting with the system during self-injection. The checklist will list all key steps associated with proper system use, including setting up for an injection, reconstituting the medication, and administering the injection. Study Staff/visiting nurse will complete the checklists for the same injections for which the subjects will complete questionnaires.

8.6.2 Safety Assessments

8.6.2.1 Adverse Events

Adverse Event Definition

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 and/or unintended 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.

In this study, individual elements of pericarditis symptomatology (including pain) are captured as an efficacy parameter. Pericarditis pain is not required to be reported as an AE. However, if, in the opinion of the Investigator, the subject experiences new symptoms that had not been previously reported in the constellation of symptoms recorded at baseline, these new symptoms should be reported as an AE.

The causal relationship between an AE and the Study Drug will be defined as below:

- **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 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 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 drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

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**: medically significant event; daily activities limited or completely halted; hospitalization or prolongation of hospitalization indicated.

Every reasonable effort will be made to follow subjects who have AEs. Any subject who has an ongoing AE at study end or early withdrawal will be followed, where possible, until resolution.

8.6.2.2 Serious Adverse Events

Serious Adverse Event Definition

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 Study Drug (e.g., car accident where 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 hospitalizations must be recorded on the medical history or physical examination page of the eCRF). Hospitalization is defined as an admission to the hospital ward or a short-stay-type unit longer than 24 hours. Prolongation of existing hospitalization is defined as 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 judgement 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 IMP.

Reporting of Serious Adverse Events

SAEs merit special concern and attention, and SAEs due to any cause, whether or not related to the Study Drug, must be reported by the Investigator to the Sponsor and designee within 24 hours of occurrence or when the Investigator becomes aware of the event. Report SAEs by fax or email using the designated SAE report to:

[redacted]

In addition, Investigator must report the SAE within 24 hours of learning of the event by telephone to:

[redacted]

If the Investigator reports an SAE by telephone, then a written report must follow within 1 business day and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable.

Other Reasons for Immediate Reporting to [redacted]

- Overdose (accidental or intentional) of the investigational product or concomitant medication, regardless of whether it is considered an AE
- Any pregnancy diagnosed in a female subject or in a female partner of a male subject during treatment with an investigational product
- Hospitalization (including Emergency Room visits) which last for less than 24 hours. A determination will be made by the Sponsor in collaboration with [redacted] as to whether it is a SAE
- Any diagnosis of malignancy (excluding basal cell skin cancer) during the study should be reported to [redacted] within 24 hours.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 8.3.5.

All hospitalizations must be reported to [redacted] and Kiniksa within 24 hours; however, hospitalizations for elective medical/surgical procedures for preexisting illnesses that were planned prior to the subject's enrollment in the study may not be considered by the Investigator to be AEs. Complications resulting from planned procedures, however, require reporting to [redacted] and Kiniksa.

Whenever possible and practical, a blood sample (collected in a light blue top CTAD [citrate, theophylline, adenosine, dipyridamole] vacutainer tube) to potentially measure plasma drug levels should be obtained upon the development of any SAE or unusual AE that is judged to be related to study treatment.

Investigator Reporting Responsibilities to Institutional Review Board (IRB)

Unanticipated problems posing risks to study subjects will be reported to the IRB per their institutional policy. Copies of each report and documentation of IRB notification and acknowledgement of receipt will be kept in the Investigator's study file.

Sponsor Reporting Responsibilities to Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

8.6.2.3 Adverse Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; i.e., where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

Unexpected Adverse Reaction Definition

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with relevant product information for the IMP. The current version of the ARCALYST® PI should be used as the Single Source Safety Reference Document when determining if an event is unexpected. Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for a list of most frequent expected AEs. All suspected adverse reactions related to an investigational medicinal product (the tested investigational medicinal products and comparators, if involved) which occur in the concerned trial, and that are both unexpected and serious are subject to expedited reporting.

Warnings and Precautions

Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for Important Safety Information.

IL-1 blockade may interfere with immune response to infections. It is therefore recommended that prior to or shortly after initiation of therapy with KPL-914 subjects receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In case a subject needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed during the active Treatment Period. However, to minimize the potential confounding of KPL-914-related AE reporting or CRP measurements during the KPL-914 Treatment Period, vaccination should not be performed during the Treatment Period (see Section 8.3.4). It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Taking KPL-914 with TNF inhibitors is not recommended because simultaneous inhibition of these two pathways may increase the risk of serious infections.

It is also possible that taking drugs 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 KPL-914.

8.6.2.4 Clinical Laboratory Variables

Clinical laboratory analyses will be performed at Study Site/Clinic or local laboratory near the subject and, for some parameters, at a central laboratory. Laboratory analyses will be used at Study Site/Clinic visits for the Investigator to assess disease status and to determine treatment response and study (drug) continuation

or withdrawal. Results for analyses performed by the Study Site/Clinic laboratory together with the laboratory reference ranges will be recorded in the eCRF and the Investigator must use clinical judgment to determine if any abnormal values are clinically significant or not.

Central laboratory samples for CRP analysis will be collected at both Study Site/Clinic and outpatient (by a visiting study nurse or at local contract laboratories) visits and the results will be used for statistical analyses and study reporting. Study Site/Clinic and local laboratory results will be used for clinical decision-making and will be available in the source documents and listed in the CSR).

The following analyses will be done at the **central laboratory**:

- C-reactive protein (CRP)/hsCRP (The CRP analyzed by the central laboratory will not be available to the investigator in a timely manner to support the clinical management of the subject. Results from the central laboratory will therefore not be transferred to the Investigator during the trial.)
- Lipid Panel
- Samples for biomarkers, PK, and anti-rilonacept (anti-KPL-914) antibody testing will be drawn and archived at all visits.

The following laboratory analyses will be done at the **Study Site/Clinic laboratories** in accordance with local procedures and guidelines to support clinical management and decision-making:

Hematology

Hemoglobin, hematocrit, coagulation parameters (prothrombin [PT], prothrombin time [PTT], D-dimer), ESR, fibrinogen, WBC count (total and differential), red blood cell (RBC) count, ESR, platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), MCH concentration (MCHC).

Clinical Chemistry

CRP/hsCRP, troponin, creatinine, creatine kinase, urea, (or blood urea nitrogen [BUN]), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol*, triglycerides*, calcium, phosphorus.

* Preferably fasting.

Urinalysis

pH, glucose, ketones, nitrites, leukocyte esterase, blood, protein and microscopy. Urine drug screen (alcohol, amphetamines, cocaine, or phencyclidine) at SCV1 only. Screening for pregnancy (urine β-HCG) at SCV1 only.

Serology

HCVAb, HBsAg, HBcAb, HBsAb and HIV tests (SCV 1 only).

Other
Screening for tuberculosis (QuantiFERON test) at SCV1 only (optional).

The amount of blood to be taken during screening will be approximately 37 mL at SCV1 and approximately 17 mL at SCV2 (if done). The amount of blood to be taken at each Study Site/Clinic visit during the Treatment Period and EP will be approximately 31 mL. The amount of blood to be taken at each outpatient visit will be approximately 21 mL. At the optional unscheduled visit, approximately 61 mL are planned. The total amount of blood to be taken during the study will be up to approximately 320 mL.

8.6.2.5 Vital Signs

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

The following measurements will be taken: oral temperature, respiratory rate, blood pressure, and pulse. Oral temperature (fever) will also be assessed as efficacy parameter (see Section 8.6.1.4).

8.6.2.6 Physical Examination

At the Screening Visits 1 and 2, at the optional Evaluation Visit during the Treatment Period, at the End-of-Trial Visit (Visit 7), at Unscheduled and Evaluation Visits during the EP and at the Final Visit (Visit 8) a full physical examination including the assessment of pericardial rub (efficacy parameter) will be performed (see also Section 8.6.1.4).

8.6.2.7 Body Weight and Height

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

8.7 Statistical Methods

A full description of the statistical analyses to be performed together with the planned tables and figures will be given in a detailed document, the SAP, which will be developed and filed prior to data base lock. Any deviation(s) from the final SAP will be described and justified in the clinical study report.

8.7.1 Statistical and Analytical Plans

8.7.1.1 Datasets to be Analyzed

The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (NSAIDs, colchicine, and/or corticosteroids, if used during screening) according to study protocol without a major protocol violation. The Safety Population will be the same as the mITT Population.

8.7.1.2 General Statistical Methods

Because of the small sample size, no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or analysis group. For categorical endpoints (e.g., responder vs. non-responder), summary statistics will be calculated and presented for each treatment and/or analysis group.

Further details will be provided in the SAP. Any deviation(s) from the original statistical plan will be described and justified in in the final study report.

8.7.1.3 Efficacy Endpoints

Primary Efficacy Endpoint

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

[redacted]

8.7.1.4 Safety Variables

AEs and SAEs, clinical laboratory evaluations, vital sign measurements, ECGs, and physical examination findings.

8.7.2 Determination of Sample Size

Approximately 10 symptomatic subjects with RIP will be enrolled as study subjects. Following review of the available data, the Sponsor, in collaboration with the Investigators, may increase the sample size to up to 20 subjects to address additional hypotheses.

Subjects who discontinue the study (withdrawals and Treatment Early Failures) may be replaced at the Sponsor's discretion.

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and research in this patient population.

8.8 Quality Assurance and Quality Control

8.8.1 Audit and Inspection

The study may be selected for audit originating from the Sponsor or external organizations acting on behalf of the Sponsor. Audits will be followed by internal reports and corrective actions, if needed.

The Investigator agrees to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved. The anonymity of the subjects must be safeguarded and data checked during audits remain confidential.

8.8.2 Monitoring

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.

The Investigator will permit study-related monitoring, audits, ethics committee review and regulatory inspection(s), providing direct access to source data and documents.

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 Good Clinical Practice (GCP) and International Conference on Harmonisation (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.

8.8.3 Data Management and Coding

The Sponsor or Clinical Research Organization (CRO) 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 the Sponsor or CRO.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and World Health Organization (WHO) Drug for therapies.

8.8.4 Record Keeping

It is the responsibility of the Investigator to ensure all essential trial documentation and source records (e.g., signed ICFs, Study Site/Clinic files, patients' hospital notes, copies of eCRFs, etc.) 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.

9 Records and Supplies

9.1 Drug Accountability

On receipt of the IMP (including rescue medication, if relevant), the Investigator (or deputy) will conduct an inventory of the supplies and verify that IMP supplies are received intact and in the correct amounts prior to completing a supplies receipt. The Investigator will retain a copy of this receipt at the study site and return the original receipt to the drug depot. The inventory of supplies at each study site will be reviewed by the study monitor.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®). All vials of used and unused Study Drug during the active Treatment Period 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.

10 Ethics

10.1 Institutional Review Board

Before initiation of the study at each investigational site, the protocol, all protocol amendments, the ICF, and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the IMP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB annually, or more frequently if requested by the IRB. On completion of the study, the Sponsor will notify the IRB that the study has ended.

10.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the Declaration of Helsinki and local regulations.

10.3 Subject Information and Consent

The Investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject and/or legal guardian has given written informed consent to participate in the study. The written consent must be given by the subject and/or the legal guardian of the subject, after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

Subjects and/or legal guardians will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IRB, Sponsor and/or CRO personnel.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

10.4 Subject Confidentiality (US Studies)

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA), applicable to national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the ethics committees approving this research, and the United States (US) FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

11 Reporting and Publication

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator(s) will be subject to mutual agreement between the Investigator and Kiniksa as outlined in the study agreement.

12 References

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13 Appendices

Appendix 1: Investigator Signature Page

Protocol Title: An open-label pilot study of KPL-914 in symptomatic Recurrent Idiopathic Pericarditis.

Protocol Number: KPL-914-C001

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and I will conduct the study as described in compliance with this protocol, GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Kiniksa Pharmaceuticals Ltd. (Kinksa) and of the IEC/IRB. I will submit the protocol modifications and/or any ICF modifications to Kiniksa and IEC/IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all Case Report Forms, laboratory samples or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Kiniksa, to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

Appendix 2: ARCALYST® Prescribing Information

ARCALYST- rilonacept injection, powder, lyophilized, for solution
Regeneron Pharmaceuticals, Inc.

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: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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			Endpoint		

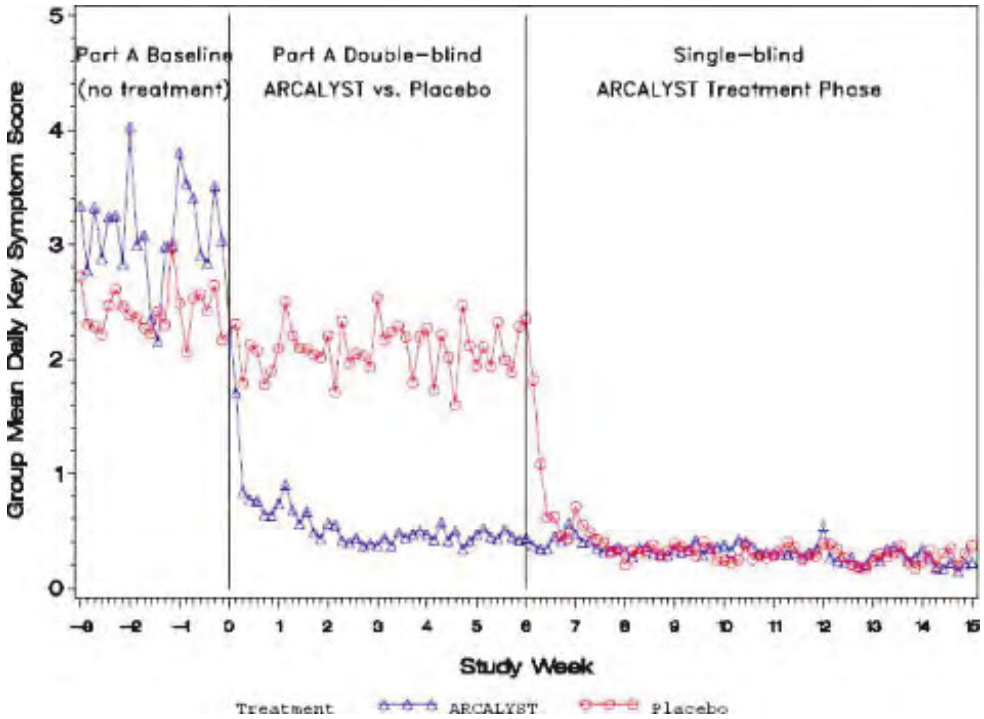
Period (Weeks 4 to 6)	2.1	0.5	Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment 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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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):

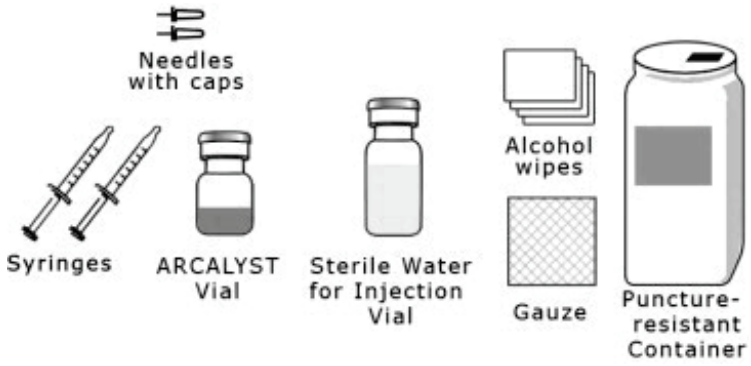


Figure 1

- 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

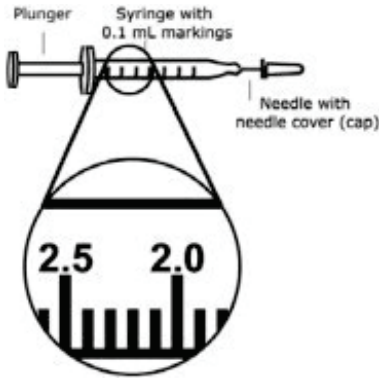


Figure 2

- 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).

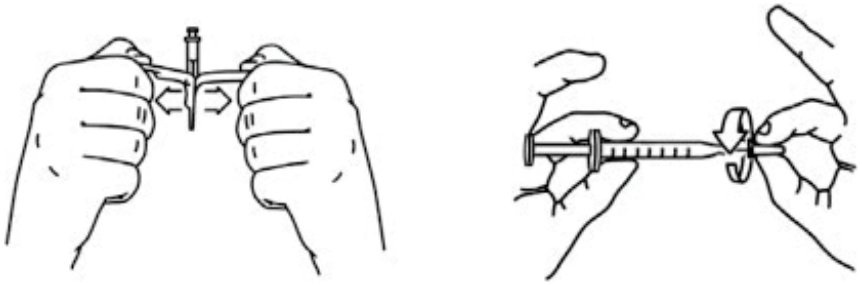


Figure 4

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).

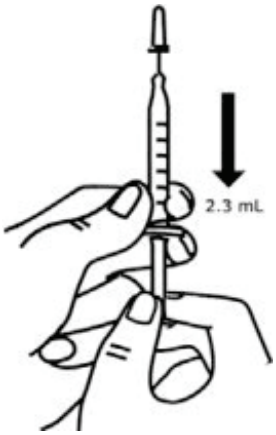


Figure 5

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).

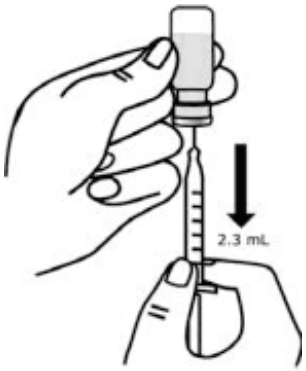


Figure 7

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).

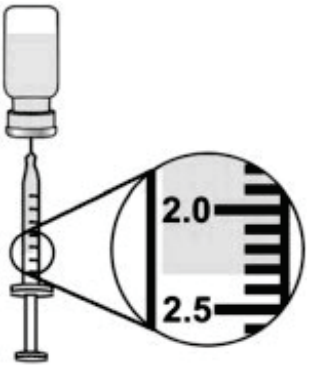


Figure 8

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).

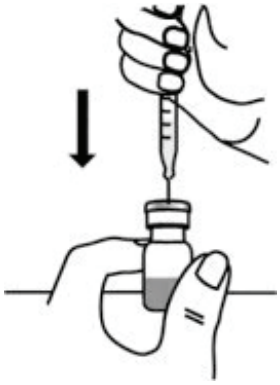


Figure 9

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.

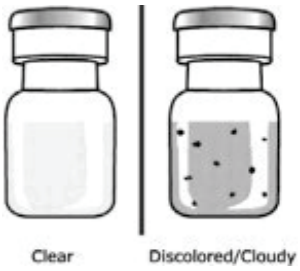


Figure 11

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).

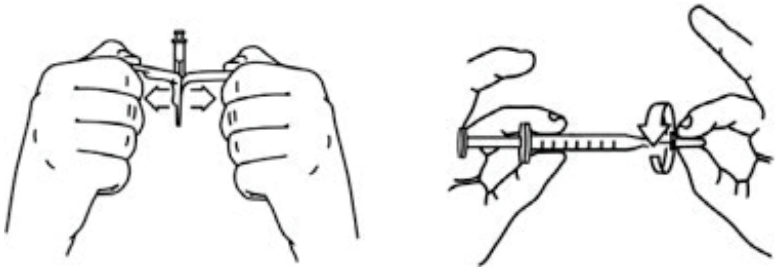


Figure 13

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).

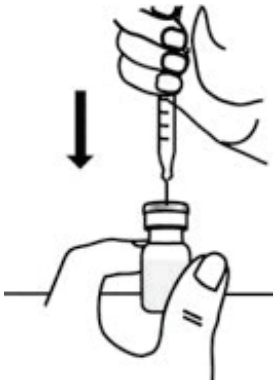


Figure 15

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).

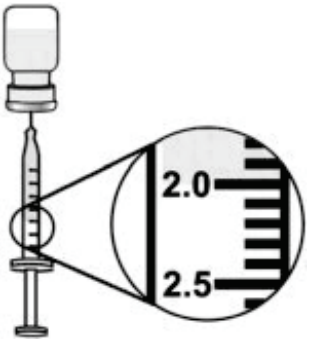


Figure 16

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.

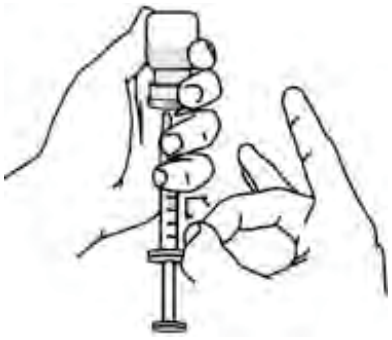


Figure 17

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)

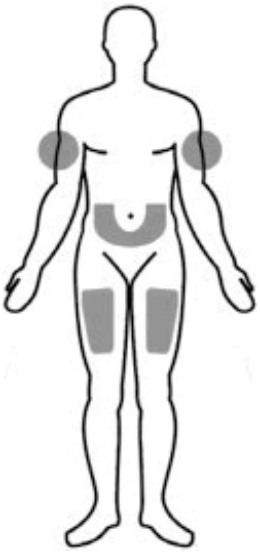


Figure 19

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).

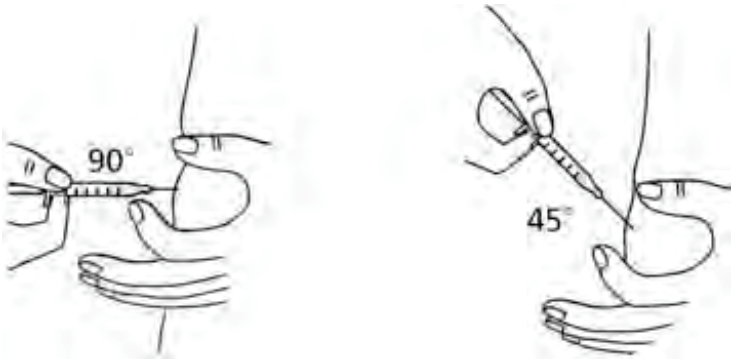


Figure 21

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).

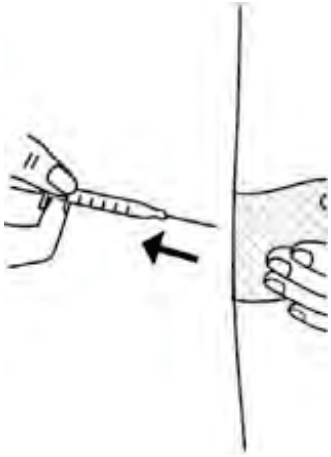


Figure 22

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:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
U.S. License Number 1760
NDC 61755-001-01

V 4.0

Principal Display Panel - Vial Carton

NDC 61755-001-01

Arcalyst®

(rilonacept)

Injection for Subcutaneous Use

220 mg sterile powder for reconstitution

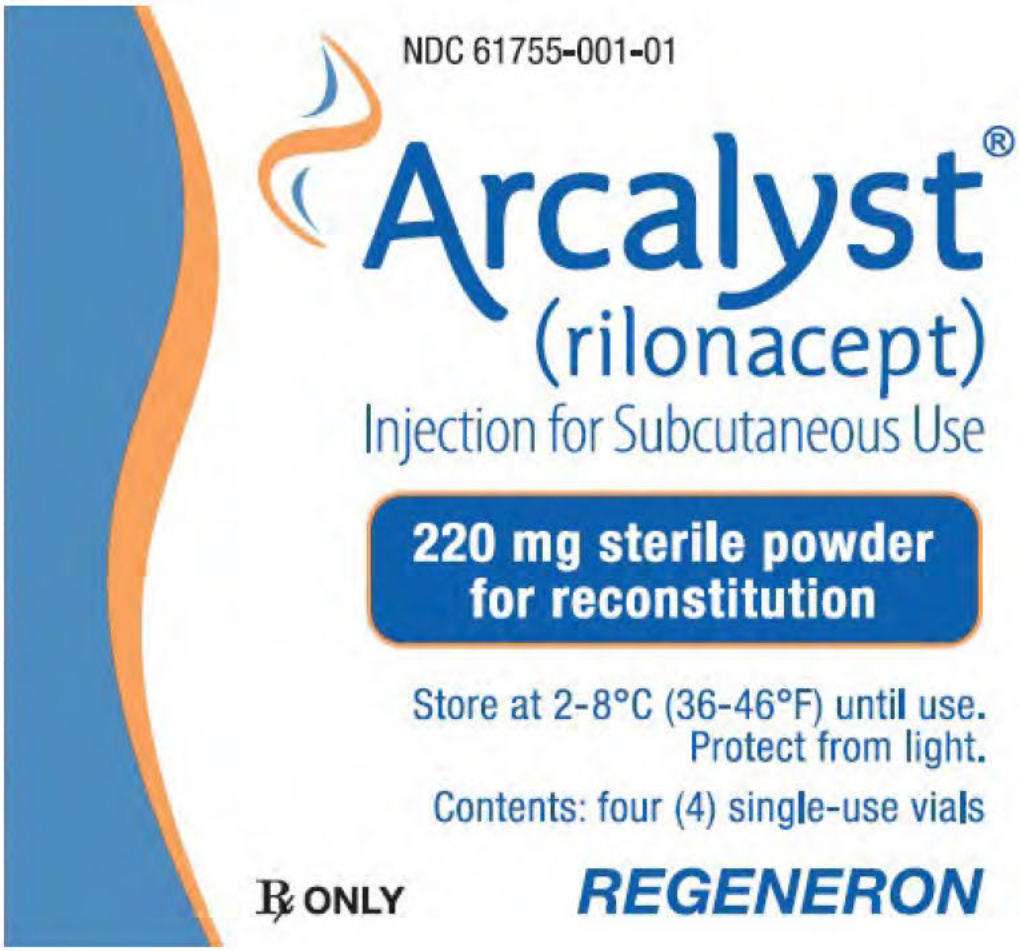
Store at 2-8°C (36-46°F) until use.

Protect from light.

Contents: four (4) single-use vials

Rx ONLY

REGENERON



ARCALYST

rilonacept injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61755 001

Route of Administration	SUBCUTANEOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
rilonacept (UNII: 8K80YB5GMG) (rilonacep UNII:8K80YB5GMG)	rilonacep	160 mg in 2 mL

Inactive Ingredients

Ingredient Name	Strength
Histidine (UNII: 4QD397987E)	
Arginine (UNII: 94ZLA3W45F)	
Polyethylene glycol 3350 (UNII: G2M7P15E5P)	
Sucrose (UNII: C151H8M554)	
Glycine (UNII: TE7660XO1C)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61755 001 01	4 in 1 CARTON	03/24/2008	
1		2 mL in 1 VIAL, SINGLE USE; Type 0: No a Combina ion Produc		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125249	02/27/2008	

Labeler - Regeneron Pharmaceuticals, Inc. (194873139)

Establishment

Name	Address	ID/FEI	Business Operations
Regeneron Pharmaceu icals, Inc.		945589711	ANALYSIS(61755 001) , API MANUFACTURE(61755 001) , LABEL(61755 001)

Appendix 3: Quality of Life Instrument

PROMIS Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global06	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Scale v1.2 – Global Health

In the past 7 days…

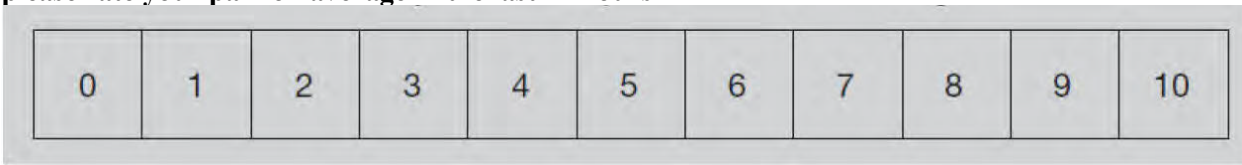
		Never	Rarely	Sometimes	Often	Always
Global10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
Global08r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global07r	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4
		☐ 5	☐ 6	☐ 7	☐ 8	☐ 9
		☐ 10 **Worst pain imaginable**				

Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011).

Subjects will be asked to select the score that best describes their average level of 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 pain on average in the last 24 hours



CLINICAL STUDY PROTOCOL

An Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis

Protocol Number:	KPL-914-C001
EudraCT Number:	Not Applicable
Investigational Medicinal Product:	KPL-914 (rilonacept)
Phase:	Phase 2
Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Medical Monitor:	[redacted]
Date of Protocol:	14 February 2018
Version of Protocol:	3.0 (Supersedes Version 2.0 dated 17 January 2018)

CONFIDENTIAL

1 Protocol Approval Signatures

1.1 Sponsor Signature

Protocol Title: An open-label pilot study of KPL-914 in recurrent pericarditis

Protocol Number: KPL-914-C001

This study will be conducted in compliance with the clinical study protocol, ICH Good Clinical Practice and applicable regulatory requirements.

[redacted]

[redacted]

2 Investigator and Administrative Structure

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Sponsor's Study Contact:	[redacted]
Sponsor's Medical Expert:	[redacted]
Drug safety/SAE-reporting:	[redacted]
Responsible CRO for Biostatistical Analysis:	[redacted]
CRO responsible for: Project Management, Monitoring, Quality Assurance, and Data Management:	[redacted]

3 Synopsis

Trial Number: KPL-914-C001
Trial Title: An open-label, pilot study of KPL-914 in recurrent pericarditis
Trial Centers: Approximately 15 sites
Development Phase: 2

Objective(s):

The study is comprised of 5 Parts.

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

Part 1:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914.

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

Part 2:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

Part 3:

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent RIP.

Part 4:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with symptomatic recurrent PPS both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with recurrent PPS treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with recurrent PPS.

Part 5:

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent recurrent PPS.

Methodology:

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

Enrollment into Part 1:

Subjects identified for participation in **Part 1** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode** before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a first **(index) episode** of acute pericarditis followed by at least **1 recurrent episode** of pericarditis prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Subjects with symptomatic RIP meeting the above diagnostic criteria may be enrolled into Part 1 only if the **CRP value at screening is > 1 mg/dL**.

Enrollment into Part 2:

Subjects identified for participation in **Part 2** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a first **(index) episode** of acute pericarditis followed by at least **1 recurrent episode** before the current enrollment-qualifying episode, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode** of pericarditis prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the eCRF.

Subjects with symptomatic RIP meeting the above diagnostic criteria but **without an elevated CRP level (i.e., ≤1mg/dl) at screening** may be enrolled into Part 2 **only if**, in the opinion of the investigator and in consultation with the Sponsor, **the low CRP value can be attributed to concomitant medications (e.g., corticosteroids) AND if there is evidence of pericardial inflammation by cardiac MRI** which has been confirmed by the MRI Core Laboratory.

Enrollment into Part 3:

Subjects identified for participation in **Part 3** in this trial will present with **corticosteroid-dependent** RIP, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes of pericarditis** and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for their RIP and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 3 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment into Part 4:

Subjects identified for participation in **Part 4** in this trial will present during a **symptomatic episode of recurrent PPS**, having previously experienced a **first (index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.
- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a first **(index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS prior to the **current enrollment-qualifying episode** of recurrent PPS and will record the criteria supporting this diagnosis in the eCRF.

In addition to meeting the above criteria for PPS, all subjects enrolled in Part 4 must have **a CRP value > 1 mg/dL at screening**.

Enrollment into Part 5:

Subjects identified for participation in **Part 5** in this trial will present with **corticosteroid-dependent** recurrent PPS, having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.
- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis

occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes** of PPS and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for the recurrent PPS and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 5 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment Process for All Parts:

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

Subjects included in Parts 1, 2 and 4 may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Subjects in Parts 3 and 5 must be receiving corticosteroids at the time of enrollment.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm study eligibility. At the SCV1, baseline subject and disease characteristics will be determined and captured in the eCRF. At Screening Visit 2 (SCV2) during the 24 - 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

After having met all the entry criteria during the Screening Period, the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 320 mg KPL-914 (2 x 160 mg) administered SC on Day 0, then 160 mg SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 4.4 mg/kg KPL-914 (2x 2.2 mg/kg; maximum total 320 mg) administered SC on Day 0, then 2.2 mg/kg (maximum 160 mg) administered SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject or will be administered to the subject by an adequately trained caregiver as an outpatient SC administration. Study center staff or a visiting study nurse will assess and record compliance with Study Drug administration

at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be administered at home or other non-clinic location or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits on Day 3 and at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the subject, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study-related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels [if applicable], etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF, and medication diary.

At the discretion of the Investigator, "Treatment Responders" will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 administration can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

Treatment response will be defined by the Investigator:

- Part 1: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit.
- Part 2: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal levels CRP, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 3: Absence of pericarditis flare and feasibility to taper corticosteroids.
- Part 4: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 5: Absence of pericarditis flare and feasibility to taper corticosteroids.

Weekly Study Drug administrations during the EP are by self-administration or by an adequately-trained caregiver, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis.

During the EP, the Investigator is encouraged to wean concomitant NSAIDs and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively taped (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering the EP (i.e., by Study Week 12) unless in the opinion of the Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. All medication changes must be recorded in source records and the eCRF. Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7/End of Trial Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing subject management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each subject and each Part.

Given the following occurrences, dosing may be halted or reduced in any Part of the study, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2 x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

Depending on treatment response observed with the 80 mg dose (or 1.1 mg/kg in subjects 6 years to <18years old), the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg (or 2.2 mg/kg in subjects 6 years to <18 years old) by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject immediately after dosing of study drug.

Number of Subjects:

Approximately up to a total of 40 subjects with RIP or recurrent PPS will be enrolled as study subjects across all Parts.

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

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria for All Parts

To be eligible to participate in the trial, a subject must meet all of the following criteria:

1. Has given consent (or assent, if applicable) and signed an Informed Consent Form (ICF) (or informed assent form, if applicable).
2. Male or female, of any ethnic origin.
3. 6 to 75 years of age, inclusive.
4. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days (although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability

is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.

5. If female of child-bearing potential, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
6. Is able to adequately maintain a medication diary.
7. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or changing exercise pattern) from the time of signature of the ICF (or informed assent form, if applicable) to the End-of-Trial Visit (Week 6).

Inclusion Criteria for Part 1:

8. Has a diagnosis of RIP based on the judgement of the Investigator.
9. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
10. Has had **at least one prior *recurrent episode*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
11. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
12. Has an **elevated CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 2:

13. Has a diagnosis of RIP based on the judgement of the Investigator.
14. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
15. Has had at least **one prior *recurrent episode*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
16. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
17. Has **CRP value < 1 mg/dL** at Screening, which in the opinion of the Investigator in consultation with the Sponsor, can be **attributed to concomitant medications**.
18. Has evidence of **pericardial inflammation by cardiac MRI** which has been confirmed by the MRI core imaging lab.

Inclusion Criteria for Part 3:

19. Has a diagnosis of RIP based on the judgement of the Investigator.
20. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
21. Has had **at least two prior *recurrent episodes*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
22. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
23. Is **"corticosteroid-dependent,"** in the judgement of the Investigator based on available data (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be withdrawn).

Inclusion Criteria for Part 4:

24. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.
25. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
26. Has had **at least one prior *recurrent episode*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
27. Has an **ongoing symptomatic episode** of recurrent PPS at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
28. Has an elevated **CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 5:

29. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.
30. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
31. Has had **at least two prior *recurrent episodes*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
32. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
33. Is "**corticosteroid-dependent**," in the judgement of the Investigator based on the available data, (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be

withdrawn).

Exclusion Criteria for all Parts:

A subject who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific excluded etiologies, including tuberculous, neoplastic, or purulent etiologies, post-myocardial infarction (early or late), thoracic trauma, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment within the 6-month period before dosing with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female subject who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A subject with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or physical exam. Have recent close contact with a person with active TB.
8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of the study.
10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.
11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.
12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks of Study Drug administration, or has been treated with intravenous (IV) antibiotics for an infection within 2 months of first Study Drug administration.

15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a subject is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 14 days prior to Study Drug administration. Rilonacept and anakinra could not have been discontinued due to lack of efficacy or due to safety.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Subject who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Subject who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

Test Products, Dosage, and Mode of Administration:

KPL-914 (rilonacept) will be provided in its commercially-available formulation as a lyophilized powder to be reconstituted for SC administration.

Subjects will receive a total of 6 doses of KPL-914 during the study active Treatment Period. Subjects who are considered to be "Treatment Responders" will be offered, at the discretion of the Investigator, participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued for a total duration of KPL-914 treatment of up to 24 weeks.

Adult subjects (≥ 18 years of age)

KPL-914 will be administered as an initial loading dose of 320 mg SC, delivered as two subcutaneous injections of 160 mg SC each on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks.

Pediatric subjects (6 to <18 years of age)

KPL-914 will be administered with an initial loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as two subcutaneous injections of 2.2 mg/kg each with a maximum single-injection volume of 2 mL. Dosing will continue with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection of up to 2 mL as outpatient self-administration or administered by an adequately trained caregiver, for 5 subsequent weeks.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

Concomitant Medication

- There is no wash-out of concomitant therapy (NSAIDs/colchicine/corticosteroids) during the Screening Period of the study.
- For the duration of the Treatment Period, concomitant pericarditis medications (e.g., NSAIDs, colchicine and corticosteroids), if used, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAIDs, colchicine, and/or corticosteroid dose is medically necessary, the NSAID, colchicine and/or corticosteroid dose can be down-titrated according to standard of care paradigms in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.
- Opioid analgesics, non-narcotic (non-NSAID) analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF.
- Medical management of pericarditis during the EP is based on Investigator discretion. For example, Investigators may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status
- Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF.
- Prohibited concomitant medicines: Other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.

Duration of Treatment:

The Study Drug will be administered for 6 weeks in the base study Treatment Period.

"Treatment Responders" will be offered participation in an optional 18-week EP at the discretion of the Investigator.

Total subject participation is expected to last for up to 171 days for those that also participate in the 18-week EP.

Efficacy Measures:

- Clinical laboratory analyses (e.g., CRP).
- Pericarditis symptoms (i.e., pain) using a 11-point NRS (Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain)
- Echocardiogram (pericardial effusion)
- ECG (for pericarditis diagnostic findings)
- Pericarditis signs (e.g., fever, pericardial rub)
- Pericardial inflammation as determined by cardiac MRI (optional assessment for Parts 1, 3, 4, 5; mandatory for Part 2)
- Quality of life (QoL) questionnaire (Appendix 3).

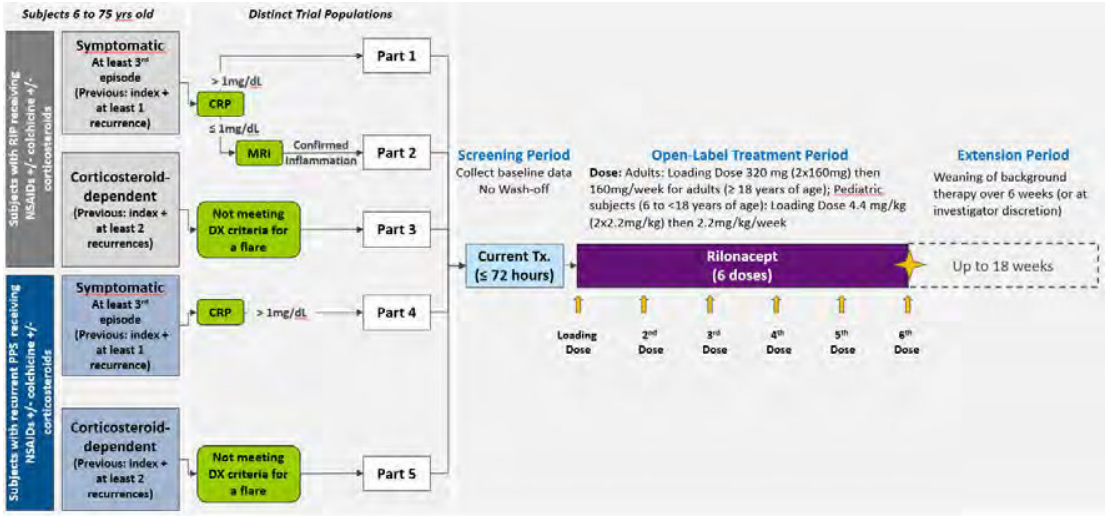
Safety Measure(s):

Safety endpoints for this study include frequency and severity of AEs and SAEs, clinical laboratory analyses (including safety laboratory measurements, anti-drug antibodies, etc.), vital sign measurements, ECGs, and physical examination findings.

Other Measure(s):

[redacted]

Overview of Trial Design



Trial Periods (all Parts)

1. Prescreening Period: Prior to enrollment, potential subjects may enter an optional prescreening period after signing a Prescreening ICF (or prescreening informed assent, if applicable) to confirm the diagnostic workup and to allow monitoring for symptoms and inflammatory markers (CRP, ESR, etc) while concomitant pericarditis medications may be managed by the Investigator or their clinician according to standard of care.
2. Screening Period: The Screening Period starts with the signing of the full study ICF (or informed assent form, if applicable) (SCV1) and may last for up to 3 days (72 hours) until SCV2. At SCV1, baseline subject and disease characteristics will be determined. At Screening Visit 2 [SCV2]), within the 24 – 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data. Under special circumstances, the Investigator in consultation with the Sponsor

can combine SCV1 and SCV2. The end of the Screening Period coincides with the start of the Treatment Period (Day 0 Visit).

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

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

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

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

   Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject.

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

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

4. Extension Period (EP): The EP is defined as the 18 weeks following the Treatment Period. Subjects who are considered to be "Treatment Responders" will be, at the discretion of the Investigator, offered participation in an optional 18-week EP, in which weekly administration of open-label KPL-914 may be continued for a total duration of 24 weeks. The weekly KPL-914 doses will be by self-administration or administered by adequately trained caregiver, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits will continue on a monthly basis. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and

discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF

Unscheduled clinic visits can be scheduled any time as determined by the Investigator/upon subject request. In addition, Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed.

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

Statistical Methods:

Each Part will be analyzed separately and per the analysis populations below, to be finalized in the Statistical Analysis Plan to be provided separately.

Analysis Populations (each Part)

The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (e.g., NSAIDs, colchicine, corticosteroids) according to study protocol without a major protocol violation. The Safety Population will be the same as the mITT Population.

General Methods

Because of the small sample size no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or analysis group. For categorical endpoints, summary statistics will be calculated and presented for each treatment and/or analysis group. Under certain circumstances, if appropriate in the context of statistical methodologies, the results of certain similar Parts might be pooled for greater statistical precision in determining therapeutic response or safety.

Further details, including, for example, the process to be followed for reviewing individual pericarditis symptomatology endpoints to be used in the construction of a composite primary endpoint for subsequent trials, will be provided in the Statistical Analysis Plan (SAP).

Primary Endpoints:

Part 1

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

Part 2

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

Part 3

Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent RIP.

Part 4

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

Part 5

Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent recurrent PPS.

[redacted]

Table 1: Schedule of Evaluations

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

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

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

Trial Period →		**Run-In Period (Up to 3 days)**			**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →	**Pre-screening Period**	**Day -3 to Day 0[a]**		**Day 0[b]**	**Day 3 [c]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial [c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 (Clinic)**	**Day 3 (Outpt)**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**N/A**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓						**Unscheduled Visits[u]**										
Investigator (or designee) phone call/virtual visit [v]					X	X	X		X	X	X		X (monthly)			

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

a. A second Screening visit (SCV2) should be performed within ~24h to 72h. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2. The last Screening and Day 0 procedures may be performed on the same day, but SCR procedures must be completed prior to Study Drug administration.

b. Subjects who do not complete the Treatment Period (withdraw consent or are discontinued before they have completed 6 weeks treatment), must be asked to complete the procedures specified at the EoT Visit.

c. Day 3 will occur ± 1 day after Day 0. Weekly intervals refer to 7 ± 1 days. The interval between Study Drug administrations must be at least 5 days.

d. Subjects should return for an optional Interval Evaluation Visit at the clinic between approximately Week 3 and 4, as determined by the Investigator.

e. Including age at first attack, number of previous attacks, and duration of attacks.

f. Drug administration training of subjects is performed at Visit 1. Study Drug will be administered in the Study Site/Clinic at Visit 1. Study Drug administrations are performed by the subjects (self-administration) or by an adequately trained caregiver on Visits (Outpatient) 2, 3, 4, 5, and 6. Participation in the Extension Phase (optional) is determined at the Week 6/EoT Visit 7 by the Investigator. Subjects who are eligible and who are willing to participate will be consented during EoT Visit 7 at the Study Site/Clinic. Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Study Site/Clinic (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7 relative to the timing of weekly dosing. Timing for dose administration is per direction of the Investigator based upon the prescribing information and study-specified dosing intervals. Continued weekly Study Drug treatment during the EP will be outpatient administration.

g. Full physical examination including assessment of pericardial rub.

h. Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.

i. Central 12-lead ECG and echocardiogram reading (including assessment of pericardial effusion). At SCV2 only the ECG will be obtained. The Study Site/Clinic reading of the ECG and the ECHO at the time of the examination will be used by the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.

j. Optional in Parts 1, 3,4 and 5. Required for Part 2.

k. At the SCV1, information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured. During the Treatment Period, changes in concomitant medication since the last Study Site/Clinic visit will be documented. During the EP, changes in pericarditis/concomitant medication will be assessed at Study Site/Clinic Visits and in monthly outpatient phone calls/virtual visits.

l. Biomarker, pharmacokinetics (PK) and anti-rilonacept antibody analysis samples will be drawn in all subjects and archived for future testing. . During each Visit at the Study Site/Clinic a sample for CRP will be obtained and sent to the central laboratory (or designated qualified laboratory) for analysis; at each Outpatient Visit; blood for central laboratory measurement of CRP will be obtained as described in the Laboratory Manual.

m. Hematology, chemistry, and urinalysis will be performed at the Study Site/Clinic laboratories, and results when available will be entered into the eCRF with appropriate reference values. Serology (HCVAb, HBsAg, HBcAb, HBsAb and HIV) and urine drug screen will be performed at SCV1 only. Hematology and urinalysis will not be performed at SCV2.

n. To be eligible to continue in the trial, a negative urine pregnancy test must be documented at the SCV1. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.

o. All AEs occurring after the subject receives the first dose of Study Drug will be captured in source records and eCRF.

p. At the SCV1, the Investigator or designee will instruct the subject about the use of the medication diary. The subject will be asked to complete a entries into the medication diary during the Screening Period and Treatment Period. Only information on pain/rescue medication will be collected. Other concomitant treatments/medications are not required to be captured.

q. At the SCV2 and all subsequent visits at the Study Center, the Investigator or designee will review the Diary entry information to verify subject compliance. If the last screening visit occurs at a different day than Visit 1, the review will also be performed at Visit 1. Diary documentation will end at the End-of-Trial visit (Visit 7).

r. Subject assessment of pericardial pain using a validated 11-point Numerical Rating Scale. The assessment will be performed on-site during clinic visits and as part of a telephone call/virtual visit during outpatient treatment weeks. If the last screening visit occurs at a different day than Visit 1, the assessment will also be performed at Visit 1, prior to Study Drug treatment. All the assessments must occur prior to study drug injection.

s. Adult subjects only. Subject global assessment of overall well-being will be assessed using a validated QoL Questionnaire (see Appendix 3). The assessment will be performed on-site during clinic visits. If SCV2 occurs at a different day than Visit 1 (Day 0), the global assessment will also be performed at Visit 1, prior to Study Drug administration.

t. Subjects may return for an optional EP Interval Evaluation Visit at the clinic between Week 15 and 20 (8 to 13 weeks after Visit 7), as determined by the Investigator.

u. Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a “Treatment Failure” may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

v. At weekly Investigator (or designee) phone calls/virtual visits during the Treatment Period, Study Drug compliance, medication diary compliance, and laboratory sample collection will be checked. The subjects will be asked using non-leading questions about any AEs occurring since the last contact (phone call/virtual visit or site visit), and NRS pain assessment will be performed. Investigator (or designee) phone calls/virtual visits will be performed monthly during the during the EP to perform NRS pain assessments, collect AE information, and review pericarditis/concomitant medications. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits.
w. During the Extension Period, Study Drug treatment is weekly by self-administration, and the study nurse visits to the home and Investigator (or designee) phone calls/virtual visits are monthly.
x. Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling and subject NRS pericardial pain rating must be repeated prior to Study Drug dosing.
y. Per Standard of Care.
z. Adult subjects only. The dosing preparation and administration questionnaire must be completed in the presence of Study Staff (via virtual visit) or visiting nurse.
aa. This lab will be drawn only during the first monthly Extension Period visit.

4 Table of Contents

List of In-text Tables

List of In-text Figures

5 List of Abbreviations and Definition of Terms

AcP	accessory protein
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
b.p.m.	beats per minute
BUN	blood urea nitrogen
CAPS	Cryopyrin Associated Periodic Syndrome
CDC	Centers for Disease Control
CHO	Chinese hamster ovary
CI	confidence interval
CRO	contract research organization
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
CTAD	citrate, theophylline, adenosine, dipyridamole
EoT	End-of-Trial
EP	Extension Period
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IL-1	Interleukin-1
IL-1RA	IL-1 receptor antagonist
IL-1RI	IL-1 type I receptor
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	intravenous
kDa	kilo Dalton
KPL-914	Study Drug; nomenclature of rilonacept (ARCALYST®) in this protocol
LDH	lactate dehydrogenase
MCH	mean cell hemoglobin
MCHC	MCH concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mITT	modified intent to treat
MWS	Muckle-Wells Syndrome

NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drugs
PI	Prescribing Information
PP	per protocol
PPD	purified protein derivative
PPS	post pericardiotomy syndrome
PRO	patient-reported outcome
PT	prothrombin
PTT	prothrombin time
QoL	quality of life
RBC	red blood cell
RIP	recurrent idiopathic pericarditis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCR	Safety Review Committee
SCV	screening visit
SD	standard deviation
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	serious and unexpected and related adverse reaction
TB	tuberculosis
[redacted]	[redacted]
TNF	tumor necrosis factor
US	United States of America
WBC	white blood cells
WHO	World Health Organization
WFI	water for injection

6 Introduction

Pericarditis accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction (Khandaker et al, 2010). 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). Diagnosis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic (ECG) changes, pericardial effusion, or elevated markers of inflammation (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Imazio et al, 2014). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define a pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-elevation or PR depression on ECG, and pericardial effusion (new or worsening). Elevations of 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 a common complication of acute pericarditis and affects 20–30% of patients (Imazio, 2014). It is characterized by the recurrence of signs and symptoms of pericarditis after a symptom-free interval of at least 4-6 weeks (Adler et al, 2015). The underlying pathogenesis of recurrent idiopathic pericarditis (RIP) remains unclear, although immune-mediated mechanisms are believed to play a key role in the pathogenesis (Imazio et al, 2005). A growing body of evidence suggests that these immune responses consist of both pathogenic autoimmune and auto-inflammatory processes (Cantarini et al, 2015; Doria et al, 2012). The presence of pro-inflammatory cytokines in the pericardial fluid of RIP patients lends direct support to both an autoimmune and/or auto-inflammatory etiopathogenesis (Pankuwait et al, 2000).

Currently available treatments for RIP include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids (Lilly, 2013). Aspirin and other NSAIDs are the first-line approach. Because high doses are often required, consideration should be given to gastric protection therapy. Colchicine is another mainstay therapy for RIP and is commonly used with NSAIDs, but a subset of patients has refractory symptoms and significant gastrointestinal side effects, including severe diarrhea, leading to discontinuation for intolerability. Glucocorticoids should be prescribed only to patients with idiopathic pericarditis who are refractory or intolerant to treatment with NSAIDs plus colchicine, because of the side effects associated with long-term corticosteroid therapy and because of a high rate of relapse when the corticosteroid is tapered or stopped (Maisch et al, 2004; Imazio, 2005; Lotrionte et al, 2010), particularly in the absence of colchicine treatment. Patients with refractory symptoms can be particularly challenging to manage, and multiple immunosuppressive medications have been used without consistent benefit (Baskar et al, 2016). In addition, a subset of corticosteroid dependent RIP subjects are also in need for new treatment options due to the side effects of high dose and/or long term corticosteroid use including osteoporosis, diabetes, weight gain and increased risk for infections.

Post-pericardiotomy syndrome (PPS) is an inflammatory syndrome involving pericardium which occurs in a subgroup of patients who have undergone cardiothoracic surgery. It is reported in approximately 9% of adult patients (Lehto el al 2015), and more commonly in pediatric/adolescent population where up to 28% of patients undergoing surgical closure of atrial septal defect were reported to develop PPS (Hechching et al, 2015).

PPS is characterized by fever, pericardial or pleuritic pain, pleural effusion or pericardial effusion with elevated serum CRP. It is associated with significant morbidity, and the leading complications include tamponade and constrictive pericarditis. Aspirin, NSAIDs, and colchicine are the mainstay of the current treatment for PPS. Although corticosteroids are used for refractory cases of PPS, they are associated with significant side effects when used for long-term treatment of this disease. Similar to RIP, there is an unmet need for new therapies, especially for the patients experiencing recurrent PPS episodes despite currently

available treatments or depend on chronic corticosteroid treatment to control their disease. (Tamarappoo, 2016).

Interleukin-1 (IL-1) is a key cytokine that drives the pathophysiology of many inflammatory processes. It is implicated as a causative factor in various inflammatory human diseases. Although the pathogenic mechanism of auto-inflammatory disease is not completely understood, there is a growing body of evidence that IL-1 may be a primary driver of the symptomology and that targeting this cytokine may provide important benefits (Hoffman & Patel, 2004).

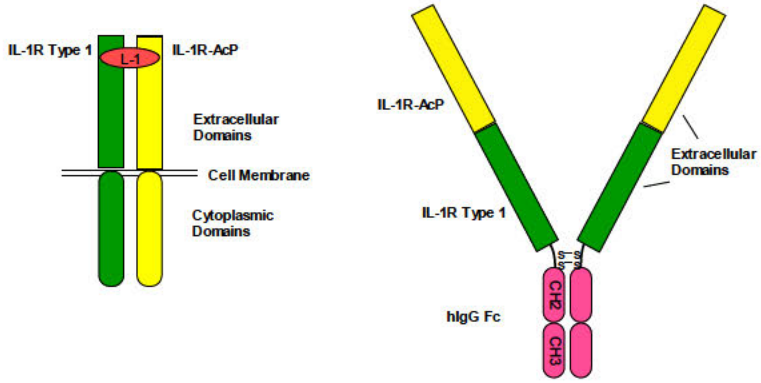
[redacted]

Rilonacept (marketed in the US under the trade name ARCALYST®; referred to as KPL-914 in this investigational study protocol) blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1α and IL-1β and prevents its interaction with IL-1 cell surface receptors. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1RA are 0.5 pM, 1.4 pM and 6.1 pM, respectively. By comparison, the IL-1 Type I receptor (IL-1RI) alone has approximately 1 nM affinity.

Rilonacept (KPL-914) is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human immunoglobulin G (IgG)1. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1RI and the IL-1 accessory protein (AcP) (Figure 1). Rilonacept was created by fusing the sequences encoding the extracellular domains of the AcP, IL-1RI, and the human Fc segment inline without any intervening linker sequences. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept is expressed in Chinese hamster ovary (CHO) cells and is purified with a series of chromatographic and filtration techniques.

The total molecular weight is ~251 kDa, of which 80% is protein (201 kDa) and 20% is carbohydrate (50 kDa).

Figure 1: Schematic of rilonacept (KPL-914)



Rilonacept was developed by Regeneron Pharmaceuticals, Inc. and is approved with the tradename ARCALYST® in the US for the treatment of Cryopyrin Associated Periodic Syndrome (CAPS), including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

Rilonacept is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. For subcutaneous (SC) administration, rilonacept is manufactured in a dosage form containing 160 mg per vial. The lyophilized powder is reconstituted with 2.3 mL of sterile Water for Injection (WFI) and drug is delivered in 2 mL at a concentration of 80 mg/mL. Clinical dosing (e.g., in CAPS) initiates with a loading dose of 320 mg SC followed by 160 mg administered SC weekly. A lower dose of 80 mg weekly (initiated with a 160 mg loading dose) was also tested in Phase 3 clinical trials in gout.

For a detailed review of the available rilonacept data, please refer to the Investigator Brochure and the ARCALYST® package insert.

Kiniksa Pharmaceuticals Ltd. (Kiniksa) is now developing rilonacept for the treatment of RIP (Rilonacept will be referred to as KPL-914 in this investigational study protocol). In this first pilot study in subjects with RIP, improvement of pericarditis symptomatology with KPL-914 administration as well as the safety and dose relationships will be assessed. Commercially-available rilonacept (ARCALYST®) will be used in the study.

The nonclinical development program for rilonacept (ARCALYST®) demonstrated biological activity and adequate safety across toxicity studies (Appendix 2: ARCALYST® Prescribing Information).

The most common adverse reactions reported by patients with CAPS treated with ARCALYST® are injection-site reactions and upper respiratory tract infections. Hypersensitivity reactions associated with rilonacept administration have been rare.

Refer to the ARCALYST® PI for Important Safety Information regarding rilonacept (Appendix 2: ARCALYST® Prescribing Information).

Based on its IL-1-antagonistic properties, its weekly-dosing pharmacokinetics, and its well-understood safety profile as shown in patients with CAPS, rilonacept (KPL-914) is a promising candidate for the treatment of RIP.

7 *Study Objectives*

The study is comprised of 5 Parts.

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

- Part 4 enrolls symptomatic subjects with recurrent post pericardiotomy syndrome (PPS) with an elevated marker of systemic inflammation (CRP > 1mg/dL).
- Part 5 enrolls subjects with corticosteroid-dependent recurrent PPS not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis.

7.1 Part 1

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914.

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

7.2 Part 2

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

7.3 Part 3

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent RIP.

7.4 Part 4:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with symptomatic recurrent PPS both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with recurrent PPS treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with recurrent PPS.

7.5 Part 5:

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent recurrent PPS.

8 Investigational Plan

8.1 Overall Study Design and Plan

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

Enrollment into Part 1:

Subjects identified for participation in **Part 1** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 1 recurrent episode** before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]).

- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode of pericarditis** prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Subjects with symptomatic RIP meeting the above diagnostic criteria may be enrolled into Part 1 only if the **CRP value at screening is > 1 mg/dL**.

Enrollment into Part 2:

Subjects identified for participation in **Part 2** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 1 recurrent episode** before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode** of pericarditis prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the eCRF.

Subjects with symptomatic RIP meeting the above diagnostic criteria but **without an elevated CRP level (i.e., ≤1mg/dl) at screening** may be enrolled into Part 2 **only if**, in the opinion of the investigator and in consultation with the Sponsor, **the low CRP value can be attributed to concomitant medications (e.g., corticosteroids) AND if there is evidence of pericardial inflammation by cardiac MRI** which has been confirmed by the MRI Core Laboratory.

Enrollment into Part 3:

Subjects identified for participation in **Part 3** in this trial will present with **corticosteroid-dependent** RIP, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes of pericarditis** and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for their RIP and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 3 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment into Part 4:

Subjects identified for participation in **Part 4** in this trial will present during a **symptomatic episode of recurrent PPS**, having previously experienced a **first (index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.

- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a first **(index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS prior to the **current enrollment-qualifying episode** of recurrent PPS and will record the criteria supporting this diagnosis in the eCRF.

In addition to meeting the above criteria for PPS, all subjects enrolled in Part 4 must have **a CRP value > 1 mg/dL at screening**.

Enrollment into Part 5:

Subjects identified for participation in **Part 5** in this trial will present with **corticosteroid-dependent** recurrent PPS, having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.
- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes** of PPS and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for the recurrent PPS and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 5 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment Process for All Parts:

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

Subjects included in Parts 1, 2 and 4 may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Subjects in Parts 3 and 5 must be receiving corticosteroids at the time of enrollment.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm study eligibility. At the SCV1, baseline subject and disease characteristics will be determined and captured in the eCRF. At Screening Visit 2 (SCV2) during the 24 - 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

After having met all the entry criteria during the Screening Period, the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 320 mg KPL-914 (2 x 160 mg) administered SC on Day 0, then 160 mg SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 4.4 mg/kg KPL-914 (2x 2.2 mg/kg; maximum total 320 mg) administered SC on Day 0, then 2.2 mg/kg (maximum 160 mg) administered SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject or will administered to the subject by an adequately trained caregiver as an outpatient SC administration. Study center staff or a visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be administered at home or other non-clinic location or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits on Day 3 and at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the subject, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels [if applicable], etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF and medication diary.

At the discretion of the Investigator, "Treatment Responders" will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

Treatment response will be defined by the Investigator:

- Part 1: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit.
- Part 2: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal levels CRP, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 3: Absence of pericarditis flare and feasibility to taper corticosteroids.
- Part 4: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 5: Absence of pericarditis flare and feasibility to taper corticosteroids.

Weekly Study Drug administrations during the EP are by self-administration or by an adequately trained caregiver, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis.

During the EP, the Investigator is encouraged to wean concomitant NSAIDs and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively taped (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering the EP (i.e., by Study Week 12) unless in the opinion of the Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. All medication changes must be recorded in source records and the eCRF. Investigators are encouraged to invite subjects to the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after the Visit 7/End of Trial Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing subject management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each subject and each Part.

Given the following occurrences, dosing may be halted or reduced in any Part of the study, in accordance with an SRC recommendation, confirmed by the Sponsor:

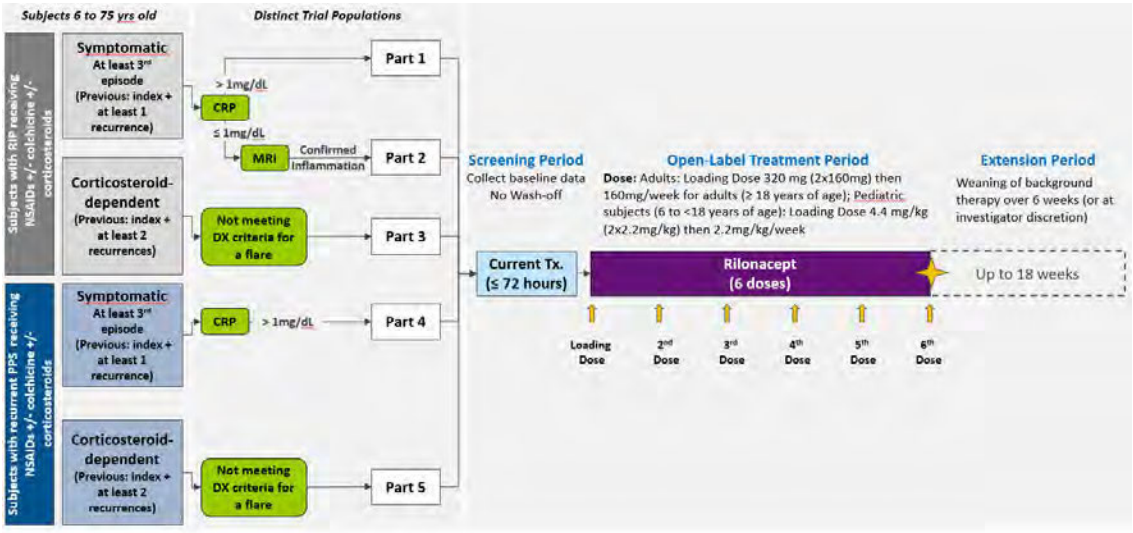
- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2 x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

Depending on treatment response observed with the 80 mg dose (or 1.1 mg/kg in subjects 6 years to <18years old), the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg (or 2.2 mg/kg in subjects 6 years to <18 years old) by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject immediately after dosing of study drug.

Figure 2: Overview of Trial Design



The study will be conducted in compliance with Good Clinical Practice regulations and other regulatory requirements.

8.2 Discussion of Study Design

Clinical information from the development of rilonacept in CAPS (ARCALYST®), the mode of action of rilonacept, as well as the inflammatory nature of idiopathic pericarditis and PPS suggest that rilonacept (KPL-914) may safely and effectively resolve recurrent pericarditis flares in idiopathic pericarditis and PPS.

[redacted]

The rationale for this pilot study is to collect time-course to pericarditis improvement data and safety information for up to 2 dose levels of KPL-914 (i.e., 160 mg and 80 mg, and corresponding pediatric doses) when administered to subjects with RIP and recurrent PPS. The study aims to provide data to support the design of future clinical studies with KPL-914 in RIP and recurrent PPS: in particular to inform inter-and intra-subject variability in CRP and NRS measurements, the time course of treatment response, and the dosage(s) of KPL-914 to be evaluated in a pivotal Phase 3 clinical trial.

The pilot study will encompass 5 Parts which enroll different subsets of subjects with RIP and recurrent PPS. It will allow evaluation of treatment responses to rilonacept in subjects with broad spectrum of recurrent pericarditis refractory to standard therapy or requiring corticosteroids to control their disease activity. Part 1 will continue to enroll subjects with symptomatic RIP and elevated CRP (>1mg/dL).

Part 2 will enroll subjects with symptomatic RIP with CRP levels (=<1mg/dL) which can be attributed to concomitant medication (e.g., corticosteroids) but with evidence of pericardial inflammation on cardiac MRI. During a corticosteroid taper a scenario may occur where the previously-suppressed pericardial inflammation begins to reactivate and symptoms begin to flare as a function of this localized inflammation, but at the same time systemic markers of humoral activation (e.g., CRP production in the liver) are still suppressed as a consequence of the intermediate steroid dose. These criteria will assure the presence of pericardial disease activity despite the absence of elevated CRP.

Part 3 will enroll corticosteroid dependent RIP subjects (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn). Corticosteroid-dependent RIP subjects are also in need for new treatment options due to the side effects of high dose and/or long-term corticosteroid use including osteoporosis, diabetes, weight gain and increased risk for infections.

Part 4 will enroll subjects with symptomatic recurrent PPS with elevated CRP (>1mg/dL).

Part 5 will enroll subjects with corticosteroid dependent recurrent PPS subjects.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

Approximately up to a total of 40 subjects with RIP or recurrent PPS will be enrolled as study subjects across all Parts.

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

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and other research in this patient population.

8.3.2 Inclusion Criteria

Inclusion Criteria for All Parts

To be eligible to participate in the trial, a subject must meet all of the following criteria:

1. Has given consent (or assent, if applicable) and signed an Informed Consent Form (ICF) (or informed assent form, if applicable).
2. Male or female, of any ethnic origin.
3. 6 to 75 years of age, inclusive.
4. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days prior to Study Drug dosing (although stable doses for a shorter period will be acceptable if, in the opinion of the Investigator in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.
5. If female of child-bearing potential, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
6. Is able to adequately maintain a medication diary.
7. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or change in exercise pattern) from the time of signature of the ICF to the End-of-Trial Visit (Week 6).

Inclusion Criteria for Part 1:

8. Has a diagnosis of RIP based on the judgement of the Investigator.
9. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
10. Has had **at least one prior recurrent episode** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
11. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
12. Has an **elevated CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 2:

13. Has a diagnosis of RIP based on the judgement of the Investigator.
14. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame

of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

15. Has had at least **one prior *recurrent episode*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
16. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
17. Has **CRP value < 1 mg/dL** at Screening, which in the opinion of the Investigator in consultation with the Sponsor, can be **attributed to concomitant medications**.
18. Has evidence of **pericardial inflammation by cardiac MRI** which has been confirmed by the MRI imaging core lab.

Inclusion Criteria for Part 3:

19. Has a diagnosis of RIP based on the judgement of the Investigator.
20. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
21. Has had **at least two prior *recurrent episodes*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
22. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
23. Is **"corticosteroid-dependent,"** in the judgement of the Investigator based on available data (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be withdrawn).

Inclusion Criteria for Part 4:

24. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.
25. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
26. Has had **at least one prior *recurrent episode*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
27. Has an **ongoing symptomatic episode** of recurrent PPS at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
28. Has an elevated **CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 5:

29. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.
30. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
31. Has had **at least two prior *recurrent episodes*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
32. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
33. Is "**corticosteroid-dependent**," in the judgement of the Investigator based on the available data, (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be withdrawn).

8.3.3 Exclusion Criteria

Exclusion Criteria for All Parts

A subject who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific excluded etiologies, including tuberculous, neoplastic, or purulent etiologies, post-myocardial infarction (early or late), thoracic trauma, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment within the 6-month period before dosing with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female subject who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A subject with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or physical exam. Have recent close contact with a person with active TB.
8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of the study.
10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis

B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.

11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.
12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks, or has been treated with IV antibiotics for an infection within 2 months of first Study Drug administration.
15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a subject is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 14 days (or 5 half-lives, whichever is longer) prior to Study Drug administration. Rilonacept and anakinra could not have been discontinued due to lack of efficacy or due to safety.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Subject who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Subject who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

8.3.4 Vaccination History and Immune status

IL-1 blockade may interfere with immune response to infections. Therefore, the Investigator should review with the subject the subject's vaccination history relative to the current medical guidelines for vaccine use. A recommended immunization schedule is available at the website of the Centers for Disease Control (CDC) (www.cdc.gov/vaccines/recs/scheduled/default.htm).

It is recommended that, prior to or shortly after initiation of therapy with KPL-914, subjects be brought up to date with all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In case a subject needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed (e.g., at the Study Site/Clinic) after the 6-week active Treatment Period. However, to minimize the potential confounding of KPL-914-related Adverse Experience reporting at initiation of KPL-914 dosing or measurements of CRP during the treatment period, vaccination should not be performed within the first 6 weeks after initiation of KPL-914 administration.

It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Administration of KPL-914 is prohibited within 12 weeks of having received a live (attenuated) vaccine. It is also possible that taking drugs that block IL-1 increases the risk of TB. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent TB infections before initiating therapy with KPL-914.

8.3.5 Removal of Subjects from Therapy or Assessments

Subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator on an ongoing basis as part of subject management. An SRC including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects in all Parts, considering trends across each.

Given the following occurrences, dosing may be halted or the dose reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

In addition, subjects may stop study treatment or may be withdrawn from treatment for any of the following reasons:

- Subject request. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment
- Use of non-permitted concurrent therapy
- Non-compliance
- Investigator request.

Treatment Failures or subjects who are withdrawn from the study for safety reasons will be replaced at the discretion of the Sponsor. Similarly, subjects who do not comply with the protocol or who withdraw from the study for other reasons can be replaced. The reason(s) for withdrawal will be documented in the source records and the eCRF.

Subjects withdrawing from the study during the Treatment Period will be asked to complete the End-of-Trial evaluations to document the status of their pericarditis disease progression at the time of withdrawal from treatment. Subjects will continue to be followed for vital status for the duration of intended treatment

to address informative censoring. Subjects withdrawing from the study during the EP will be asked to complete the Final Visit evaluations.

All reasonable efforts will be made to contact subjects who are lost to follow-up.

The Sponsor has the right to terminate the study at any time in case of safety concerns (e.g., SUSARs) or if special circumstances concerning the Investigational Medicinal Product (IMP) 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.

Pregnancy

Pregnant or lactating female subjects are excluded from study enrollment. While not explicitly stated in the rilonacept (ARCALYST®) PI (Appendix 2: ARCALYST® Prescribing Information), for the purposes of this experimental protocol, females of child-bearing potential (i.e., not postmenopausal and not sterilized) must use an active method of birth control during the course of the study, e.g., oral, implanted or injected contraceptive hormones, an intrauterine device, or a barrier method (e.g., diaphragm, condoms, spermicides).

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator without delay. If pregnancy is confirmed, the Investigator must notify the Sponsor within 24 hours and the subject must not receive (additional) Study Drug and must be discharged from the study. The subject must be asked regarding their willingness to complete the End-of-Trial Visit.

In the event that a subject is found to be pregnant after having received at least one Study Drug dose, the pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Instances of perinatal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment, will be reported to the Sponsor within 24 hours.

Full details will be recorded on the pregnancy form.

8.4 Investigational Medicinal Products

8.4.1 Investigational Medicinal Products Administered

During the Treatment Period, KPL-914 will be administered as an initial loading dose of 320 mg SC, delivered as two subcutaneous injections of 160 mg SC each on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks (18 years or older). Subjects aged 6 years to <18 years will receive an initial loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as two subcutaneous injections of 2.2 mg/kg each with a maximum single-injection volume of 2 mL. Dosing will continue with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection of up to 2 mL as outpatient administration or by an adequately trained caregiver, for 5 subsequent weeks.

Subjects will receive a total of 6 doses of KPL-914 during the study active Treatment Period. Subjects who are considered to be “Treatment Responders” will be offered, at the discretion of the Investigator, participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued for a total duration of KPL-914 treatment of up to 24 weeks.

Sites for SC 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.

No placebo or active comparator drug will be used.

8.4.2 Identity of Investigational Medicinal Products

KPL-914 (rilonacept/ARCALYST®) is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. It 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 WFI is required prior to SC administration of the drug. The reconstituted drug product is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

After the addition of preservative-free sterile WFI, the vial contents should be reconstituted by gently shaking the vial for approximately 1 minute and then allowing it to sit for 1 minute. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for SC administration only.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®) as a lyophilized powder to be reconstituted for SC administration. The sites will receive Study Drug for on-site administration at Study Site/Clinic visits. Drug will be disseminated to the trial subjects for outpatient self-administration according to a supply chain described in the Pharmacy Manual.

The lyophilized Study Drug (KPL-914 also called rilonacept, US tradename: ARCALYST®) is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. After reconstitution, KPL-914 may be kept at room temperature, should be protected from light, and should be used within 3 hours of reconstitution. Unused portions of KPL-914 product must not be injected. All vials of used and unused Study Drug during the active Treatment Period must be returned to the clinical site for cataloguing and documentation of compliance.

The Sponsor through Regeneron Pharmaceuticals, Inc. will ensure that the Study Drug and certificates of analysis are available before the start of the study and at all times during the study.

ARCALYST® is a registered trademark of Regeneron Pharmaceuticals, Inc.

8.4.3 Method of Assigning Subjects to Treatment Groups

Subjects who meet all the inclusion criteria in a specific Part and none of the exclusion criteria will enter the Treatment Period at Visit 1 (Day 0).

Since this is an open-label, single-active-arm study, all subjects will receive KPL-914 active treatment. Assignment to treatment groups is not applicable.

8.4.4 Selection of Doses in the Study

This protocol is a pilot study intended to evaluate the safety, efficacy, and dose response of KPL-914 in the treatment of patients with RIP.

[redacted] treatment will be as follows.

Adult subjects (≥ 18 years of age)

KPL-914 will be administered as an initial loading dose of 320 mg SC, delivered as two subcutaneous injections of 160 mg SC each on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks. (Appendix 2: ARCALYST® Prescribing Information).

Pediatric subjects (6 to <18 years of age)

KPL-914 will be administered with an initial loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as two subcutaneous injections of 2.2 mg/kg each with a maximum single-injection volume of 2 mL. Dosing will continue with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection of up to 2 mL as outpatient administration or administered by an adequately trained caregiver, for 5 subsequent weeks (Ilowite et al, 2014, Lovell et al, 2013, Garg et al, 2017, Autmizguine et al, 2015).

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

8.4.5 Selection and Timing of Dose for Each Subject

The first administration of KPL-914 (and training for outpatient self-administration) will be performed under the supervision of a qualified healthcare professional at Visit 1 (Day 0). Afterwards, subjects or an adequately trained caregiver will administer the Study Drug as an outpatient during the Treatment Period (and during the EP, as applicable). Study Drug administration will be performed once a week (every 7 ± 1 days). The interval between Study Drug administrations must be at least 5 days. Subjects will be instructed to not administer KPL-914 more often than once weekly and to administer only one syringe of Study Drug per week.

At Visit 1, subjects or adequately trained caregivers will be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously will be assessed to ensure proper administration of KPL-914, including rotation of injection sites. Subjects will be instructed in proper vial, syringe, and needle disposal, and will be cautioned against reuse of these items. All used and unused Study Drug vials must be returned to the Study Site/Clinic for drug accountability assessment.

8.4.6 Blinding

Not applicable.

8.4.7 Prior and Concomitant Therapy

Subjects included in Parts 1, 2 and 4 may be using NSAIDs, colchicine, and/or corticosteroids in any combination at the time of study enrollment, but the dose levels must be stable for have been stable for at least 7 days, although stable doses for shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Subjects in Parts 3 and 5 must be receiving corticosteroids at the time of enrollment.

For the duration of the Treatment Period, pericarditis medications (e.g., concomitant NSAIDs, colchicine and/or corticosteroids, if used) should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Subjects who received, within the 6-month period before dosing, immunomodulatory therapy other than, for example, corticosteroids or mycophenolate, which in the opinion of the Investigator (in consultation with the Sponsor) may interfere with the study endpoints, or subjects who used commercially-available rilonacept (ARCALYST®) within 90 days before the Screening Visit are excluded from participation.

Throughout the Treatment Period opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF. Other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) and tumor necrosis factor (TNF) inhibitors are prohibited for the duration of the study.

Medical management of pericarditis during the EP is based on Investigator discretion. For example, Investigators may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status

Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject on a real-time basis.

8.4.8 Treatment Compliance

Study Drug will be administered to the subject by the Investigator or qualified study center staff at the Study Site/Clinic Visit 1 (Day 0). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject or an adequately trained caregiver as an outpatient SC administration. The study center staff or a visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site. All medication use (for pericarditis and use of rescue [pain] medication) will be documented by the subject in the medication diary during the Treatment Period.

All vials of used and unused Study Drug during the active Treatment Period and the EP must be retained by the Study Site/Clinic and the subject to allow for cataloguing and documentation of compliance. Subjects must return all used and unused medication to the Study Site/Clinic. Drug accountability and documentation thereof is described in the Pharmacy Manual.

Study Drug compliance by the subject will be monitored during the Treatment Period by phone calls/virtual visits (made by qualified site staff). Subjects will be reminded of recording all pericarditis and rescue pain medication information in the medication diary. The medication diary will be returned to the site by the subject and reviewed by the Investigator/qualified staff. During the EP, Study Drug use will be documented during monthly phone calls/virtual visits or Study Site/Clinic visits.

8.5 Study Procedures

All data of Study Site/Clinic visit assessments as well as Investigator (or designee) phone calls/virtual visits will be documented in source records and in the eCRF.

8.5.1 Prescreening Period

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

The Prescreening Period starts with the signing of the Prescreening ICF (or prescreening assent form, if applicable), and lasts until the subject enters the Screening Period by signing the ICF for the full study or is withdrawn (see section 8.3.5).

8.5.2 Screening Period

The Screening Period starts with the signature of the ICF (or informed assent form, if applicable), and may last for up to 3 days. During this period, subject eligibility for entry into the Treatment Period will be determined. A rheumatology consultation during the Screening Period is optional.

At SCV1, baseline subject and disease characteristics will be determined. At Screening Visit 2 [SCV2]), within the 24 – 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data Under special circumstances, the Investigator in consultation with the Sponsor, can combine SCV1 and SCV2.

The end of the Screening Period may coincide with the start of the Treatment Period.

8.5.2.1 Screening Visit 1 (SCV1)

- At the SCV1, written informed consent (or assent, if applicable) will be obtained before any protocol-specific assessments are made.
- All subjects will be assessed for eligibility against the inclusion and exclusion criteria.
- Demographic data, such as ethnic origin, date of birth and sex will be recorded.
- The subject's full medical history, including age at first attack, number of previous attacks, duration of attacks as well as concomitant illnesses/diseases will be documented.
- Information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured.
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
- A pregnancy test (urine dip-stick) will be done. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.
- 12-lead ECG and full echocardiogram (ECHO) will be performed. ECHO will include assessment of pericardial effusion. The Study Site/Clinic readings at the time of the examination will be available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- A cardiac MRI may be performed (optional). If done, the images will be assessed by a central reader. The Study Site/Clinic reading at the time of the examination may be used by the Investigator for clinical decision-making.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
        - Serology (HCVAb, HBsAg, HBcAB, HBsAb and HIV)
        - A QuantiFERON® test for tuberculosis (TB) can be performed (optional).
    - Screening for drugs of abuse and alcohol abuse will be performed on urine samples collected at this visit.
    - Central Laboratory Assessments:
        - CRP/hsCRP
- Samples for archive biomarker, pharmacokinetics (PK), and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- A medication diary for documentation of pericarditis medication use and use of any rescue (pain) medication will be handed to the subject. The study Investigator or designated personnel will instruct the subject about the use of the medication diary. The subjects will be asked to complete entries immediately following administration.
- The subjects will assess their pericardial pain based on a 11-point NRS.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.2.2 Screening Visit 2 (SCV2)

The end of the Screening Period (SCV2) coincides with the start of the Treatment Period (Day 0, Visit 1). All Screening assessments need to be completed prior to the first Study Drug administration.

- SCV2 should take place when the laboratory test results from SCV1 are available.
- Subjects will be reassessed for eligibility against the inclusion and exclusion criteria.

- Any changes in concomitant medications since SCV1 will be documented.
- A full physical examination will be performed, including re-assessment of pericardial rub.
- Vital signs will be measured.
- 12-lead ECG will be performed. The Study Site/Clinic reading at the time of the examination will be used by the Investigator for clinical decision-making. In addition, the ECG will be sent to a core laboratory for additional analysis.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full chemistry (including CRP) panel only
    - Central Laboratory Assessments:
        - CRP/hsCRP
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- The subjects will assess their pericardial pain based on the 11-point NRS (Figure 3).

When all screening procedures have been performed and the Investigator has confirmed the subject's eligibility for the study, the Study Drug will be administered to the subject (see Study Site/Clinic Visit 1).

8.5.3 Treatment Period

8.5.3.1 Visit 1 (Study Site/Clinic) - Day 0

Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling (including CRP), medication diary compliance verification and reminding, and subject NRS pericardial pain rating (see Figure 3) must be repeated prior to Study Drug dosing.

- Sample for lipid panel to be sent to the Central Laboratory for analysis
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected prior to Study Drug dosing, sent to the central laboratory, and stored for analysis.
- The subject's global overall well-being will be assessed prior to Study Drug dosing using a validated Quality of Life Questionnaire (Appendix 3).
- The initial dose of Study Drug will be administered at the Study Site/Clinic.
- Subjects will be trained for outpatient Study Drug self-administration and reminded of completion of the daily medication diary.
- Any AEs occurring during or after the subject receives the first dose of Study Drug will be captured.

When all Visit 1 procedures have been performed, an appointment for the first weekly phone call/virtual visit will be scheduled. Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

8.5.3.2 Day 3 (Outpatient)

- Day 3 will ± 1 day after Visit 1.
- An Investigator (or designee) telephone call/virtual visit will occur to evaluate safety (AE evaluations) and patient-reported pericardial pain using a validated 11-point NRS instrument.

8.5.3.3 Visits 2 to 6 (Outpatient) - Weeks 2, 3, 4, 5, 6

- Visits 2, 3, 4, 5, 6 will take place within intervals of 7 ± 1 days each after Visit 1.

- Subjects self-administer the Study Drug or be administered Study Drug by an adequately trained caregiver during Weeks 2 to 5. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site.
- Samples for laboratory tests will be collected.
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected (either by a visiting study nurse or at the Study Site or at a qualified local laboratory) and stored for analysis after shipment to the central laboratory.
- After dosing at Week 3 and Week 6, a questionnaire to assess the dosing system will be completed by the subject and by the study center staff or visiting nurse observing the dosing
- Any AEs that have occurred since the last contact will be assessed by non-leading questions as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Compliance with self-administration of drug, compliance with the medication diary, and compliance with laboratory blood sampling will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.

Subjects withdrawing from the study any time during study weeks 2 to 6 will be asked to return to the Study Site/Clinic for the Visit 7/End-of-Trial visit assessments.

8.5.3.4 Interval Evaluation Visit (Study Site/Clinic) - Week 3-4

An in-person Interval Evaluation Visit during approximately Weeks 3-4 of the Treatment Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator. The Interval Evaluation Visit may also be used to review the vaccination status of a study subject.

At the Interval Evaluation Visit, the following parameters will be assessed:

- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.3.5 Unscheduled Visits (Study Site/Clinic) During the Treatment Period

Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. During the Unscheduled Visit, selected or comprehensive (see Interval Evaluation Visit) clinical and laboratory assessments may be performed.

Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

All study withdrawals must complete the Visit 7/End-of-trial Visit either at the Unscheduled Visit or at a separate Visit 7/End-of-trial Visit.

8.5.3.6 Visit 7/ End-of-Trial (Study Site/Clinic) - Week 6

At Visit 7, "Treatment Responders" (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week EP, at the discretion of the Investigator. During the EP, weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

- Visit 7 will take place during Week 6 (or as soon as possible after study withdrawal if a subject has discontinued from Study Drug therapy).
- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since last Study Site visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Lipid panel
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

When all of these procedures have been performed, the next Study Site/Clinic visit should be scheduled for those who continue KPL-914 treatment during the EP (Treatment Responders). Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Clinic/Site (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7. Continued weekly Study Drug treatment during the EP will be outpatient administration.

8.5.4 Extension Period

Subjects will self-administer the Study Drug or be administered by an adequately trained caregiver weekly basis and complete the medication diary during the Extension Period. Study nurse visits to the subject's home will continue on a monthly basis. Investigator (or designee) phone calls/virtual visits will be performed monthly during the EP to perform NRS pain assessments, collect AE information, and document pericarditis/concomitant medication use. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF

8.5.4.1 Unscheduled Visits (Study Site/Clinic) during the EP

Unscheduled Study Site/Clinic visits can take place during the Extension Period, as agreed upon by the Investigator and the subject or as needed.

- A physical examination will be performed.
- Vital signs will be measured.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- A 12-lead ECG and a full ECHO will be performed as determined by the Investigator. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).

8.5.4.2 Interval Evaluation Visit During Extension Period (Study Site/Clinic) - Week 15-20

An in-person Interval Evaluation Visit during approximately Weeks 15-20 of the Extension Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator.

At the Extension Period Interval Evaluation Visit, the following parameters will be assessed:

- A physical examination will be performed.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.4.3 Visit 8/Final Visit (Study Site/Clinic) - Week 25

- Visit 8 will take place 18 weeks after Visit 7 (or as soon as possible after study withdrawal during the EP).
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
- 12-lead ECG and ECHO will be performed. Echocardiogram will include assessment of pericardial effusion. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
- An MRI can be performed (optional).
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Lipid panel
    - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.5 Duration of Treatment

The overall study duration for subjects participating in the study until Visit 8 will be up to 171 days.

The test product will be administered weekly for 6 weeks in the base study Treatment Period. Treatment Responders will be offered participation in an optional 18-week EP at the discretion of the Investigator. During this EP the subject can receive 18 additional weekly doses of KPL-914.

8.6 Efficacy and Safety Variables

The Schedule of Evaluations in Table 1 shows the planned study assessments.

8.6.1 Individual Efficacy Assessments

8.6.1.1 C-Reactive Protein, Biomarker, and PK Assessments

CRP will be determined at Study Site/Clinic laboratory tests at Screening (SCV1 and SCV2) and during the Treatment Period (Visit 1 prior to dosing, if separate from SCV2, Interval Evaluation Visit [if applicable], and Visit 7/End-of-Trial). Results from the Study Site/Clinic CRP testing will inform the Investigator on the subject's pericarditis status for clinical decision-making and support decisions on classifications of subjects as Treatment Responders or Treatment Failures and on subsequent disease management during the Extension Period.

Central laboratory assessments of CRP will be performed at each Study Site/Clinic or outpatient study visit (samples collected by a visiting study nurse or at the Study Site/Clinic or a local laboratory). Centrally determined CRP values will be used for statistical evaluations and report writing but will not be used as basis of the Investigator's management of the subject.

All subjects must present with elevated CRP values ≥1 mg/dL at the time of study enrollment. CRP changes and the time course to decrease and resolution of CRP to normal values ≤0.5 mg/dL will be assessed.

Samples from each study visit will be archived at the central laboratory for potential biomarker and/or PK analysis.

8.6.1.2 Echocardiogram (Pericardial Effusion)

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

Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart and is one of the common features of pericarditis. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening.

For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECHO images will be assessed by a central reader. The Study Site/Clinic reading of the ECHO at the time of the examination will be made available to the Investigator for clinical decision-making.

8.6.1.3 Electrocardiogram (Pericarditis Diagnostic Findings)

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

Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-elevation or PR depression. Changes in ECG findings will help determine the pericarditis status of a subject.

The Study Site/Clinic reading of the ECG at the time of the examination will be made available to the Investigator for clinical decision-making. For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECG tracings will be assessed by a central reader.

8.6.1.4 Pericarditis Signs (Fever, Pericardial Rub)

Common pericarditis signs include fever and pericardial rub. These pericarditis signs will be assessed via documentation of vital signs and physical examinations.

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

8.6.1.5 Pericarditis Pain (Chest Pain)

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011). The assessment will be performed at all study visits - on-site during Study Site/Clinic visits and as part of telephone calls/virtual visits during outpatient visits/treatment weeks (weekly during the Treatment Period and monthly during the EP).

Subjects will be asked to select the score that best describes their average level of pain over the previous 24 hours using a validated 11-point NRS instrument (Figure 3), 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 pain on average in the last 24 hours

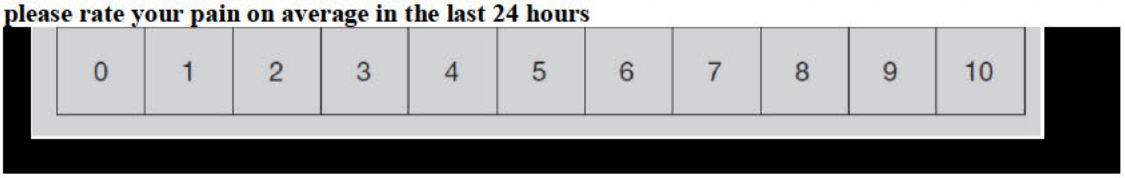


Figure 3: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

8.6.1.6 Magnetic Resonance Imaging

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

For the purposes of the analysis of treatment response in all subjects at the end of the study, all cardiac MRI images will be assessed by a central reader. The Study Site/Clinic reading of the MRI at the time of the examination may be used by the Investigator for clinical decision-making.

8.6.1.7 Quality of Life Questionnaire

A validated Quality of Life Questionnaires will be used to assess changes in the subject's overall well-being (Hays et al 2009). The subject's global assessment will be performed at screening (SCV1), at Visit 1 (Day 0), at the Interval Evaluation Visit (Week 3-4), at the end of the Treatment Period (Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP, and at the Final Visit (Visit 8).

The Quality of Life Questionnaire to be used is presented in Appendix 3.

8.6.1.8 Dosing Procedure Questionnaire

A questionnaire will be used to assess the dose preparation and administration procedure immediately after self-injecting the Study Drug in the presence of the Study Staff (either in person or via virtual visit) or of the visiting nurse. Each subject will complete a questionnaire after the third self-injection (third dose, Week 3) and the sixth self-injection (sixth dose, Week 6), and once during the extension period. The Study Staff/visiting nurse observing the injection will also complete an observation checklist for observing subjects interacting with the system during self-injection. The checklist will list all key steps associated with proper system use, including setting up for an injection, reconstituting the medication, and administering the injection. Study Staff/visiting nurse will complete the checklists for the same injections for which the subjects will complete questionnaires.

8.6.2 Safety Assessments

8.6.2.1 Adverse Events

Adverse Event Definition

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 and/or unintended 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.

In this study, individual elements of pericarditis symptomatology (including pain) are captured as an efficacy parameter. Pericarditis pain is not required to be reported as an AE. However, if, in the opinion of the Investigator, the subject experiences new symptoms that had not been previously reported in the constellation of symptoms recorded at baseline, these new symptoms should be reported as an AE.

The causal relationship between an AE and the Study Drug will be defined as below:

- **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 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 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 drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

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**: medically significant event; daily activities limited or completely halted; hospitalization or prolongation of hospitalization indicated.

Every reasonable effort will be made to follow subjects who have AEs. Any subject who has an ongoing AE at study end or early withdrawal will be followed, where possible, until resolution.

8.6.2.2 Serious Adverse Events

Serious Adverse Event Definition

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 Study Drug (e.g., car accident where 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 hospitalizations must be recorded on the medical history or physical examination page of the eCRF). Hospitalization is defined as an admission to the hospital ward or a short-stay-type unit longer than 24 hours. Prolongation of existing hospitalization is defined as 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 judgement 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 IMP.

Reporting of Serious Adverse Events

SAEs merit special concern and attention, and SAEs due to any cause, whether or not related to the Study Drug, must be reported by the Investigator to the Sponsor and designee within 24 hours of occurrence or when the Investigator becomes aware of the event. Report SAEs by fax or email using the designated SAE report to:

In addition, Investigator must report the SAE within 24 hours of learning of the event by telephone to:

If the Investigator reports an SAE by telephone, then a written report must follow within 1 business day and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable.

Other Reasons for Immediate Reporting to [redacted]

- Overdose (accidental or intentional) of the investigational product or concomitant medication, regardless of whether it is considered an AE
- Any pregnancy diagnosed in a female subject or in a female partner of a male subject during treatment with an investigational product
- Hospitalization (including Emergency Room visits) which last for less than 24 hours. A determination will be made by the Sponsor in collaboration with [redacted] as to whether it is a SAE
- Any diagnosis of malignancy (excluding basal cell skin cancer) during the study should be reported to [redacted] within 24 hours.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 8.3.5.

All hospitalizations must be reported to [redacted] and Kiniksa within 24 hours; however, hospitalizations for elective medical/surgical procedures for preexisting illnesses that were planned prior to the subject's enrollment in the study may not be considered by the Investigator to be AEs. Complications resulting from planned procedures, however, require reporting to [redacted] and Kiniksa.

Whenever possible and practical, a blood sample (collected in a light blue top CTAD [citrate, theophylline, adenosine, dipyridamole] vacutainer tube) to potentially measure plasma drug levels should be obtained upon the development of any SAE or unusual AE that is judged to be related to study treatment.

Investigator Reporting Responsibilities to Institutional Review Board (IRB)

Unanticipated problems posing risks to study subjects will be reported to the IRB per their institutional policy. Copies of each report and documentation of IRB notification and acknowledgement of receipt will be kept in the Investigator's study file.

Sponsor Reporting Responsibilities to Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

8.6.2.3 Adverse Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; i.e., where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

Unexpected Adverse Reaction Definition

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with relevant product information for the IMP. The current version of the ARCALYST® PI should be used as the Single Source Safety Reference Document when determining if an event is unexpected. Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for a list of most frequent expected AEs. All suspected adverse reactions related to an investigational medicinal product (the tested investigational medicinal products and comparators, if involved) which occur in the concerned trial, and that are both unexpected and serious are subject to expedited reporting.

Warnings and Precautions

Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for Important Safety Information.

IL-1 blockade may interfere with immune response to infections. It is therefore recommended that prior to or shortly after initiation of therapy with KPL-914 subjects receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In case a subject needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed during the active Treatment Period. However, to minimize the potential confounding of KPL-914-related AE reporting or CRP measurements during the KPL-914 Treatment Period, vaccination should not be performed during the Treatment Period (see Section 8.3.4). It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Taking KPL-914 with TNF inhibitors is not recommended because simultaneous inhibition of these two pathways may increase the risk of serious infections.

It is also possible that taking drugs 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 KPL-914.

8.6.2.4 Clinical Laboratory Variables

Clinical laboratory analyses will be performed at Study Site/Clinic or local laboratory near the subject and, for some parameters, at a central laboratory. Laboratory analyses will be used at Study Site/Clinic visits for the Investigator to assess disease status and to determine treatment response and study (drug) continuation

or withdrawal. Results for analyses performed by the Study Site/Clinic laboratory together with the laboratory reference ranges will be recorded in the eCRF and the Investigator must use clinical judgment to determine if any abnormal values are clinically significant or not.

Central laboratory samples for CRP analysis will be collected at both Study Site/Clinic and outpatient (by a visiting study nurse or at local contract laboratories) visits and the results will be used for statistical analyses and study reporting. Study Site/Clinic and local laboratory results will be used for clinical decision-making and will be available in the source documents and listed in the CSR).

The following analyses will be done at the **central laboratory**:

- C-reactive protein (CRP)/hsCRP (The CRP analyzed by the central laboratory will not be available to the investigator in a timely manner to support the clinical management of the subject. Results from the central laboratory will therefore not be transferred to the Investigator during the trial.)
- Lipid Panel
- Samples for biomarkers, PK, and anti-rilonacept (anti-KPL-914) antibody testing will be drawn and archived at all visits.

The following laboratory analyses will be done at the **Study Site/Clinic laboratories** in accordance with local procedures and guidelines to support clinical management and decision-making:

Hematology

Hemoglobin, hematocrit, coagulation parameters (prothrombin [PT], prothrombin time [PTT], D-dimer), ESR, fibrinogen, WBC count (total and differential), red blood cell (RBC) count, ESR, platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), MCH concentration (MCHC).

Clinical Chemistry

CRP/hsCRP, troponin, creatinine, creatine kinase, urea, (or blood urea nitrogen [BUN]), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol*, triglycerides*, calcium, phosphorus.

* Preferably fasting.

Urinalysis

pH, glucose, ketones, nitrites, leukocyte esterase, blood, protein and microscopy. Urine drug screen (alcohol, amphetamines, cocaine, or phencyclidine) at SCV1 only. Screening for pregnancy (urine β-HCG) at SCV1 only.

Serology

HCVAb, HBsAg, HBcAb, HBsAb and HIV tests (SCV 1 only).

Other
Screening for tuberculosis (QuantiFERON test) at SCV1 only (optional).

The amount of blood to be taken during screening will be approximately 37 mL at SCV1 and approximately 17 mL at SCV2 (if done). The amount of blood to be taken at each Study Site/Clinic visit during the Treatment Period and EP will be approximately 31 mL. The amount of blood to be taken at each outpatient visit will be approximately 21 mL. At the optional unscheduled visit, approximately 61 mL are planned. The total amount of blood to be taken during the study will be up to approximately 320 mL.

8.6.2.5 Vital Signs

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

The following measurements will be taken: oral temperature, respiratory rate, blood pressure, and pulse. Oral temperature (fever) will also be assessed as efficacy parameter (see Section 8.6.1.4).

8.6.2.6 Physical Examination

At the Screening Visits 1 and 2, at the optional Evaluation Visit during the Treatment Period, at the End-of-Trial Visit (Visit 7), at Unscheduled and Evaluation Visits during the EP and at the Final Visit (Visit 8) a full physical examination including the assessment of pericardial rub (efficacy parameter) will be performed (see also Section 8.6.1.4).

8.6.2.7 Body Weight and Height

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

8.7 Statistical Methods

Each Part will be analyzed separately and per the analysis populations below, to be finalized in the Statistical Analysis Plan (SAP) to be provided separately. A full description of the statistical analyses to be performed together with the planned tables and figures will be given in a detailed document, the SAP, which will be developed and filed prior to data base lock. Any deviation(s) from the final SAP will be described and justified in the clinical study report.

8.7.1 Statistical and Analytical Plans

8.7.1.1 Datasets to be Analyzed for Each Part

Each Part will be analyzed separately and per the analysis populations below. The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (NSAIDs, colchicine, and/or corticosteroids, if used during screening) according to study protocol without a major protocol violation. The Safety Population will be the same as the mITT Population.

8.7.1.2 General Statistical Methods

Because of the small sample size, no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or analysis group. For categorical endpoints (e.g., responder vs. non-responder), summary statistics will be calculated and presented for each treatment and/or analysis group. Under certain circumstances, if

appropriate in the context of statistical methodologies, the results of certain similar Parts might be pooled for greater statistical precision in determining therapeutic response or safety.

Further details will be provided in the SAP. Any deviation(s) from the original statistical plan will be described and justified in in the final study report.

8.7.1.3 Efficacy Endpoints

Primary Efficacy Endpoints

Part 1
Determine inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with RIP both at baseline and while on active KPL-914 treatment in order to inform power calculations for future trials in pericarditis.

Part 2
Determine inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with RIP both at baseline and while on active KPL-914 treatment in order to inform power calculations for future trials in pericarditis.

Part 3
Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent RIP.

Part 4
Determine inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with recurrent PPS both at baseline and while on active KPL-914 treatment in order to inform power calculations for future trials in pericarditis.

Part 5
Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent recurrent PPS.

[redacted]

8.7.1.4 Safety Variables

AEs and SAEs, clinical laboratory evaluations, vital sign measurements, ECGs, and physical examination findings.

8.7.2 Determination of Sample Size

Approximately up to a total of 40 subjects with RIP or PPS will be enrolled as study subjects across all Parts.

Subjects who discontinue the study (withdrawals and Treatment Early Failures) may be replaced at the Sponsor's discretion.

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and research in this patient population.

8.8 Quality Assurance and Quality Control

8.8.1 Audit and Inspection

The study may be selected for audit originating from the Sponsor or external organizations acting on behalf of the Sponsor. Audits will be followed by internal reports and corrective actions, if needed.

The Investigator agrees to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved. The anonymity of the subjects must be safeguarded and data checked during audits remain confidential.

8.8.2 Monitoring

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 (or informed assent form, if applicable),.

The Investigator will permit study-related monitoring, audits, ethics committee review and regulatory inspection(s), providing direct access to source data and documents.

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 Good Clinical Practice (GCP) and International Conference on Harmonisation (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.

8.8.3 Data Management and Coding

The Sponsor or Clinical Research Organization (CRO) 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 the Sponsor or CRO.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and World Health Organization (WHO) Drug for therapies.

8.8.4 Record Keeping

It is the responsibility of the Investigator to ensure all essential trial documentation and source records (e.g., signed ICFs/assent forms, Study Site/Clinic files, patients' hospital notes, copies of eCRFs, etc.) 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.

9 Records and Supplies

9.1 Drug Accountability

On receipt of the IMP (including rescue medication, if relevant), the Investigator (or deputy) will conduct an inventory of the supplies and verify that IMP supplies are received intact and in the correct amounts prior to completing a supplies receipt. The Investigator will retain a copy of this receipt at the study site and return the original receipt to the drug depot. The inventory of supplies at each study site will be reviewed by the study monitor.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®). All vials of used and unused Study Drug during the active Treatment Period 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.

10 Ethics

10.1 Institutional Review Board

Before initiation of the study at each investigational site, the protocol, all protocol amendments, the ICF, the informed assent form and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the IMP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the informed consent form (or assent, if applicable), the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB annually, or more frequently if requested by the IRB. On completion of the study, the Sponsor will notify the IRB that the study has ended.

10.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the Declaration of Helsinki and local regulations.

10.3 Subject Information and Consent

The Investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject and/or legal guardian has given written informed consent (or informed assent, if applicable) to participate in the study. The written consent (or informed assent, if applicable) must be given by the subject and/or the legal guardian of the subject, after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

Subjects and/or legal guardians will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IRB, Sponsor and/or CRO personnel.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. 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 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 informed assent and the informed consent are required prior to participation in the trial.

10.4 Subject Confidentiality (US Studies)

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA), applicable to national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the ethics committees approving this research, and the United States (US) FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

11 Reporting and Publication

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator(s) will be subject to mutual agreement between the Investigator and Kiniksa as outlined in the study agreement.

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13 Appendices

Appendix 1: Investigator Signature Page

Protocol Title: An open-label pilot study of KPL-914 in symptomatic Recurrent Idiopathic Pericarditis.

Protocol Number: KPL-914-C001

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and I will conduct the study as described in compliance with this protocol, GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Kiniksa Pharmaceuticals Ltd. (Kinksa) and of the IEC/IRB. I will submit the protocol modifications and/or any ICF/assent modifications to Kiniksa and IEC/IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all Case Report Forms, laboratory samples or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Kiniksa, to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

Appendix 2: ARCALYST® Prescribing Information

ARCALYST- rilonacept injection, powder, lyophilized, for solution
Regeneron Pharmaceuticals, Inc.

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: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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			Endpoint		

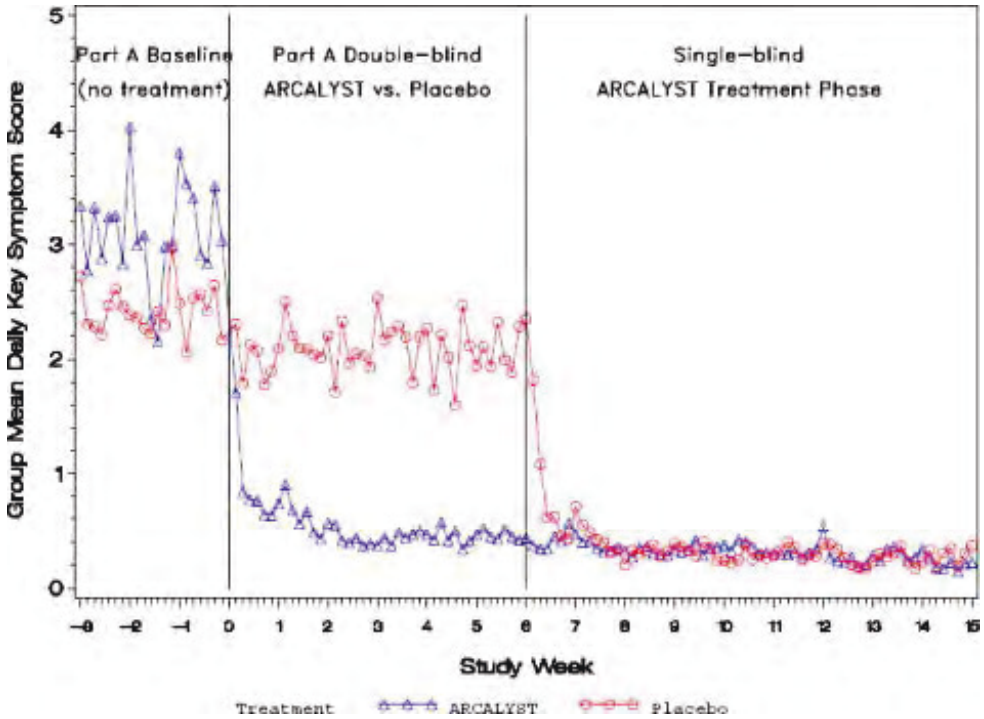
Period (Weeks 4 to 6)	2.1	0.5	Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment 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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U.S. License Number 1760
NDC 61755-001-01

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):

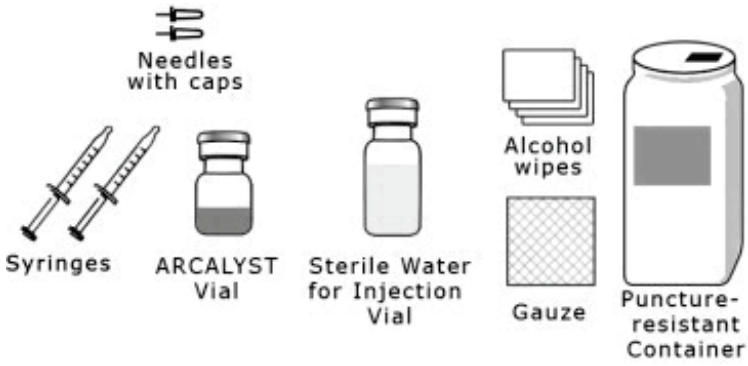


Figure 1

- 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

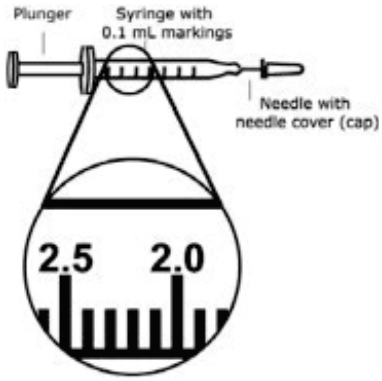


Figure 2

- 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).

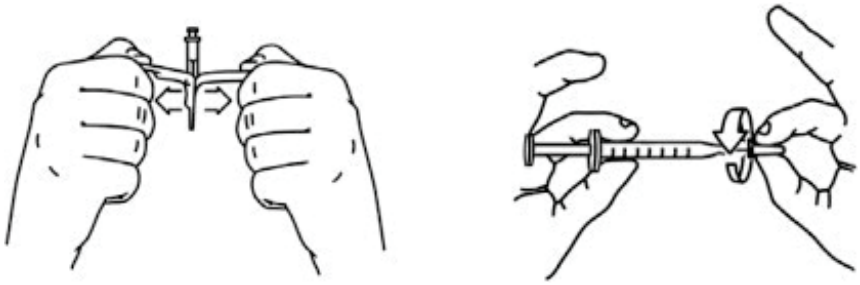


Figure 4

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).

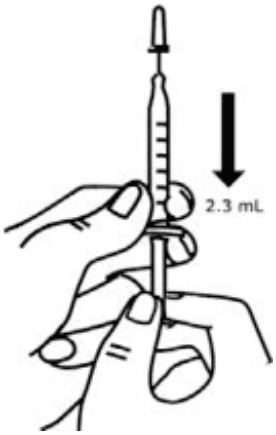


Figure 5

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).

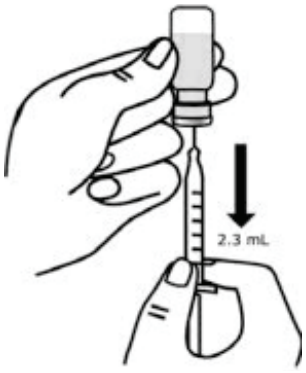


Figure 7

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).

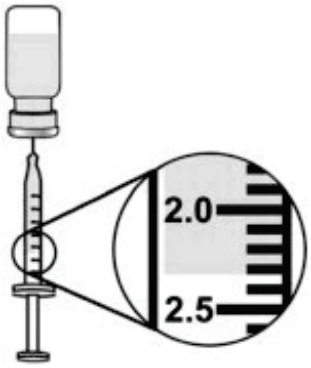


Figure 8

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).

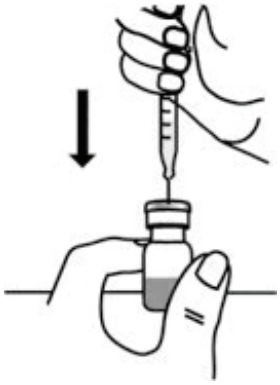


Figure 9

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.

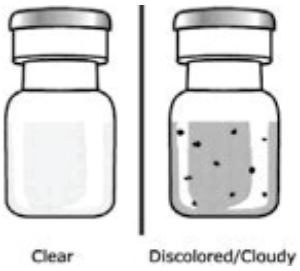


Figure 11

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).

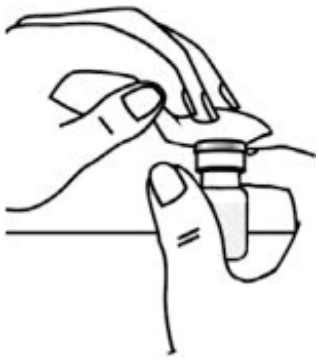


Figure 12

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

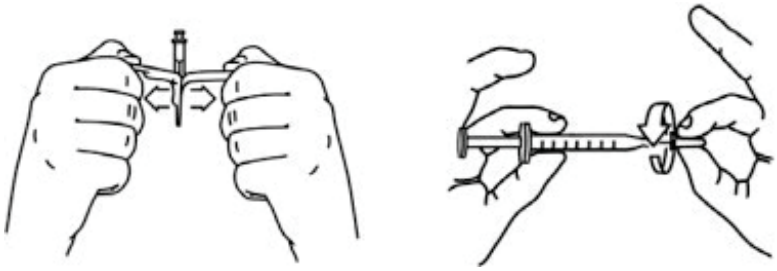


Figure 13

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).

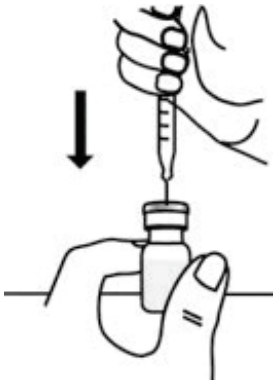


Figure 15

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).

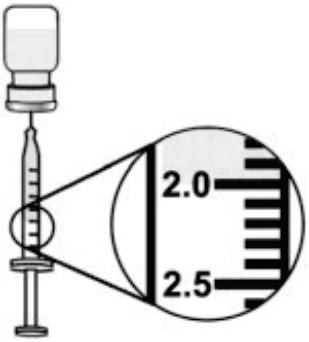


Figure 16

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.

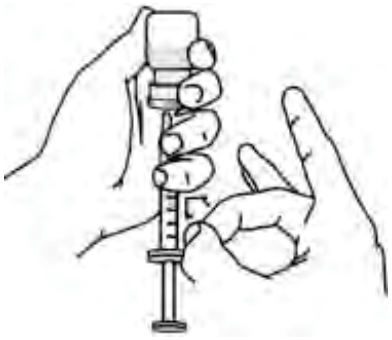


Figure 17

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)

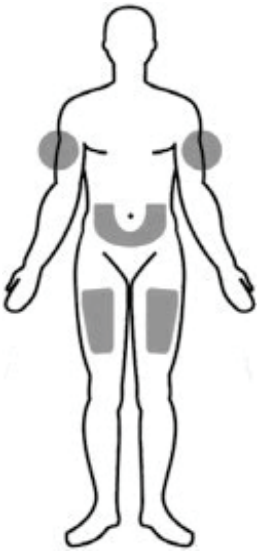


Figure 19

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).

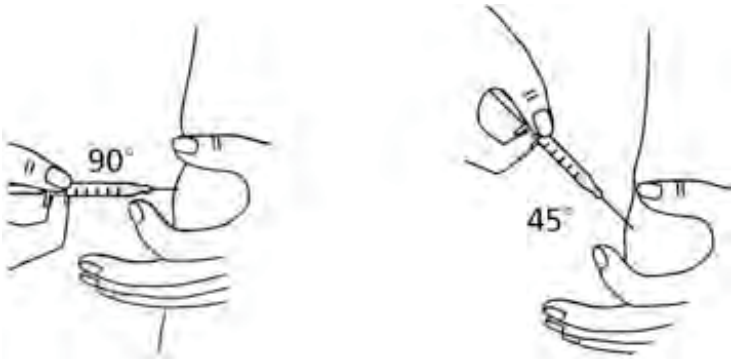


Figure 21

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).

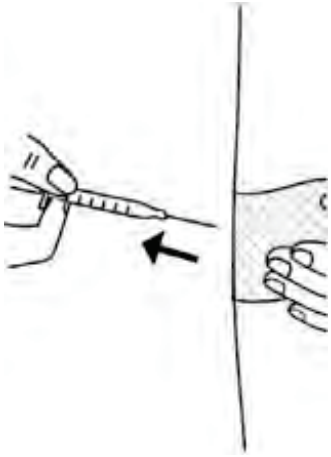


Figure 22

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:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
U.S. License Number 1760
NDC 61755-001-01

V 4.0

Principal Display Panel - Vial Carton

NDC 61755-001-01

Arcalyst®

(rilonacept)

Injection for Subcutaneous Use

220 mg sterile powder for reconstitution

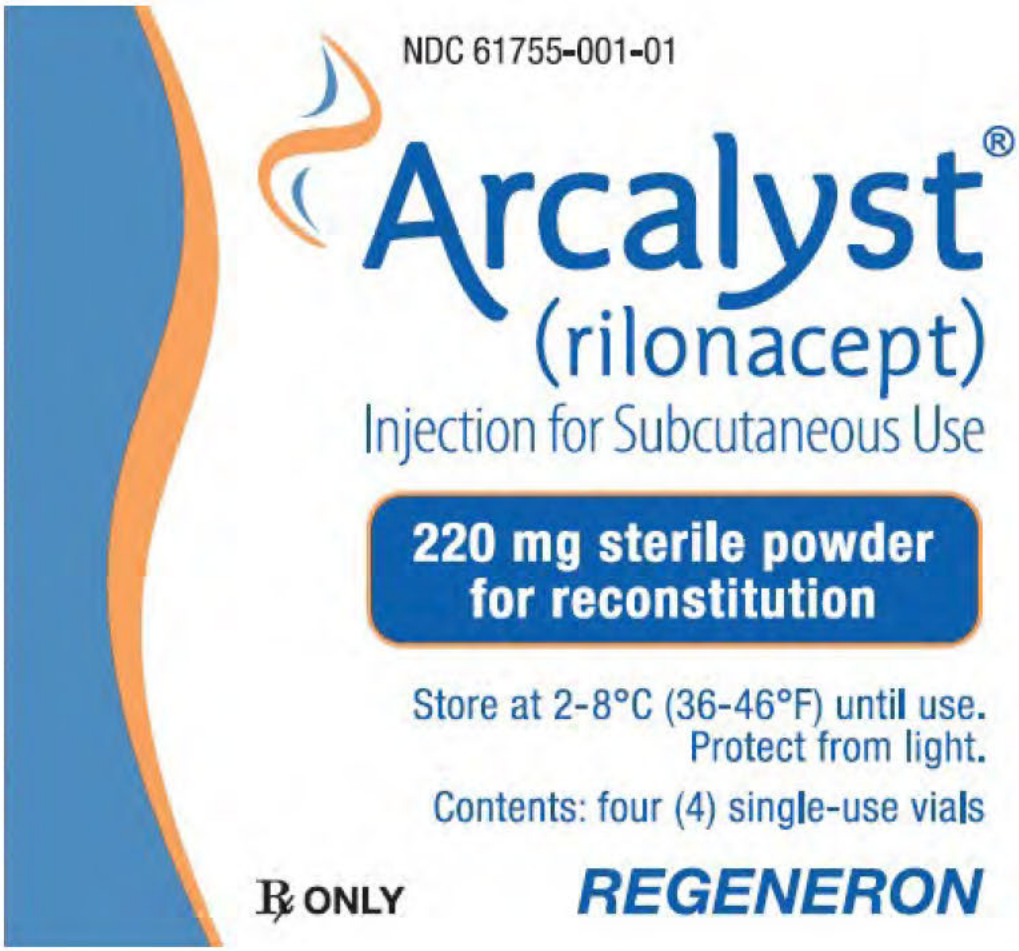
Store at 2-8°C (36-46°F) until use.

Protect from light.

Contents: four (4) single-use vials

Rx ONLY

REGENERON



ARCALYST

rilonacept injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61755 001

Route of Administration	SUBCUTANEOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
rilonacept (UNII: 8K80YB5GMG) (rilonacep UNII:8K80YB5GMG)	rilonacep	160 mg in 2 mL

Inactive Ingredients

Ingredient Name	Strength
Histidine (UNII: 4QD397987E)	
Arginine (UNII: 94ZLA3W45F)	
Polyethylene glycol 3350 (UNII: G2M7P15E5P)	
Sucrose (UNII: C151H8M554)	
Glycine (UNII: TE7660XO1C)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61755 001 01	4 in 1 CARTON	03/24/2008	
1		2 mL in 1 VIAL, SINGLE USE; Type 0: No a Combina ion Produc		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125249	02/27/2008	

Labeler - Regeneron Pharmaceuticals, Inc. (194873139)

Establishment

Name	Address	ID/FEI	Business Operations
Regeneron Pharmaceu icals, Inc.		945589711	ANALYSIS(61755 001) , API MANUFACTURE(61755 001) , LABEL(61755 001)

Appendix 3: Quality of Life Instrument

PROMIS Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global06r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Scale v1.2 – Global Health

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

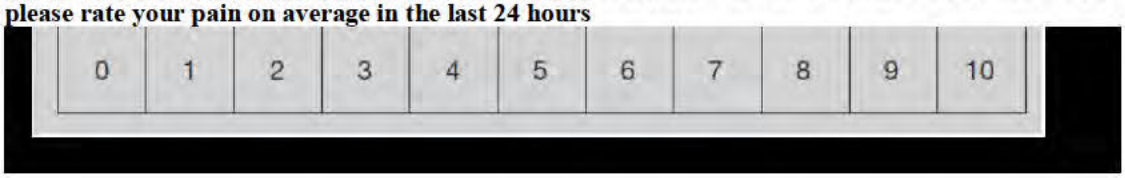
How would you rate your pain on average? ..... ☐ 0 **No pain** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 **Worst pain imagiuable**

Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011).

Subjects will be asked to select the score that best describes their average level of 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 pain on average in the last 24 hours



CLINICAL STUDY PROTOCOL

An Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis

Protocol Number:	KPL-914-C001
EudraCT Number:	Not Applicable
Investigational Medicinal Product:	KPL-914 (rilonacept)
Phase:	Phase 2
Sponsor:	Kiniksa Pharmaceuticals, Ltd.
Medical Monitor:	[redacted]
Date of Protocol:	19 February 2019
Version of Protocol:	4.0 (Supersedes Version 3.0 dated 14 February 2018)

CONFIDENTIAL

1 Protocol Approval Signatures

1.1 Sponsor Signature

Protocol Title: An open-label pilot study of KPL-914 in recurrent pericarditis

Protocol Number: KPL-914-C001

This study will be conducted in compliance with the clinical study protocol, ICH Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatory

[redacted]

[redacted]

2 Investigator and Administrative Structure

Sponsor:	Kiniksa Pharmaceuticals, Ltd. [redacted]
Sponsor's Study Contact:	[redacted]
Sponsor's Medical Expert:	[redacted]
Drug safety/SAE-reporting:	[redacted]
Responsible CRO for Biostatistical Analysis:	[redacted]
CRO responsible for: Project Management, Monitoring, Quality Assurance, and Data Management:	[redacted]

3 Synopsis

Trial Number: KPL-914-C001
Trial Title: An open-label, pilot study of KPL-914 in recurrent pericarditis
Trial Centers: Approximately 15 sites
Development Phase: 2

Objective(s):

The study is comprised of 5 Parts.

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

Part 1:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914.

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

Part 2:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

Part 3:

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent RIP.

Part 4:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with symptomatic recurrent PPS both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with recurrent PPS treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with recurrent PPS.

Part 5:

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent recurrent PPS.

Methodology:

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

Enrollment into Part 1:

Subjects identified for participation in **Part 1** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode** before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a first **(index) episode** of acute pericarditis followed by at least **1 recurrent episode** of pericarditis prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Subjects with symptomatic RIP meeting the above diagnostic criteria may be enrolled into Part 1 only if the **CRP value at screening is > 1 mg/dL**.

Enrollment into Part 2:

Subjects identified for participation in **Part 2** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a first **(index) episode** of acute pericarditis followed by at least **1 recurrent episode** before the current enrollment-qualifying episode, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode** of pericarditis prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the eCRF.

Subjects with symptomatic RIP meeting the above diagnostic criteria but **without an elevated CRP level (i.e., ≤1mg/dl) at screening** may be enrolled into Part 2 **only if**, in the opinion of the investigator and in consultation with the Sponsor, **the low CRP value can be attributed to concomitant medications (e.g., corticosteroids) AND if there is evidence of pericardial inflammation by cardiac MRI** which has been confirmed by the MRI Core Laboratory.

Enrollment into Part 3:

Subjects identified for participation in **Part 3** in this trial will present with **corticosteroid-dependent** RIP, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes of pericarditis** and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for their RIP and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 3 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment into Part 4:

Subjects identified for participation in **Part 4** in this trial will present during a **symptomatic episode of recurrent PPS**, having previously experienced a **first (index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.
- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a first **(index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS prior to the **current enrollment-qualifying episode** of recurrent PPS and will record the criteria supporting this diagnosis in the eCRF.

In addition to meeting the above criteria for PPS, all subjects enrolled in Part 4 must have **a CRP value > 1 mg/dL at screening**.

Enrollment into Part 5:

Subjects identified for participation in **Part 5** in this trial will present with **corticosteroid-dependent** recurrent PPS, having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.
- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis

occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes** of PPS and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for the recurrent PPS and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 5 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment Process for All Parts:

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

Subjects included in Parts 1, 2 and 4 may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Subjects in Parts 3 and 5 must be receiving corticosteroids at the time of enrollment.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm study eligibility. At the SCV1, baseline subject and disease characteristics will be determined and captured in the eCRF. At Screening Visit 2 (SCV2) during the 24 - 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

After having met all the entry criteria during the Screening Period, the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 320 mg KPL-914 (2 x 160 mg) administered SC on Day 0, then 160 mg SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 4.4 mg/kg KPL-914 (2x 2.2 mg/kg; maximum total 320 mg) administered SC on Day 0, then 2.2 mg/kg (maximum 160 mg) administered SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject or will be administered to the subject by an adequately trained caregiver as an outpatient SC administration. Study center staff or a visiting study nurse will assess and record compliance with Study Drug administration

at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be administered at home or other non-clinic location or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits on Day 3 and at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the subject, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study-related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels [if applicable], etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF, and medication diary.

At the discretion of the Investigator, "Treatment Responders" will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 administration can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

Treatment response will be defined by the Investigator:

- Part 1: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit.
- Part 2: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal levels CRP, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 3: Absence of pericarditis flare and feasibility to taper corticosteroids.
- Part 4: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 5: Absence of pericarditis flare and feasibility to taper corticosteroids.

Weekly Study Drug administrations during the EP are by self-administration or by an adequately-trained caregiver, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis.

During the EP, the Investigator is encouraged to wean concomitant NSAIDs and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively taped (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering the EP (i.e., by Study Week 12) unless in the opinion of the Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. All medication changes must be recorded in source records and the eCRF. Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7/End of Trial Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing subject management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each subject and each Part.

Given the following occurrences, dosing may be halted or reduced in any Part of the study, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2 x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

Depending on treatment response observed with the 80 mg dose (or 1.1 mg/kg in subjects 6 years to <18years old), the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg (or 2.2 mg/kg in subjects 6 years to <18 years old) by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject immediately after dosing of study drug.

Number of Subjects:

Approximately up to a total of 40 subjects with RIP or recurrent PPS will be enrolled as study subjects across all Parts.

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

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria for All Parts

To be eligible to participate in the trial, a subject must meet all of the following criteria:

1. Has given consent (or assent, if applicable) and signed an Informed Consent Form (ICF) (or informed assent form, if applicable).
2. Male or female, of any ethnic origin.
3. 6 to 75 years of age, inclusive.
4. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days (although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability

is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.

5. If female of child-bearing potential, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
6. Is able to adequately maintain a medication diary.
7. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or changing exercise pattern) from the time of signature of the ICF (or informed assent form, if applicable) to the End-of-Trial Visit (Week 6).

Inclusion Criteria for Part 1:

8. Has a diagnosis of RIP based on the judgement of the Investigator.
9. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
10. Has had **at least one prior *recurrent episode*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
11. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
12. Has an **elevated CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 2:

13. Has a diagnosis of RIP based on the judgement of the Investigator.
14. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
15. Has had at least **one prior *recurrent episode*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
16. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
17. Has **CRP value < 1 mg/dL** at Screening, which in the opinion of the Investigator in consultation with the Sponsor, can be **attributed to concomitant medications**.
18. Has evidence of **pericardial inflammation by cardiac MRI** which has been confirmed by the MRI core imaging lab.

Inclusion Criteria for Part 3:

19. Has a diagnosis of RIP based on the judgement of the Investigator.
20. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
21. Has had **at least two prior *recurrent episodes*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
22. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
23. Is **"corticosteroid-dependent,"** in the judgement of the Investigator based on available data (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be withdrawn).

Inclusion Criteria for Part 4:

24. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.
25. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
26. Has had **at least one prior *recurrent episode*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
27. Has an **ongoing symptomatic episode** of recurrent PPS at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
28. Has an elevated **CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 5:

29. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.
30. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
31. Has had **at least two prior *recurrent episodes*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
32. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
33. Is "**corticosteroid-dependent**," in the judgement of the Investigator based on the available data, (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be

withdrawn).

Exclusion Criteria for all Parts:

A subject who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific excluded etiologies, including tuberculous, neoplastic, or purulent etiologies, post-myocardial infarction (early or late), thoracic trauma, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment within the 6-month period before dosing with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female subject who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A subject with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or physical exam. Have recent close contact with a person with active TB.
8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of the study.
10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.
11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.
12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks of Study Drug administration, or has been treated with intravenous (IV) antibiotics for an infection within 2 months of first Study Drug administration.

15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a subject is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 14 days prior to Study Drug administration. Rilonacept and anakinra could not have been discontinued due to lack of efficacy or due to safety.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Subject who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Subject who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

Test Products, Dosage, and Mode of Administration:

KPL-914 (rilonacept) will be provided in its commercially-available formulation as a lyophilized powder to be reconstituted for SC administration.

Subjects will receive a total of 6 doses of KPL-914 during the study active Treatment Period. Subjects who are considered to be "Treatment Responders" will be offered, at the discretion of the Investigator, participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued for a total duration of KPL-914 treatment of up to 24 weeks.

Adult subjects (≥ 18 years of age)

KPL-914 will be administered as an initial loading dose of 320 mg SC, delivered as two subcutaneous injections of 160 mg SC each on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks.

Pediatric subjects (6 to <18 years of age)

KPL-914 will be administered with an initial loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as two subcutaneous injections of 2.2 mg/kg each with a maximum single-injection volume of 2 mL. Dosing will continue with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection of up to 2 mL as outpatient self-administration or administered by an adequately trained caregiver, for 5 subsequent weeks.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

Concomitant Medication

- There is no wash-out of concomitant therapy (NSAIDs/colchicine/corticosteroids) during the Screening Period of the study.
- For the duration of the Treatment Period, concomitant pericarditis medications (e.g., NSAIDs, colchicine and corticosteroids), if used, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAIDs, colchicine, and/or corticosteroid dose is medically necessary, the NSAID, colchicine and/or corticosteroid dose can be down-titrated according to standard of care paradigms in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.
- Opioid analgesics, non-narcotic (non-NSAID) analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF.
- Medical management of pericarditis during the EP is based on Investigator discretion. For example, Investigators may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status
- Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF.
- Prohibited concomitant medicines: Other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.

Duration of Treatment:

The Study Drug will be administered for 6 weeks in the base study Treatment Period.

"Treatment Responders" will be offered participation in an optional 18-week EP at the discretion of the Investigator.

Total subject participation is expected to last for up to 171 days for those that also participate in the 18-week EP.

Efficacy Measures:

- Clinical laboratory analyses (e.g., CRP).
- Pericarditis symptoms (i.e., pain) using a 11-point NRS (Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain)
- Echocardiogram (pericardial effusion)
- ECG (for pericarditis diagnostic findings)
- Pericarditis signs (e.g., fever, pericardial rub)
- Pericardial inflammation as determined by cardiac MRI (optional assessment for Parts 1, 3, 4, 5; mandatory for Part 2)
- Quality of life (QoL) questionnaire (Appendix 3).

Safety Measure(s):

Safety endpoints for this study include frequency and severity of AEs and SAEs, clinical laboratory analyses (including safety laboratory measurements, anti-drug antibodies, etc.), vital sign measurements, ECGs, and physical examination findings.

Other Measure(s):

[redacted]

Overview of Trial Design

Trial Periods (all Parts)

1. Prescreening Period: Prior to enrollment, potential subjects may enter an optional prescreening period after signing a Prescreening ICF (or prescreening informed assent, if applicable) to confirm the diagnostic workup and to allow monitoring for symptoms and inflammatory markers (CRP, ESR, etc) while concomitant pericarditis medications may be managed by the Investigator or their clinician according to standard of care.
2. Screening Period: The Screening Period starts with the signing of the full study ICF (or informed assent form, if applicable) (SCV1) and may last for up to 3 days (72 hours) until SCV2. At SCV1, baseline subject and disease characteristics will be determined. At Screening Visit 2 [SCV2]), within the 24 – 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data. Under special circumstances, the Investigator in consultation with the Sponsor

can combine SCV1 and SCV2. The end of the Screening Period coincides with the start of the Treatment Period (Day 0 Visit).

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

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

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

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

   Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject.

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

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

4. Extension Period (EP): The EP is defined as the 18 weeks following the Treatment Period. Subjects who are considered to be "Treatment Responders" will be, at the discretion of the Investigator, offered participation in an optional 18-week EP, in which weekly administration of open-label KPL-914 may be continued for a total duration of 24 weeks. The weekly KPL-914 doses will be by self-administration or administered by adequately trained caregiver, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits will continue on a monthly basis. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and

discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF

Unscheduled clinic visits can be scheduled any time as determined by the Investigator/upon subject request. In addition, Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed.

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

Statistical Methods:

Each Part will be analyzed separately and per the analysis populations below, to be finalized in the Statistical Analysis Plan to be provided separately.

Analysis Populations (each Part)

The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (e.g., NSAIDs, colchicine, corticosteroids) according to study protocol without a major protocol violation. The Safety Population will be the same as the mITT Population.

General Methods

Because of the small sample size no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or analysis group. For categorical endpoints, summary statistics will be calculated and presented for each treatment and/or analysis group. Under certain circumstances, if appropriate in the context of statistical methodologies, the results of certain similar Parts might be pooled for greater statistical precision in determining therapeutic response or safety.

Further details, including, for example, the process to be followed for reviewing individual pericarditis symptomatology endpoints to be used in the construction of a composite primary endpoint for subsequent trials, will be provided in the Statistical Analysis Plan (SAP).

Primary Endpoints:

Part 1

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

Part 2

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

Part 3

Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent RIP.

Part 4

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

Part 5

Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent recurrent PPS.

[redacted]

Table 1: Schedule of Evaluations

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

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

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

Trial Period →	**Pre-screening Period**	**Run-In Period (Up to 3 days)**			**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →		**Day -3 to Day 0[a]**		**Day 0[b]**	**Day 3 [c]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial [c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 (Clinic)**	**Day 3 (Outpt)**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**N/A**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓						**Unscheduled Visits[u]**										
Investigator (or designee) phone call/virtual visit [v]					X	X	X		X	X	X		X (monthly)			

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

a. A second Screening visit (SCV2) should be performed within ~24h to 72h. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2. The last Screening and Day 0 procedures may be performed on the same day, but SCR procedures must be completed prior to Study Drug administration.

b. Subjects who do not complete the Treatment Period (withdraw consent or are discontinued before they have completed 6 weeks treatment), must be asked to complete the procedures specified at the EoT Visit.

c. Day 3 will occur ± 1 day after Day 0. Weekly intervals refer to 7 ± 1 days. The interval between Study Drug administrations must be at least 5 days.

d. Subjects should return for an optional Interval Evaluation Visit at the clinic between approximately Week 3 and 4, as determined by the Investigator.

e. Including age at first attack, number of previous attacks, and duration of attacks.

f. Drug administration training of subjects is performed at Visit 1. Study Drug will be administered in the Study Site/Clinic at Visit 1. Study Drug administrations are performed by the subjects (self-administration) or by an adequately trained caregiver on Visits (Outpatient) 2, 3, 4, 5, and 6. Participation in the Extension Phase (optional) is determined at the Week 6/EoT Visit 7 by the Investigator. Subjects who are eligible and who are willing to participate will be consented during EoT Visit 7 at the Study Site/Clinic. Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Study Site/Clinic (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7 relative to the timing of weekly dosing. Timing for dose administration is per direction of the Investigator based upon the prescribing information and study-specified dosing intervals. Continued weekly Study Drug treatment during the EP will be outpatient administration.

g. Full physical examination including assessment of pericardial rub.

h. Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.

i. Central 12-lead ECG and echocardiogram reading (including assessment of pericardial effusion). At SCV2 only the ECG will be obtained. The Study Site/Clinic reading of the ECG and the ECHO at the time of the examination will be used by the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory.

j. Optional in Parts 1, 3,4 and 5. Required for Part 2.

k. At the SCV1, information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured. During the Treatment Period, changes in concomitant medication since the last Study Site/Clinic visit will be documented. During the EP, changes in pericarditis/concomitant medication will be assessed at Study Site/Clinic Visits and in monthly outpatient phone calls/virtual visits.

l. Biomarker, pharmacokinetics (PK) and anti-rilonacept antibody analysis samples will be drawn in all subjects and archived for future testing. . During each Visit at the Study Site/Clinic a sample for CRP will be obtained and sent to the central laboratory (or designated qualified laboratory) for analysis; at each Outpatient Visit; blood for central laboratory measurement of CRP will be obtained as described in the Laboratory Manual.

m. Hematology, chemistry, and urinalysis will be performed at the Study Site/Clinic laboratories, and results when available will be entered into the eCRF with appropriate reference values. Serology (HCVAb, HBsAg, HBcAb, HBsAb and HIV) and urine drug screen will be performed at SCV1 only. Hematology and urinalysis will not be performed at SCV2.

n. To be eligible to continue in the trial, a negative urine pregnancy test must be documented at the SCV1. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.

o. All AEs occurring after the subject receives the first dose of Study Drug will be captured in source records and eCRF.

p. At the SCV1, the Investigator or designee will instruct the subject about the use of the medication diary. The subject will be asked to complete entries into the medication diary during the Screening Period and Treatment Period. Only information on pain/rescue medication will be collected. Other concomitant treatments/medications are not required to be captured.

q. At the SCV2 and all subsequent visits at the Study Center, the Investigator or designee will review the Diary entry information to verify subject compliance. If the last screening visit occurs at a different day than Visit 1, the review will also be performed at Visit 1. Diary documentation will end at the End-of-Trial visit (Visit 7).

r. Subject assessment of pericardial pain using a validated 11-point Numerical Rating Scale. The assessment will be performed on-site during clinic visits and as part of a telephone call/virtual visit during outpatient treatment weeks. If the last screening visit occurs at a different day than Visit 1, the assessment will also be performed at Visit 1, prior to Study Drug treatment. All the assessments must occur prior to study drug injection.

s. Adult subjects only. Subject global assessment of overall well-being will be assessed using a validated QoL Questionnaire (see Appendix 3). The assessment will be performed on-site during clinic visits. If SCV2 occurs at a different day than Visit 1 (Day 0), the global assessment will also be performed at Visit 1, prior to Study Drug administration.

t. Subjects may return for an optional EP Interval Evaluation Visit at the clinic between Week 15 and 20 (8 to 13 weeks after Visit 7), as determined by the Investigator.

u. Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a “Treatment Failure” may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

v. At weekly Investigator (or designee) phone calls/virtual visits during the Treatment Period, Study Drug compliance, medication diary compliance, and laboratory sample collection will be checked. The subjects will be asked using non-leading questions about any AEs occurring since the last contact (phone call/virtual visit or site visit), and NRS pain assessment will be performed. Investigator (or designee) phone calls/virtual visits will be performed monthly during the during the EP to perform NRS pain assessments, collect AE information, and review pericarditis/concomitant medications. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits.
w. During the Extension Period, Study Drug treatment is weekly by self-administration, and the study nurse visits to the home and Investigator (or designee) phone calls/virtual visits are monthly.
x. Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling and subject NRS pericardial pain rating must be repeated prior to Study Drug dosing.
y. Per Standard of Care.
z. Adult subjects only. The dosing preparation and administration questionnaire must be completed in the presence of Study Staff (via virtual visit) or visiting nurse.
aa. This lab will be drawn only during the first monthly Extension Period visit.

4 Table of Contents

List of In-text Tables

List of In-text Figures

5 List of Abbreviations and Definition of Terms

AcP	accessory protein
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
b.p.m.	beats per minute
BUN	blood urea nitrogen
CAPS	Cryopyrin Associated Periodic Syndrome
CDC	Centers for Disease Control
CHO	Chinese hamster ovary
CI	confidence interval
CRO	contract research organization
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
CTAD	citrate, theophylline, adenosine, dipyridamole
EoT	End-of-Trial
EP	Extension Period
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FCAS	Familial Cold Auto-Inflammatory Syndrome
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IL-1	Interleukin-1
IL-1RA	IL-1 receptor antagonist
IL-1RI	IL-1 type I receptor
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	intravenous
kDa	kilo Dalton
KPL-914	Study Drug; nomenclature of rilonacept (ARCALYST®) in this protocol
LDH	lactate dehydrogenase
MCH	mean cell hemoglobin
MCHC	MCH concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mITT	modified intent to treat
MWS	Muckle-Wells Syndrome

NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drugs
PI	Prescribing Information
PP	per protocol
PPD	purified protein derivative
PPS	post pericardiotomy syndrome
PRO	patient-reported outcome
PT	prothrombin
PTT	prothrombin time
QoL	quality of life
RBC	red blood cell
RIP	recurrent idiopathic pericarditis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCR	Safety Review Committee
SCV	screening visit
SD	standard deviation
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	serious and unexpected and related adverse reaction
TB	tuberculosis
[redacted]	[redacted]
TNF	tumor necrosis factor
US	United States of America
WBC	white blood cells
WHO	World Health Organization
WFI	water for injection

6 Introduction

Pericarditis accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction (Khandaker et al, 2010). 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). Diagnosis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic (ECG) changes, pericardial effusion, or elevated markers of inflammation (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Imazio et al, 2014). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define a pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-elevation or PR depression on ECG, and pericardial effusion (new or worsening). Elevations of 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 a common complication of acute pericarditis and affects 20–30% of patients (Imazio, 2014). It is characterized by the recurrence of signs and symptoms of pericarditis after a symptom-free interval of at least 4-6 weeks (Adler et al, 2015). The underlying pathogenesis of recurrent idiopathic pericarditis (RIP) remains unclear, although immune-mediated mechanisms are believed to play a key role in the pathogenesis (Imazio et al, 2005). A growing body of evidence suggests that these immune responses consist of both pathogenic autoimmune and auto-inflammatory processes (Cantarini et al, 2015; Doria et al, 2012). The presence of pro-inflammatory cytokines in the pericardial fluid of RIP patients lends direct support to both an autoimmune and/or auto-inflammatory etiopathogenesis (Pankuwait et al, 2000).

Currently available treatments for RIP include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids (Lilly, 2013). Aspirin and other NSAIDs are the first-line approach. Because high doses are often required, consideration should be given to gastric protection therapy. Colchicine is another mainstay therapy for RIP and is commonly used with NSAIDs, but a subset of patients has refractory symptoms and significant gastrointestinal side effects, including severe diarrhea, leading to discontinuation for intolerability. Glucocorticoids should be prescribed only to patients with idiopathic pericarditis who are refractory or intolerant to treatment with NSAIDs plus colchicine, because of the side effects associated with long-term corticosteroid therapy and because of a high rate of relapse when the corticosteroid is tapered or stopped (Maisch et al, 2004; Imazio, 2005; Lotrionte et al, 2010), particularly in the absence of colchicine treatment. Patients with refractory symptoms can be particularly challenging to manage, and multiple immunosuppressive medications have been used without consistent benefit (Baskar et al, 2016). In addition, a subset of corticosteroid dependent RIP subjects are also in need for new treatment options due to the side effects of high dose and/or long term corticosteroid use including osteoporosis, diabetes, weight gain and increased risk for infections.

Post-pericardiotomy syndrome (PPS) is an inflammatory syndrome involving pericardium which occurs in a subgroup of patients who have undergone cardiothoracic surgery. It is reported in approximately 9% of adult patients (Lehto el al 2015), and more commonly in pediatric/adolescent population where up to 28% of patients undergoing surgical closure of atrial septal defect were reported to develop PPS (Hechching et al, 2015).

PPS is characterized by fever, pericardial or pleuritic pain, pleural effusion or pericardial effusion with elevated serum CRP. It is associated with significant morbidity, and the leading complications include tamponade and constrictive pericarditis. Aspirin, NSAIDs, and colchicine are the mainstay of the current treatment for PPS. Although corticosteroids are used for refractory cases of PPS, they are associated with significant side effects when used for long-term treatment of this disease. Similar to RIP, there is an unmet need for new therapies, especially for the patients experiencing recurrent PPS episodes despite currently

available treatments or depend on chronic corticosteroid treatment to control their disease. (Tamarappoo, 2016).

Interleukin-1 (IL-1) is a key cytokine that drives the pathophysiology of many inflammatory processes. It is implicated as a causative factor in various inflammatory human diseases. Although the pathogenic mechanism of auto-inflammatory disease is not completely understood, there is a growing body of evidence that IL-1 may be a primary driver of the symptomology and that targeting this cytokine may provide important benefits (Hoffman & Patel, 2004).

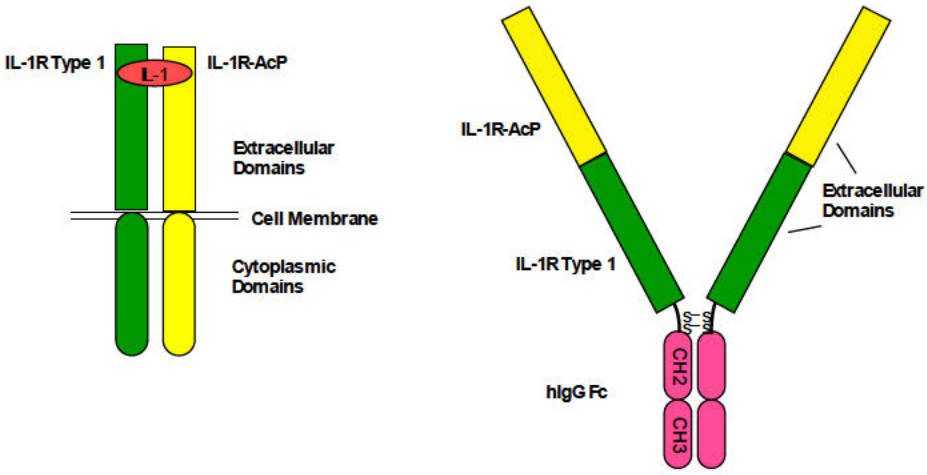
[redacted]

Rilonacept (marketed in the US under the trade name ARCALYST®; referred to as KPL-914 in this investigational study protocol) blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1α and IL-1β and prevents its interaction with IL-1 cell surface receptors. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1RA are 0.5 pM, 1.4 pM and 6.1 pM, respectively. By comparison, the IL-1 Type I receptor (IL-1RI) alone has approximately 1 nM affinity.

Rilonacept (KPL-914) is a recombinant fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human immunoglobulin G (IgG)1. Rilonacept incorporates in a single molecule the extracellular domains of both receptors required for IL-1 signaling: the IL-1RI and the IL-1 accessory protein (AcP) (Figure 1). Rilonacept was created by fusing the sequences encoding the extracellular domains of the AcP, IL-1RI, and the human Fc segment inline without any intervening linker sequences. The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept is expressed in Chinese hamster ovary (CHO) cells and is purified with a series of chromatographic and filtration techniques.

The total molecular weight is ~251 kDa, of which 80% is protein (201 kDa) and 20% is carbohydrate (50 kDa).

Figure 1: Schematic of rilonacept (KPL-914)



Rilonacept was developed by Regeneron Pharmaceuticals, Inc. and is approved with the tradename ARCALYST® in the US for the treatment of Cryopyrin Associated Periodic Syndrome (CAPS), including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

Rilonacept is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. For subcutaneous (SC) administration, rilonacept is manufactured in a dosage form containing 160 mg per vial. The lyophilized powder is reconstituted with 2.3 mL of sterile Water for Injection (WFI) and drug is delivered in 2 mL at a concentration of 80 mg/mL. Clinical dosing (e.g., in CAPS) initiates with a loading dose of 320 mg SC followed by 160 mg administered SC weekly. A lower dose of 80 mg weekly (initiated with a 160 mg loading dose) was also tested in Phase 3 clinical trials in gout.

For a detailed review of the available rilonacept data, please refer to the Investigator Brochure and the ARCALYST® package insert.

Kiniksa Pharmaceuticals Ltd. (Kiniksa) is now developing rilonacept for the treatment of RIP (Rilonacept will be referred to as KPL-914 in this investigational study protocol). In this first pilot study in subjects with RIP, improvement of pericarditis symptomatology with KPL-914 administration as well as the safety and dose relationships will be assessed. Commercially-available rilonacept (ARCALYST®) will be used in the study.

The nonclinical development program for rilonacept (ARCALYST®) demonstrated biological activity and adequate safety across toxicity studies (Appendix 2: ARCALYST® Prescribing Information).

The most common adverse reactions reported by patients with CAPS treated with ARCALYST® are injection-site reactions and upper respiratory tract infections. Hypersensitivity reactions associated with rilonacept administration have been rare.

Refer to the ARCALYST® PI for Important Safety Information regarding rilonacept (Appendix 2: ARCALYST® Prescribing Information).

Based on its IL-1-antagonistic properties, its weekly-dosing pharmacokinetics, and its well-understood safety profile as shown in patients with CAPS, rilonacept (KPL-914) is a promising candidate for the treatment of RIP.

7 Study Objectives

The study is comprised of 5 Parts.

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

- Part 4 enrolls symptomatic subjects with recurrent post pericardiotomy syndrome (PPS) with an elevated marker of systemic inflammation (CRP > 1mg/dL).
- Part 5 enrolls subjects with corticosteroid-dependent recurrent PPS not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis.

7.1 Part 1

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914.

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

7.2 Part 2

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with RIP both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with RIP.

7.3 Part 3

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent RIP.

7.4 Part 4:

Primary Objective:

To collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with symptomatic recurrent PPS both at baseline and on treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

Secondary Objectives:

To explore the time course to improvement of pericarditis parameters in symptomatic subjects with recurrent PPS treated with KPL-914

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in symptomatic subjects with recurrent PPS.

7.5 Part 5:

Primary Objective:

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

Secondary Objectives:

To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.

To evaluate the safety of KPL-914 in subjects with corticosteroid-dependent recurrent PPS.

8 Investigational Plan

8.1 Overall Study Design and Plan

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

Enrollment into Part 1:

Subjects identified for participation in **Part 1** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 1 recurrent episode** before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]).

- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode of pericarditis** prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the electronic case report form (eCRF).

Subjects with symptomatic RIP meeting the above diagnostic criteria may be enrolled into Part 1 only if the **CRP value at screening is > 1 mg/dL**.

Enrollment into Part 2:

Subjects identified for participation in **Part 2** of this trial will present during a **symptomatic episode of RIP**, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 1 recurrent episode** before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by at least **1 recurrent episode** of pericarditis prior to the **current enrollment-qualifying episode** of RIP and will record the criteria supporting this diagnosis in the eCRF.

Subjects with symptomatic RIP meeting the above diagnostic criteria but **without an elevated CRP level (i.e., ≤1mg/dl) at screening** may be enrolled into Part 2 **only if**, in the opinion of the investigator and in consultation with the Sponsor, **the low CRP value can be attributed to concomitant medications (e.g., corticosteroids) AND if there is evidence of pericardial inflammation by cardiac MRI** which has been confirmed by the MRI Core Laboratory.

Enrollment into Part 3:

Subjects identified for participation in **Part 3** in this trial will present with **corticosteroid-dependent** RIP, having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on electrocardiogram (ECG), and pericardial effusion (new or worsening). Additional supportive findings would have included elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
- *Recurrence* of RIP would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute pericarditis followed by **at least 2 recurrent episodes of pericarditis** and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for their RIP and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 3 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment into Part 4:

Subjects identified for participation in **Part 4** in this trial will present during a **symptomatic episode of recurrent PPS**, having previously experienced a **first (index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS before the **current enrollment-qualifying episode**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.

- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a first **(index) episode** of acute PPS followed by **at least 1 recurrent episode** of PPS prior to the **current enrollment-qualifying episode** of recurrent PPS and will record the criteria supporting this diagnosis in the eCRF.

In addition to meeting the above criteria for PPS, all subjects enrolled in Part 4 must have **a CRP value > 1 mg/dL at screening**.

Enrollment into Part 5:

Subjects identified for participation in **Part 5** in this trial will present with **corticosteroid-dependent** recurrent PPS, having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes**, using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference:

- The *index episode* of acute pericarditis would have been characterized by an inflammatory pericardial syndrome with at least 2 of the following 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion, or elevated CRP.
- *Recurrence* of PPS would have been characterized as a subsequent episode of pericarditis occurring after a symptom-free interval of 4-6 weeks or longer.

For the purposes of this study, the Investigator will determine, based on his/her judgement of the available data, if a subject has met these criteria for having previously experienced a **first (index) episode** of acute PPS followed by **at least 2 recurrent episodes** of PPS and will record the criteria supporting this diagnosis in the eCRF.

Subjects who are taking corticosteroids for the recurrent PPS and who are not currently experiencing symptoms which, in the opinion of the Investigator, would meet the above diagnostic criteria for a flare may be enrolled into Part 5 only if, in the opinion of the Investigator and in consultation with the Sponsor, they are considered to be **"corticosteroid- dependent"** (i.e.; the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

Enrollment Process for All Parts:

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

Subjects included in Parts 1, 2 and 4 may be receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), and/or colchicine, and/or oral corticosteroid treatment in any combination, provided the dosages of these medications have been stable for at least 7 days, although stable doses for a shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Subjects in Parts 3 and 5 must be receiving corticosteroids at the time of enrollment.

Baseline therapy and disease characteristics will be determined during a Screening Period of up to 72 hours, as needed, to confirm study eligibility. At the SCV1, baseline subject and disease characteristics will be determined and captured in the eCRF. At Screening Visit 2 (SCV2) during the 24 - 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2, and the subject can proceed directly to the Day 0 dosing visit.

After having met all the entry criteria during the Screening Period, the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 320 mg KPL-914 (2 x 160 mg) administered SC on Day 0, then 160 mg SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 4.4 mg/kg KPL-914 (2x 2.2 mg/kg; maximum total 320 mg) administered SC on Day 0, then 2.2 mg/kg (maximum 160 mg) administered SC weekly for 5 additional doses.

The first Study Drug dose on Day 0 will be administered at the Study Site/Clinic (Visit 1). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject or will administered to the subject by an adequately trained caregiver as an outpatient SC administration. Study center staff or a visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End of Trial, Study Drug may be administered at home or other non-clinic location or administered at the study site. Weekly assessments of safety and treatment response, including administration of the 11-point NRS instrument to assess pericardial pain, will be done at the Study Site/Clinic at Visit 1 (Day 0) and Visit 7 (Week 6/End-of-Trial), and via Investigator (or designee) phone calls/ virtual visits on Day 3 and at Weeks 2 to 5 (Visits 2 to 5). Weekly outpatient blood samples for central laboratory testing will be collected at the Study Site/Clinic, or at a qualified laboratory site in the vicinity of the subject, or by a visiting study nurse.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. During this visit a full assessment including physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed as well as the recording of adverse events (AEs) and other study related assessments as needed.

At any time point during the Treatment Period, subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit, in which select or comprehensive clinical assessments can be performed. Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels [if applicable], etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and may receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Subjects participating for the complete length of the active study Treatment Period will receive a total of 6 doses of KPL-914. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, eCRF and medication diary.

At the discretion of the Investigator, "Treatment Responders" will be offered participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

Treatment response will be defined by the Investigator:

- Part 1: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit.
- Part 2: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal levels CRP, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 3: Absence of pericarditis flare and feasibility to taper corticosteroids.
- Part 4: A clinically significant reduction in pericardial pain using the 11-point NRS, normal or near normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit
- Part 5: Absence of pericarditis flare and feasibility to taper corticosteroids.

Weekly Study Drug administrations during the EP are by self-administration or by an adequately trained caregiver, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits are to continue on a monthly basis.

During the EP, the Investigator is encouraged to wean concomitant NSAIDs and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively taped (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering the EP (i.e., by Study Week 12) unless in the opinion of the Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. All medication changes must be recorded in source records and the eCRF. Investigators are encouraged to invite subjects to the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after the Visit 7/End of Trial Visit) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram (ECHO), and laboratory testing can be performed at the discretion of the Investigator.

Available safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator as part of ongoing subject management. A Safety Review Committee (SRC) including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects, considering trends across each subject and each Part.

Given the following occurrences, dosing may be halted or reduced in any Part of the study, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2 x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

Depending on treatment response observed with the 80 mg dose (or 1.1 mg/kg in subjects 6 years to <18years old), the weekly dose administered to either these subjects or subsequent subjects may be changed back to 160 mg (or 2.2 mg/kg in subjects 6 years to <18 years old) by the Investigator in collaboration with the Sponsor. For any given subject, the KPL-914 dose level received at the end of the Treatment Period should be continued into the EP (if administration is continued); however, a change in the KPL-914 dose level during the EP for any individual subject can be made at the discretion of the Investigator in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject immediately after dosing of study drug.

Figure 2: Overview of Trial Design

The study will be conducted in compliance with Good Clinical Practice regulations and other regulatory requirements.

8.2 Discussion of Study Design

Clinical information from the development of rilonacept in CAPS (ARCALYST®), the mode of action of rilonacept, as well as the inflammatory nature of idiopathic pericarditis and PPS suggest that rilonacept (KPL-914) may safely and effectively resolve recurrent pericarditis flares in idiopathic pericarditis and PPS.

[redacted]

The rationale for this pilot study is to collect time-course to pericarditis improvement data and safety information for up to 2 dose levels of KPL-914 (i.e., 160 mg and 80 mg, and corresponding pediatric doses) when administered to subjects with RIP and recurrent PPS. The study aims to provide data to support the design of future clinical studies with KPL-914 in RIP and recurrent PPS: in particular to inform inter-and intra-subject variability in CRP and NRS measurements, the time course of treatment response, and the dosage(s) of KPL-914 to be evaluated in a pivotal Phase 3 clinical trial.

The pilot study will encompass 5 Parts which enroll different subsets of subjects with RIP and recurrent PPS. It will allow evaluation of treatment responses to rilonacept in subjects with broad spectrum of recurrent pericarditis refractory to standard therapy or requiring corticosteroids to control their disease activity. Part 1 will continue to enroll subjects with symptomatic RIP and elevated CRP (>1mg/dL).

Part 2 will enroll subjects with symptomatic RIP with CRP levels (=<1mg/dL) which can be attributed to concomitant medication (e.g., corticosteroids) but with evidence of pericardial inflammation on cardiac MRI. During a corticosteroid taper a scenario may occur where the previously-suppressed pericardial inflammation begins to reactivate and symptoms begin to flare as a function of this localized inflammation, but at the same time systemic markers of humoral activation (e.g., CRP production in the liver) are still suppressed as a consequence of the intermediate steroid dose. These criteria will assure the presence of pericardial disease activity despite the absence of elevated CRP.

Part 3 will enroll corticosteroid dependent RIP subjects (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn). Corticosteroid-dependent RIP subjects are also in need for new treatment options due to the side effects of high dose and/or long-term corticosteroid use including osteoporosis, diabetes, weight gain and increased risk for infections.

Part 4 will enroll subjects with symptomatic recurrent PPS with elevated CRP (>1mg/dL).

Part 5 will enroll subjects with corticosteroid dependent recurrent PPS subjects.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

Approximately up to a total of 40 subjects with RIP or recurrent PPS will be enrolled as study subjects across all Parts.

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

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and other research in this patient population.

8.3.2 Inclusion Criteria

Inclusion Criteria for All Parts

To be eligible to participate in the trial, a subject must meet all of the following criteria:

1. Has given consent (or assent, if applicable) and signed an Informed Consent Form (ICF) (or informed assent form, if applicable).
2. Male or female, of any ethnic origin.
3. 6 to 75 years of age, inclusive.
4. If used, has received NSAIDs, and/or colchicine and/or corticosteroids (in any combination) at stable dose levels for at least 7 days prior to Study Drug dosing (although stable doses for a shorter period will be acceptable if, in the opinion of the Investigator in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values) and is anticipated to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.
5. If female of child-bearing potential, must be nonpregnant and nonlactating and must agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
6. Is able to adequately maintain a medication diary.
7. Agrees to refrain from making any new, major life-style changes that may affect pericarditis symptoms (e.g., starting a new diet or change in exercise pattern) from the time of signature of the ICF to the End-of-Trial Visit (Week 6).

Inclusion Criteria for Part 1:

8. Has a diagnosis of RIP based on the judgement of the Investigator.
9. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
10. Has had **at least one prior recurrent episode** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
11. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
12. Has an **elevated CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 2:

13. Has a diagnosis of RIP based on the judgement of the Investigator.
14. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG,

and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

15. Has had at least **one prior *recurrent episode*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
16. Has **an ongoing symptomatic episode** of pericarditis at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
17. Has **CRP value < 1 mg/dL** at Screening, which in the opinion of the Investigator in consultation with the Sponsor, can be **attributed to concomitant medications**.
18. Has evidence of **pericardial inflammation by cardiac MRI** which has been confirmed by the MRI imaging core lab.

Inclusion Criteria for Part 3:

19. Has a diagnosis of RIP based on the judgement of the Investigator.
20. Has previously had an ***index (first) episode*** of pericarditis which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference -- i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supportive findings could include elevations of markers of inflammation (i.e., CRP, ESR, or WBC count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).
21. Has had **at least two prior *recurrent episodes*** of pericarditis, in the judgement of the Investigator, based upon the available diagnostic information.
22. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
23. Is **"corticosteroid-dependent,"** in the judgement of the Investigator based on available data (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be withdrawn).

Inclusion Criteria for Part 4:

24. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.
25. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
26. Has had **at least one prior *recurrent episode*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
27. Has an **ongoing symptomatic episode** of recurrent PPS at the time of study enrollment in the judgement of the Investigator, based upon the available diagnostic information.
28. Has an elevated **CRP** value (i.e., >1 mg/dL) at the time of Screening.

Inclusion Criteria for Part 5:

29. Has a diagnosis of recurrent PPS based on the judgement of the Investigator.

30. Has previously had an ***index (first) episode*** of PPS which, in the judgement of the Investigator based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, 2015) as a frame of reference, i.e., met at least 2 of the 5 clinical findings after cardiac surgery: fever without alternative causes, pericardial chest pain, pericardial rub, evidence for pericardial effusion with elevated CRP
31. Has had **at least two prior *recurrent episodes*** of PPS, in the judgement of the Investigator, based upon the available diagnostic information.
32. Is not currently (at Screening) experiencing symptoms which, in the judgment of the Investigator based on the available diagnostic information, would meet the diagnostic criteria for a flare of pericarditis.
33. Is "**corticosteroid-dependent**," in the judgement of the Investigator based on the available data, (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were to be withdrawn).

8.3.3 Exclusion Criteria

Exclusion Criteria for All Parts

A subject who meets any of the following criteria will not be eligible to participate in the trial:

1. Has a diagnosis of pericarditis that was secondary to specific excluded etiologies, including tuberculous, neoplastic, or purulent etiologies, post-myocardial infarction (early or late), thoracic trauma, myocarditis, or systemic diseases including autoinflammatory diseases, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.).
2. Has a history of immunodepression, including a positive human immunodeficiency virus test result.
3. Has received treatment within the 6-month period before dosing with any systemic immunosuppressants (other than, for example, corticosteroids or mycophenolate) which, in the opinion of the Investigator (in consultation with the Sponsor), may interfere with the study endpoints.
4. Currently receiving other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) or tumor necrosis factor (TNF) inhibitors.
5. Has a history of myeloproliferative disorder, demyelinating disease, or symptoms suggestive of multiple sclerosis.
6. Female subject who is pregnant or lactating or who does not agree to use an effective method of contraception, e.g., hormonal contraception or double-barrier birth control.
7. Has a history of active or latent treated tuberculosis (TB), or had a positive QuantiFERON (QFT-TB G In-Tube) test result, or a chest radiograph during the 3 months prior to Study Drug dosing suggestive of prior TB infection. A subject with a positive purified protein derivative (PPD) test result (≥5-mm induration) after the first attack of pericarditis is excluded unless he/she has had either a negative chest x-ray result or a negative QuantiFERON test result. 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, night sweats) upon review of medical history and/or physical exam. Have recent close contact with a person with active TB.
8. Chest radiograph (or historic results within 3 months of SCV1) that shows evidence of malignancy or any abnormalities suggestive of prior TB infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This does not include non-caseating granulomata.
9. Has received immunization with a live (attenuated) vaccine within 12 weeks before the start of the study.

10. Has history of or positive or intermediate results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at SCV1.
11. Has an estimated glomerular filtration rate (eGFR) <30 mL/min.
12. Has a history of malignancy of any organ system within the past 5 years (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
13. 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.
14. Has had a serious infection, has been hospitalized for an infection, has been treated with oral antibiotics within 2 weeks, or has been treated with IV antibiotics for an infection within 2 months of first Study Drug administration.
15. Has had an organ transplant.
16. In the Investigator's judgement, has a history of alcoholism or drug/chemical abuse within 2 years prior to Study Drug administration.
17. Has a drug screen positive for amphetamines, cocaine, or phencyclidine or positive alcohol test at SCV1. Exceptions may be made if a subject is on an approved medication for a stable concomitant condition that explains the positive screen.
18. Has taken commercially-available rilonacept (ARCALYST®) or participated in a rilonacept clinical study during the 90 days before SCV1. Has used anakinra within 14 days (or 5 half-lives, whichever is longer) prior to Study Drug administration. Rilonacept and anakinra could not have been discontinued due to lack of efficacy or due to safety.
19. Has a history of hypersensitivity to rilonacept or to any of the excipients contained in the Study Drug.
20. Has received an investigational drug during the 30 days before SCV1 or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
21. In the Investigator's judgement, has any other medical condition that could adversely affect the subject's participation or interfere with study evaluations.
22. Subject who, in the opinion of the Investigator, is not likely to be compliant with the study protocol.
23. Subject who, in the opinion of the Investigator in consultation with the Sponsor, should not participate in this study.

8.3.4 Vaccination History and Immune status

IL-1 blockade may interfere with immune response to infections. Therefore, the Investigator should review the subject's vaccination history relative to the current medical guidelines for vaccine use. A recommended immunization schedule is available at the website of the Centers for Disease Control (CDC) (www.cdc.gov/vaccines/recs/scheduled/default.htm).

It is recommended that, prior to or shortly after initiation of therapy with KPL-914, subjects be brought up to date with all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In case a subject needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed (e.g., at the Study Site/Clinic) after the 6-week active Treatment Period. However, to minimize the potential confounding of KPL-914-related Adverse Experience reporting at initiation of KPL-914 dosing or measurements of CRP during the treatment period, vaccination should not be performed within the first 6 weeks after initiation of KPL-914 administration.

It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Administration of KPL-914 is prohibited within 12 weeks of having received a live (attenuated) vaccine. It is also possible that taking drugs that block IL-1 increases the risk of TB. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent TB infections before initiating therapy with KPL-914.

8.3.5 Removal of Subjects from Therapy or Assessments

Subjects reporting worsening of pericarditis symptoms or AEs may be brought into the Study Site/Clinic at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

Safety, tolerability, and efficacy data for each subject will be reviewed by the Investigator on an ongoing basis as part of subject management. An SRC including selected Investigator(s) and Sponsor representatives will review on a monthly basis (at a minimum) all available data for all subjects in all Parts, considering trends across each.

Given the following occurrences, dosing may be halted or the dose reduced, in accordance with an SRC recommendation, confirmed by the Sponsor:

- One or more subjects experience a serious and unexpected adverse event that is considered by the Investigator to be related to Study Drug (SUSAR), or 2 or more subjects experience similar severe (non-serious) and unexpected AEs that are considered by the Investigator to be related to Study Drug.

In addition, subjects may stop study treatment or may be withdrawn from treatment for any of the following reasons:

- Subject request. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment
- Use of non-permitted concurrent therapy
- Non-compliance
- Investigator request.

Treatment Failures or subjects who are withdrawn from the study for safety reasons will be replaced at the discretion of the Sponsor. Similarly, subjects who do not comply with the protocol or who withdraw from the study for other reasons can be replaced. The reason(s) for withdrawal will be documented in the source records and the eCRF.

Subjects withdrawing from the study during the Treatment Period will be asked to complete the End-of-Trial evaluations to document the status of their pericarditis disease progression at the time of withdrawal from treatment. Subjects will continue to be followed for vital status for the duration of intended treatment

to address informative censoring. Subjects withdrawing from the study during the EP will be asked to complete the Final Visit evaluations.

All reasonable efforts will be made to contact subjects who are lost to follow-up.

The Sponsor has the right to terminate the study at any time in case of safety concerns (e.g., SUSARs) or if special circumstances concerning the Investigational Medicinal Product (IMP) 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.

Pregnancy

Pregnant or lactating female subjects are excluded from study enrollment. While not explicitly stated in the rilonacept (ARCALYST®) PI (Appendix 2: ARCALYST® Prescribing Information), for the purposes of this experimental protocol, females of child-bearing potential (i.e., not postmenopausal and not sterilized) must use an active method of birth control during the course of the study, e.g., oral, implanted or injected contraceptive hormones, an intrauterine device, or a barrier method (e.g., diaphragm, condoms, spermicides).

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator without delay. If pregnancy is confirmed, the Investigator must notify the Sponsor within 24 hours and the subject must not receive (additional) Study Drug and must be discharged from the study. The subject must be asked regarding their willingness to complete the End-of-Trial Visit.

In the event that a subject is found to be pregnant after having received at least one Study Drug dose, the pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Instances of perinatal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment, will be reported to the Sponsor within 24 hours.

Full details will be recorded on the pregnancy form.

8.4 Investigational Medicinal Products

8.4.1 Investigational Medicinal Products Administered

During the Treatment Period, KPL-914 will be administered as an initial loading dose of 320 mg SC, delivered as two subcutaneous injections of 160 mg SC each on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks (18 years or older). Subjects aged 6 years to <18 years will receive an initial loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as two subcutaneous injections of 2.2 mg/kg each with a maximum single-injection volume of 2 mL. Dosing will continue with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection of up to 2 mL as outpatient administration or by an adequately trained caregiver, for 5 subsequent weeks.

Subjects will receive a total of 6 doses of KPL-914 during the study active Treatment Period. Subjects who are considered to be “Treatment Responders” will be offered, at the discretion of the Investigator, participation in an optional 18-week Extension Period (EP), in which weekly open-label KPL-914 can be continued for a total duration of KPL-914 treatment of up to 24 weeks.

Sites for SC 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.

No placebo or active comparator drug will be used.

8.4.2 Identity of Investigational Medicinal Products

KPL-914 (rilonacept/ARCALYST®) is prepared as a lyophilized formulation containing histidine, polyethylene glycol 3350, glycine, arginine, and sucrose at pH 6.5. It 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 WFI is required prior to SC administration of the drug. The reconstituted drug product is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

After the addition of preservative-free sterile WFI, the vial contents should be reconstituted by gently shaking the vial for approximately 1 minute and then allowing it to sit for 1 minute. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for SC administration only.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®) as a lyophilized powder to be reconstituted for SC administration. The sites will receive Study Drug for on-site administration at Study Site/Clinic visits. Drug will be disseminated to the trial subjects for outpatient self-administration according to a supply chain described in the Pharmacy Manual.

The lyophilized Study Drug (KPL-914 also called rilonacept, US tradename: ARCALYST®) is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. After reconstitution, KPL-914 may be kept at room temperature, should be protected from light, and should be used within 3 hours of reconstitution. Unused portions of KPL-914 product must not be injected. All vials of used and unused Study Drug during the active Treatment Period must be returned to the clinical site for cataloguing and documentation of compliance.

The Sponsor through Regeneron Pharmaceuticals, Inc. will ensure that the Study Drug and certificates of analysis are available before the start of the study and at all times during the study.

ARCALYST® is a registered trademark of Regeneron Pharmaceuticals, Inc.

8.4.3 Method of Assigning Subjects to Treatment Groups

Subjects who meet all the inclusion criteria in a specific Part and none of the exclusion criteria will enter the Treatment Period at Visit 1 (Day 0).

Since this is an open-label, single-active-arm study, all subjects will receive KPL-914 active treatment. Assignment to treatment groups is not applicable.

8.4.4 Selection of Doses in the Study

This protocol is a pilot study intended to evaluate the safety, efficacy, and dose response of KPL-914 in the treatment of patients with RIP.

[redacted], treatment will be as follows.

Adult subjects (≥ 18 years of age)

KPL-914 will be administered as an initial loading dose of 320 mg SC, delivered as two subcutaneous injections of 160 mg SC each on Day 0, then 160 mg SC dosed once weekly for 5 subsequent weeks. (Appendix 2: ARCALYST® Prescribing Information).

Pediatric subjects (6 to <18 years of age)

KPL-914 will be administered with an initial loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as two subcutaneous injections of 2.2 mg/kg each with a maximum single-injection volume of 2 mL. Dosing will continue with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection of up to 2 mL as outpatient administration or administered by an adequately trained caregiver, for 5 subsequent weeks (Ilowite et al, 2014, Lovell et al, 2013, Garg et al, 2017, Autmizguine et al, 2015).

After an initial group of subjects has been treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment response early in the Treatment Period), the Sponsor in collaboration with the Investigators may elect to decrease the KPL-914 dose administered to a subsequent consecutive group of subjects (in any Part of the Study): the adult subjects (18 years or older) entering the Treatment Period will receive a loading dose of 160 mg KPL-914 (2 x 80mg) SC on Day 0, then 80 mg administered SC weekly for 5 additional doses. Subjects aged 6 years to <18 years will receive a loading dose of 2.2 mg/kg KPL-914 (2x 1.1 mg/kg; maximum total 160 mg) administered SC on Day 0, then 1.1 mg/kg (maximum 80 mg) administered SC weekly for 5 additional doses, in order to explore efficacy at a lower dose.

8.4.5 Selection and Timing of Dose for Each Subject

The first administration of KPL-914 (and training for outpatient self-administration) will be performed under the supervision of a qualified healthcare professional at Visit 1 (Day 0). Afterwards, subjects or an adequately trained caregiver will administer the Study Drug as an outpatient during the Treatment Period (and during the EP, as applicable). Study Drug administration will be performed once a week (every 7 ± 1 days). The interval between Study Drug administrations must be at least 5 days. Subjects will be instructed to not administer KPL-914 more often than once weekly and to administer only one syringe of Study Drug per week.

At Visit 1, subjects or adequately trained caregivers will be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously will be assessed to ensure proper administration of KPL-914, including rotation of injection sites. Subjects will be instructed in proper vial, syringe, and needle disposal, and will be cautioned against reuse of these items. All used and unused Study Drug vials must be returned to the Study Site/Clinic for drug accountability assessment.

8.4.6 Blinding

Not applicable.

8.4.7 Prior and Concomitant Therapy

Subjects included in Parts 1, 2 and 4 may be using NSAIDs, colchicine, and/or corticosteroids in any combination at the time of study enrollment, but the dose levels must be stable for have been stable for at least 7 days, although stable doses for shorter period will be acceptable if in the opinion of the Investigator, in consultation with the Sponsor, a shorter period of stability is not anticipated to alter the baseline CRP values.

Subjects in Parts 3 and 5 must be receiving corticosteroids at the time of enrollment.

For the duration of the Treatment Period, pericarditis medications (e.g., concomitant NSAIDs, colchicine and/or corticosteroids, if used) should be continued at pre-study dose levels until after the 6-dose Study Drug Treatment Period has concluded; however, should the Investigator determine that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine and/or corticosteroid dose can be down-titrated in consultation with the Sponsor, and the modification of dose should be recorded in the source records and the eCRF.

Subjects who received, within the 6-month period before dosing, immunomodulatory therapy other than, for example, corticosteroids or mycophenolate, which in the opinion of the Investigator (in consultation with the Sponsor) may interfere with the study endpoints, or subjects who used commercially-available rilonacept (ARCALYST®) within 90 days before the Screening Visit are excluded from participation.

Throughout the Treatment Period opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary by the Investigator, after consultation with the Sponsor. Any rescue medication use must be recorded in source records, the medication diary and the eCRF. Other interleukin (IL)-1 or IL-6 blockers, janus-activating kinase (JAK) and tumor necrosis factor (TNF) inhibitors are prohibited for the duration of the study.

Medical management of pericarditis during the EP is based on Investigator discretion. For example, Investigators may continue subjects on KPL-914 at the same dosage level, wean-off or discontinue Study Drug. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status

Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and the eCRF.

During the Screening and Treatment Periods, subjects will enter information concerning the use of pericarditis and rescue (pain) medication into a medication diary. Such information will be entered by the subject on a real-time basis.

8.4.8 Treatment Compliance

Study Drug will be administered to the subject by the Investigator or qualified study center staff at the Study Site/Clinic Visit 1 (Day 0). Subsequent weekly Study Drug doses from Weeks 2 to 5 will be self-administered by the subject or an adequately trained caregiver as an outpatient SC administration. The study center staff or a visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site. All medication use (for pericarditis and use of rescue [pain] medication) will be documented by the subject in the medication diary during the Treatment Period.

All vials of used and unused Study Drug during the active Treatment Period and the EP must be retained by the Study Site/Clinic and the subject to allow for cataloguing and documentation of compliance. Subjects must return all used and unused medication to the Study Site/Clinic. Drug accountability and documentation thereof is described in the Pharmacy Manual.

Study Drug compliance by the subject will be monitored during the Treatment Period by phone calls/virtual visits (made by qualified site staff). Subjects will be reminded of recording all pericarditis and rescue pain medication information in the medication diary. The medication diary will be returned to the site by the subject and reviewed by the Investigator/qualified staff. During the EP, Study Drug use will be documented during monthly phone calls/virtual visits or Study Site/Clinic visits.

8.5 Study Procedures

All data of Study Site/Clinic visit assessments as well as Investigator (or designee) phone calls/virtual visits will be documented in source records and in the eCRF.

8.5.1 Prescreening Period

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

The Prescreening Period starts with the signing of the Prescreening ICF (or prescreening assent form, if applicable), and lasts until the subject enters the Screening Period by signing the ICF for the full study or is withdrawn (see section 8.3.5).

8.5.2 Screening Period

The Screening Period starts with the signature of the ICF (or informed assent form, if applicable), and may last for up to 3 days. During this period, subject eligibility for entry into the Treatment Period will be determined. A rheumatology consultation during the Screening Period is optional.

At SCV1, baseline subject and disease characteristics will be determined. At Screening Visit 2 [SCV2]), within the 24 – 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data under special circumstances, the Investigator in consultation with the Sponsor, can combine SCV1 and SCV2.

The end of the Screening Period may coincide with the start of the Treatment Period.

8.5.2.1 Screening Visit 1 (SCV1)

- At the SCV1, written informed consent (or assent, if applicable) will be obtained before any protocol-specific assessments are made.
- All subjects will be assessed for eligibility against the inclusion and exclusion criteria.
- Demographic data, such as ethnic origin, date of birth and sex will be recorded.
- The subject's full medical history, including age at first attack, number of previous attacks, duration of attacks as well as concomitant illnesses/diseases will be documented.
- Information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured.
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
- A pregnancy test (urine dip-stick) will be done. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.
- 12-lead ECG and full echocardiogram (ECHO) will be performed. ECHO will include assessment of pericardial effusion. The Study Site/Clinic readings at the time of the examination will be available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory.
- A cardiac MRI may be performed (optional). If done, the images will be assessed by a central reader. The Study Site/Clinic reading at the time of the examination may be used by the Investigator for clinical decision-making.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
        - Serology (HCVAb, HBsAg, HBcAB, HBsAb and HIV)
        - A QuantiFERON® test for tuberculosis (TB) can be performed (optional).
    - Screening for drugs of abuse and alcohol abuse will be performed on urine samples collected at this visit.
    - Central Laboratory Assessments:
        - CRP/hsCRP
- Samples for archive biomarker, pharmacokinetics (PK), and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- A medication diary for documentation of pericarditis medication use and use of any rescue (pain) medication will be handed to the subject. The study Investigator or designated personnel will instruct the subject about the use of the medication diary. The subjects will be asked to complete entries immediately following administration.
- The subjects will assess their pericardial pain based on a 11-point NRS.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.2.2 Screening Visit 2 (SCV2)

The end of the Screening Period (SCV2) coincides with the start of the Treatment Period (Day 0, Visit 1). All Screening assessments need to be completed prior to the first Study Drug administration.

- SCV2 should take place when the laboratory test results from SCV1 are available.
- Subjects will be reassessed for eligibility against the inclusion and exclusion criteria.

- Any changes in concomitant medications since SCV1 will be documented.
- A full physical examination will be performed, including re-assessment of pericardial rub.
- Vital signs will be measured.
- 12-lead ECG will be performed. The Study Site/Clinic reading at the time of the examination will be used by the Investigator for clinical decision-making. In addition, the ECG will be sent to a core laboratory for additional analysis.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full chemistry (including CRP) panel only
    - Central Laboratory Assessments:
        - CRP/hsCRP
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- The subjects will assess their pericardial pain based on the 11-point NRS (Figure 3).

When all screening procedures have been performed and the Investigator has confirmed the subject's eligibility for the study, the Study Drug will be administered to the subject (see Study Site/Clinic Visit 1).

8.5.3 Treatment Period

8.5.3.1 Visit 1 (Study Site/Clinic) - Day 0

Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling (including CRP), medication diary compliance verification and reminding, and subject NRS pericardial pain rating (see Figure 3) must be repeated prior to Study Drug dosing.

- Sample for lipid panel to be sent to the Central Laboratory for analysis
- Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected prior to Study Drug dosing, sent to the central laboratory, and stored for analysis.
- The subject's global overall well-being will be assessed prior to Study Drug dosing using a validated Quality of Life Questionnaire (Appendix 3).
- The initial dose of Study Drug will be administered at the Study Site/Clinic.
- Subjects will be trained for outpatient Study Drug self-administration and reminded of completion of the daily medication diary.
- Any AEs occurring during or after the subject receives the first dose of Study Drug will be captured.

When all Visit 1 procedures have been performed, an appointment for the first weekly phone call/virtual visit will be scheduled. Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

8.5.3.2 Day 3 (Outpatient)

- Day 3 will ± 1 day after Visit 1.
- An Investigator (or designee) telephone call/virtual visit will occur to evaluate safety (AE evaluations) and patient-reported pericardial pain using a validated 11-point NRS instrument.

8.5.3.3 Visits 2 to 6 (Outpatient) - Weeks 2, 3, 4, 5, 6

- Visits 2, 3, 4, 5, 6 will take place within intervals of 7 ± 1 days each after Visit 1.

- Subjects self-administer the Study Drug or be administered Study Drug by an adequately trained caregiver during Weeks 2 to 5. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the study site.
- Samples for laboratory tests will be collected.
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected (either by a visiting study nurse or at the Study Site or at a qualified local laboratory) and stored for analysis after shipment to the central laboratory.
- After dosing at Week 3 and Week 6, a questionnaire to assess the dosing system will be completed by the subject and by the study center staff or visiting nurse observing the dosing
- Any AEs that have occurred since the last contact will be assessed by non-leading questions as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Compliance with self-administration of drug, compliance with the medication diary, and compliance with laboratory blood sampling will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed as part of the weekly telephone call/virtual visit from the Study Site/Clinic.

Subjects withdrawing from the study any time during study weeks 2 to 6 will be asked to return to the Study Site/Clinic for the Visit 7/End-of-Trial visit assessments.

8.5.3.4 Interval Evaluation Visit (Study Site/Clinic) - Week 3-4

An in-person Interval Evaluation Visit during approximately Weeks 3-4 of the Treatment Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator. The Interval Evaluation Visit may also be used to review the vaccination status of a study subject.

At the Interval Evaluation Visit, the following parameters will be assessed:

- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel and the subject reminded on the diary use.
- Pericardial pain based on the 11-point NRS (Figure 3) will be assessed.
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.3.5 Unscheduled Visits (Study Site/Clinic) During the Treatment Period

Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. During the Unscheduled Visit, selected or comprehensive (see Interval Evaluation Visit) clinical and laboratory assessments may be performed.

Any subject who is determined by the Investigator as not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.

All study withdrawals must complete the Visit 7/End-of-trial Visit either at the Unscheduled Visit or at a separate Visit 7/End-of-trial Visit.

8.5.3.6 Visit 7/ End-of-Trial (Study Site/Clinic) - Week 6

At Visit 7, "Treatment Responders" (defined by the Investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week EP, at the discretion of the Investigator. During the EP, weekly open-label KPL-914 can be continued at the same dose as in the Treatment Period for a total duration of Study Drug treatment of up to 24 weeks.

- Visit 7 will take place during Week 6 (or as soon as possible after study withdrawal if a subject has discontinued from Study Drug therapy).
- A full physical examination will be performed, including assessment of pericardial rub.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory.
- Changes in concomitant medication since last Study Site visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Lipid panel
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Medication diary compliance will be assessed by the Investigator/designated personnel.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

When all of these procedures have been performed, the next Study Site/Clinic visit should be scheduled for those who continue KPL-914 treatment during the EP (Treatment Responders). Study Drug for outpatient administration will be provided to the subjects according to a process laid out in the pharmacy manual.

Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Clinic/Site (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7. Continued weekly Study Drug treatment during the EP will be outpatient administration.

8.5.4 Extension Period

Subjects will self-administer the Study Drug or be administered by an adequately trained caregiver on a weekly basis and complete the medication diary during the Extension Period. Study nurse visits to the subject's home will continue on a monthly basis. Investigator (or designee) phone calls/virtual visits will be performed monthly during the EP to perform NRS pain assessments, collect AE information, and document pericarditis/concomitant medication use. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF

8.5.4.1 Unscheduled Visits (Study Site/Clinic) during the EP

Unscheduled Study Site/Clinic visits can take place during the Extension Period, as agreed upon by the Investigator and the subject or as needed.

- A physical examination will be performed.
- Vital signs will be measured.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- A 12-lead ECG and a full ECHO will be performed as determined by the Investigator. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).

8.5.4.2 Interval Evaluation Visit During Extension Period (Study Site/Clinic) - Week 15-20

An in-person Interval Evaluation Visit during approximately Weeks 15-20 of the Extension Period is recommended to assist the Investigator in the clinical management of the subject. The visit can be held at the discretion of the Investigator.

At the Extension Period Interval Evaluation Visit, the following parameters will be assessed:

- A physical examination will be performed.
- Vital signs will be measured.
- A 12-lead ECG and a full ECHO will be performed. The Study Site/Clinic readings at the time of the examination will be made available to the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory.
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.4.3 Visit 8/Final Visit (Study Site/Clinic) - Week 25

- Visit 8 will take place 18 weeks after Visit 7 (or as soon as possible after study withdrawal during the EP).
- A full physical examination will be performed, including assessment of pericardial rub.
- Body weight and height will be assessed.
- Vital signs will be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
- 12-lead ECG and ECHO will be performed. Echocardiogram will include assessment of pericardial effusion. In addition, both the ECG and ECHO will be sent to a core laboratory.
- An MRI can be performed (optional).
- Changes in concomitant medication since the last Study Site/Clinic visit will be documented.
- Samples for laboratory tests will be collected.
    - Local Lab Assessments:
        - Full hematology (including ESR), chemistry (including CRP), and urinalysis
    - Central Laboratory Assessments:
        - CRP/hsCRP
        - Lipid panel
    - Samples for archive biomarker, PK and anti-rilonacept (anti-KPL-914) antibody testing will be collected, sent to the central laboratory, and stored for analysis.
- Any AEs that have occurred since the last visit (Study Site/Clinic or outpatient) will be documented.
- Pericardial pain based on the 11-point NRS will be assessed (Figure 3).
- The subject's global overall well-being will be assessed using a validated Quality of Life Questionnaire (Appendix 3).

8.5.5 Duration of Treatment

The overall study duration for subjects participating in the study until Visit 8 will be up to 171 days.

The test product will be administered weekly for 6 weeks in the base study Treatment Period. Treatment Responders will be offered participation in an optional 18-week EP at the discretion of the Investigator. During this EP the subject can receive 18 additional weekly doses of KPL-914.

8.6 Efficacy and Safety Variables

The Schedule of Evaluations in Table 1 shows the planned study assessments.

8.6.1 Individual Efficacy Assessments

8.6.1.1 C-Reactive Protein, Biomarker, and PK Assessments

CRP will be determined at Study Site/Clinic laboratory tests at Screening (SCV1 and SCV2) and during the Treatment Period (Visit 1 prior to dosing, if separate from SCV2, Interval Evaluation Visit [if applicable], and Visit 7/End-of-Trial). Results from the Study Site/Clinic CRP testing will inform the Investigator on the subject's pericarditis status for clinical decision-making and support decisions on classifications of subjects as Treatment Responders or Treatment Failures and on subsequent disease management during the Extension Period.

Central laboratory assessments of CRP will be performed at each Study Site/Clinic or outpatient study visit (samples collected by a visiting study nurse or at the Study Site/Clinic or a local laboratory). Centrally determined CRP values will be used for statistical evaluations and report writing but will not be used as basis of the Investigator's management of the subject.

All subjects must present with elevated CRP values ≥1 mg/dL at the time of study enrollment. CRP changes and the time course to decrease and resolution of CRP to normal values ≤0.5 mg/dL will be assessed.

Samples from each study visit will be archived at the central laboratory for potential biomarker and/or PK analysis.

8.6.1.2 Echocardiogram (Pericardial Effusion)

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

Pericardial effusion is characterized by accumulation of excess fluid in the pericardial space surrounding the heart and is one of the common features of pericarditis. Echocardiography is a sensitive tool and the most widely used imaging technique for the detection of pericardial effusion and/or thickening.

ECHO images may be assessed by a central reader after the study end. The Study Site/Clinic reading of the ECHO at the time of the examination will be made available to the Investigator for clinical decision-making, and will be used for analysis of treatment response.

8.6.1.3 Electrocardiogram (Pericarditis Diagnostic Findings)

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

Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-elevation or PR depression. Changes in ECG findings will help determine the pericarditis status of a subject.

The Study Site/Clinic reading of the ECG at the time of the examination will be made available to the Investigator for clinical decision-making and will be used for analyses of treatment response. In all subjects ECG tracings will be assessed by a central reader and used for central read ECG analysis.

8.6.1.4 Pericarditis Signs (Fever, Pericardial Rub)

Common pericarditis signs include fever and pericardial rub. These pericarditis signs will be assessed via documentation of vital signs and physical examinations.

Physical examinations and vital sign assessments for pericarditis signs will be performed at screening (SCV1 and SCV2), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP [if applicable], and the Final Study Visit/Visit 8. If applicable, assessment of pericarditis signs will also be performed at unscheduled visits.

8.6.1.5 Pericarditis Pain (Chest Pain)

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011). The assessment will be performed at all study visits - on-site during Study Site/Clinic visits and as part of telephone calls/virtual visits during outpatient visits/treatment weeks (weekly during the Treatment Period and monthly during the EP).

Subjects will be asked to select the score that best describes their average level of pain over the previous 24 hours using a validated 11-point NRS instrument (Figure 3), 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 pain on average in the last 24 hours

0	1	2	3	4	5	6	7	8	9	10

Figure 3: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

8.6.1.6 Magnetic Resonance Imaging

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

For the purposes of the analysis of treatment response in all subjects at the end of the study, all cardiac MRI images will be assessed by a central reader. The Study Site/Clinic reading of the MRI at the time of the examination may be used by the Investigator for clinical decision-making.

8.6.1.7 Quality of Life Questionnaire

A validated Quality of Life Questionnaire will be used to assess changes in the subject's overall well-being (Hays et al 2009). The subject's global assessment of quality of life will be performed at screening (SCV1), at Visit 1 (Day 0), at the Interval Evaluation Visit (Week 3-4), at the end of the Treatment Period (Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP, and at the Final Visit (Visit 8).

The Quality of Life Questionnaire to be used is presented in Appendix 3.

8.6.1.8 Dosing Procedure Questionnaire

A questionnaire will be used to assess the dose preparation and administration procedure immediately after self-injecting the Study Drug in the presence of the Study Staff (either in person or via virtual visit) or of the visiting nurse. Each subject will complete a questionnaire after the third self-injection (third dose, Week 3) and the sixth self-injection (sixth dose, Week 6), and once during the extension period. The Study Staff/visiting nurse observing the injection will also complete an observation checklist for observing subjects interacting with the system during self-injection. The checklist will list all key steps associated with proper system use, including setting up for an injection, reconstituting the medication, and administering the injection. Study Staff/visiting nurse will complete the checklists for the same injections for which the subjects will complete questionnaires.

8.6.2 Safety Assessments

8.6.2.1 Adverse Events

Adverse Event Definition

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 and/or unintended 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.

In this study, individual elements of pericarditis symptomatology (including pain) are captured as an efficacy parameter. Pericarditis pain is not required to be reported as an AE. However, if, in the opinion of the Investigator, the subject experiences new symptoms that had not been previously reported in the constellation of symptoms recorded at baseline, these new symptoms should be reported as an AE.

The causal relationship between an AE and the Study Drug will be defined as below:

- **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 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 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 drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

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**: medically significant event; daily activities limited or completely halted; hospitalization or prolongation of hospitalization indicated.

Every reasonable effort will be made to follow subjects who have AEs. Any subject who has an ongoing AE at study end or early withdrawal will be followed, where possible, until resolution.

8.6.2.2 Serious Adverse Events

Serious Adverse Event Definition

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 Study Drug (e.g., car accident where 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 hospitalizations must be recorded on the medical history or physical examination page of the eCRF). Hospitalization is defined as an admission to the hospital ward or a short-stay-type unit longer than 24 hours. Prolongation of existing hospitalization is defined as 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 judgement 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 IMP.

Reporting of Serious Adverse Events

SAEs merit special concern and attention, and SAEs due to any cause, whether or not related to the Study Drug, must be reported by the Investigator to the Sponsor and designee within 24 hours of occurrence or when the Investigator becomes aware of the event. Report SAEs by fax or email using the designated SAE report to:

In addition, Investigator must report the SAE within 24 hours of learning of the event by telephone to:

If the Investigator reports an SAE by telephone, then a written report must follow within 1 business day and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable.

Other Reasons for Immediate Reporting to

- Overdose (accidental or intentional) of the investigational product or concomitant medication, regardless of whether it is considered an AE
- Any pregnancy diagnosed in a female subject or in a female partner of a male subject during treatment with an investigational product
- Hospitalization (including Emergency Room visits) which last for less than 24 hours. A determination will be made by the Sponsor in collaboration with as to whether it is a SAE
- Any diagnosis of malignancy (excluding basal cell skin cancer) during the study should be reported to within 24 hours.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 8.3.5.

All hospitalizations must be reported to and Kiniksa within 24 hours; however, hospitalizations for elective medical/surgical procedures for preexisting illnesses that were planned prior to the subject's enrollment in the study may not be considered by the Investigator to be AEs. Complications resulting from planned procedures, however, require reporting to and Kiniksa.

Whenever possible and practical, a blood sample (collected in a light blue top CTAD [citrate, theophylline, adenosine, dipyridamole] vacutainer tube) to potentially measure plasma drug levels should be obtained upon the development of any SAE or unusual AE that is judged to be related to study treatment.

Investigator Reporting Responsibilities to Institutional Review Board (IRB)

Unanticipated problems posing risks to study subjects will be reported to the IRB per their institutional policy. Copies of each report and documentation of IRB notification and acknowledgement of receipt will be kept in the Investigator's study file.

Sponsor Reporting Responsibilities to Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

8.6.2.3 Adverse Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; i.e., where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

Unexpected Adverse Reaction Definition

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with relevant product information for the IMP. The current version of the ARCALYST® PI should be used as the Single Source Safety Reference Document when determining if an event is unexpected. Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for a list of most frequent expected AEs. All suspected adverse reactions related to an investigational medicinal product (the tested investigational medicinal products and comparators, if involved) which occur in the concerned trial, and that are both unexpected and serious are subject to expedited reporting.

Warnings and Precautions

Refer to the ARCALYST® PI (Appendix 2: ARCALYST® Prescribing Information) for Important Safety Information.

IL-1 blockade may interfere with immune response to infections. It is therefore recommended that prior to or shortly after initiation of therapy with KPL-914 subjects receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. In case a subject needs vaccination after initiation of KPL-914 treatment, vaccination with inactive vaccine(s) may be performed during the active Treatment Period. However, to minimize the potential confounding of KPL-914-related AE reporting or CRP measurements during the KPL-914 Treatment Period, vaccination should not be performed during the Treatment Period (see Section 8.3.4). It is recommended that all vaccinations be documented as up-to-date at or shortly after Visit 7, at which point subjects are being considered for longer-term treatment with KPL-914.

Taking KPL-914 with TNF inhibitors is not recommended because simultaneous inhibition of these two pathways may increase the risk of serious infections.

It is also possible that taking drugs 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 KPL-914.

8.6.2.4 Clinical Laboratory Variables

Clinical laboratory analyses will be performed at Study Site/Clinic or local laboratory near the subject and, for some parameters, at a central laboratory. Laboratory analyses will be used at Study Site/Clinic visits for the Investigator to assess disease status and to determine treatment response and study (drug) continuation or withdrawal. Results for analyses performed by the Study Site/Clinic laboratory together with the laboratory reference ranges will be recorded in the eCRF and the Investigator must use clinical judgment to determine if any abnormal values are clinically significant or not.

Central laboratory samples for CRP analysis will be collected at both Study Site/Clinic and outpatient (by a visiting study nurse or at local contract laboratories) visits and the results will be used for statistical analyses and study reporting. Study Site/Clinic and local laboratory results will be used for clinical decision-making and will be available in the source documents and listed in the CSR).

The following analyses will be done at the **central laboratory**:

- C-reactive protein (CRP)/hsCRP (The CRP analyzed by the central laboratory will not be available to the investigator in a timely manner to support the clinical management of the subject. Results from the central laboratory will therefore not be transferred to the Investigator during the trial.)
- Lipid Panel
- Samples for biomarkers, PK, and anti-rilonacept (anti-KPL-914) antibody testing will be drawn and archived at all visits.

The following laboratory analyses will be done at the **Study Site/Clinic laboratories** in accordance with local procedures and guidelines to support clinical management and decision-making:

Hematology

Hemoglobin, hematocrit, coagulation parameters (prothrombin [PT], prothrombin time [PTT], D-dimer), ESR, fibrinogen, WBC count (total and differential), red blood cell (RBC) count, ESR, platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), MCH concentration (MCHC).

Clinical Chemistry

CRP/hsCRP, troponin, creatinine, creatine kinase, urea, (or blood urea nitrogen [BUN]), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol*, triglycerides*, calcium, phosphorus.

* Preferably fasting.

Urinalysis

pH, glucose, ketones, nitrites, leukocyte esterase, blood, protein and microscopy. Urine drug screen (alcohol, amphetamines, cocaine, or phencyclidine) at SCV1 only. Screening for pregnancy (urine β-HCG) at SCV1 only.

Serology

HCVAb, HBsAg, HBcAb, HBsAb and HIV tests (SCV 1 only).

Other
Screening for tuberculosis (QuantiFERON test) at SCV1 only (optional).

The amount of blood to be taken during screening will be approximately 37 mL at SCV1 and approximately 17 mL at SCV2 (if done). The amount of blood to be taken at each Study Site/Clinic visit during the Treatment Period and EP will be approximately 31 mL. The amount of blood to be taken at each outpatient

visit will be approximately 21 mL. At the optional unscheduled visit, approximately 61 mL are planned. The total amount of blood to be taken during the study will be up to approximately 320 mL.

8.6.2.5 Vital Signs

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

The following measurements will be taken: oral temperature, respiratory rate, blood pressure, and pulse. Oral temperature (fever) will also be assessed as efficacy parameter (see Section 8.6.1.4).

8.6.2.6 Physical Examination

At the Screening Visits 1 and 2, at the optional Evaluation Visit during the Treatment Period, at the End-of-Trial Visit (Visit 7), at Unscheduled and Evaluation Visits during the EP and at the Final Visit (Visit 8) a full physical examination including the assessment of pericardial rub (efficacy parameter) will be performed (see also Section 8.6.1.4).

8.6.2.7 Body Weight and Height

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

8.7 Statistical Methods

Each Part will be analyzed separately and per the analysis populations below, to be finalized in the Statistical Analysis Plan (SAP) to be provided separately. A full description of the statistical analyses to be performed together with the planned tables and figures will be given in a detailed document, the SAP, which will be developed and filed prior to data base lock. Any deviation(s) from the final SAP will be described and justified in the clinical study report.

8.7.1 Statistical and Analytical Plans

8.7.1.1 Datasets to be Analyzed for Each Part

Each Part will be analyzed separately and per the analysis populations below. The modified Intention to Treat (mITT) Population will consist of all subjects who received at least one dose of Study Drug. The Per Protocol (PP) Population will consist of all subjects who received all 6 doses of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (NSAIDs, colchicine, and/or corticosteroids, if used during screening) according to study protocol without a major protocol violation. The Safety Population will be the same as the mITT Population.

8.7.1.2 General Statistical Methods

Because of the small sample size, no inferential statistical analyses or hierarchical testing are planned.

For analysis of continuous endpoints (e.g., change from baseline), summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated and presented for each treatment and/or analysis group. For categorical endpoints (e.g., responder vs. non-responder), summary statistics will be calculated and presented for each treatment and/or analysis group. Under certain circumstances, if appropriate in the context of statistical methodologies, the results of certain similar Parts might be pooled for greater statistical precision in determining therapeutic response or safety.

Further details will be provided in the SAP. Any deviation(s) from the original statistical plan will be described and justified in in the final study report.

8.7.1.3 Efficacy Endpoints

Primary Efficacy Endpoints

Part 1
Determine inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with RIP both at baseline and while on active KPL-914 treatment in order to inform power calculations for future trials in pericarditis.

Part 2
Determine inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with RIP both at baseline and while on active KPL-914 treatment in order to inform power calculations for future trials in pericarditis.

Part 3
Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent RIP.

Part 4
Determine inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with recurrent PPS both at baseline and while on active KPL-914 treatment in order to inform power calculations for future trials in pericarditis.

Part 5
Evaluate disease activity after corticosteroid taper in subjects with corticosteroid dependent recurrent PPS.

[redacted]

8.7.1.4 Safety Variables

AEs and SAEs, clinical laboratory evaluations, vital sign measurements, ECGs, and physical examination findings.

8.7.2 Determination of Sample Size

Approximately up to a total of 40 subjects with RIP or PPS will be enrolled as study subjects across all Parts.

Subjects who discontinue the study (withdrawals and Treatment Early Failures) may be replaced at the Sponsor's discretion.

The sample size was chosen on an empirical basis, based on experience with other rilonacept trials and research in this patient population.

8.8 Quality Assurance and Quality Control

8.8.1 Audit and Inspection

The study sites may be selected for an audit originating from the Sponsor or external organizations acting on behalf of the Sponsor. Audits will be followed by internal reports and corrective actions, if needed.

The Investigator agrees to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved. The anonymity of the subjects must be safeguarded and data checked during audits remain confidential.

8.8.2 Monitoring

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 (or informed assent form, if applicable).

The Investigator will permit study-related monitoring, audits, ethics committee review and regulatory inspection(s), providing direct access to source data and documents.

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 Good Clinical Practice (GCP) and International Conference on Harmonisation (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.

8.8.3 Data Management and Coding

The Sponsor or Clinical Research Organization (CRO) 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 the Sponsor or CRO.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and World Health Organization (WHO) Drug for therapies.

8.8.4 Record Keeping

It is the responsibility of the Investigator to ensure all essential trial documentation and source records (e.g., signed ICFs/assent forms, Study Site/Clinic files, patients' hospital notes, copies of eCRFs, etc.) 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.

9 Records and Supplies

9.1 Drug Accountability

On receipt of the IMP (including rescue medication, if relevant), the Investigator (or deputy) will conduct an inventory of the supplies and verify that IMP supplies are received intact and in the correct amounts prior to completing a supplies receipt. The Investigator will retain a copy of this receipt at the study site and return the original receipt to the drug depot. The inventory of supplies at each study site will be reviewed by the study monitor.

KPL-914 (rilonacept) will be provided by the Sponsor to the study sites and to the study subjects in its commercially-available formulation (ARCALYST®). All vials of used and unused Study Drug during the active Treatment Period 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.

10 Ethics

10.1 Institutional Review Board

Before initiation of the study at each investigational site, the protocol, all protocol amendments, the ICF, the informed assent form and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the IMP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the

informed consent form (or assent, if applicable), the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB annually, or more frequently if requested by the IRB. On completion of the study, the Sponsor will notify the IRB that the study has ended.

10.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the Declaration of Helsinki and local regulations.

10.3 Subject Information and Consent

The Investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject and/or legal guardian has given written informed consent (or informed assent, if applicable) to participate in the study. The written consent (or informed assent, if applicable) must be given by the subject and/or the legal guardian of the subject, after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

Subjects and/or legal guardians will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IRB, Sponsor and/or CRO personnel.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. 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 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 informed assent and the informed consent are required prior to participation in the trial.

10.4 Subject Confidentiality (US Studies)

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA), applicable to national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the ethics committees approving this research, and the United States (US) FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

11 Reporting and Publication

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator(s) will be subject to mutual agreement between the Investigator and Kiniksa as outlined in the study agreement.

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13 Appendices

Appendix 1: Investigator Signature Page

Protocol Title: An Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis

Protocol Number: KPL-914-C001

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and I will conduct the study as described in compliance with this protocol, GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Kiniksa Pharmaceuticals Ltd. (Kinksa) and of the IEC/IRB. I will submit the protocol modifications and/or any ICF/assent modifications to Kiniksa and IEC/IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all Case Report Forms, laboratory samples or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Kiniksa, to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

Appendix 2: ARCALYST® Prescribing Information

ARCALYST- rilonacept injection, powder, lyophilized, for solution
Regeneron Pharmaceuticals, Inc.

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: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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			Endpoint		

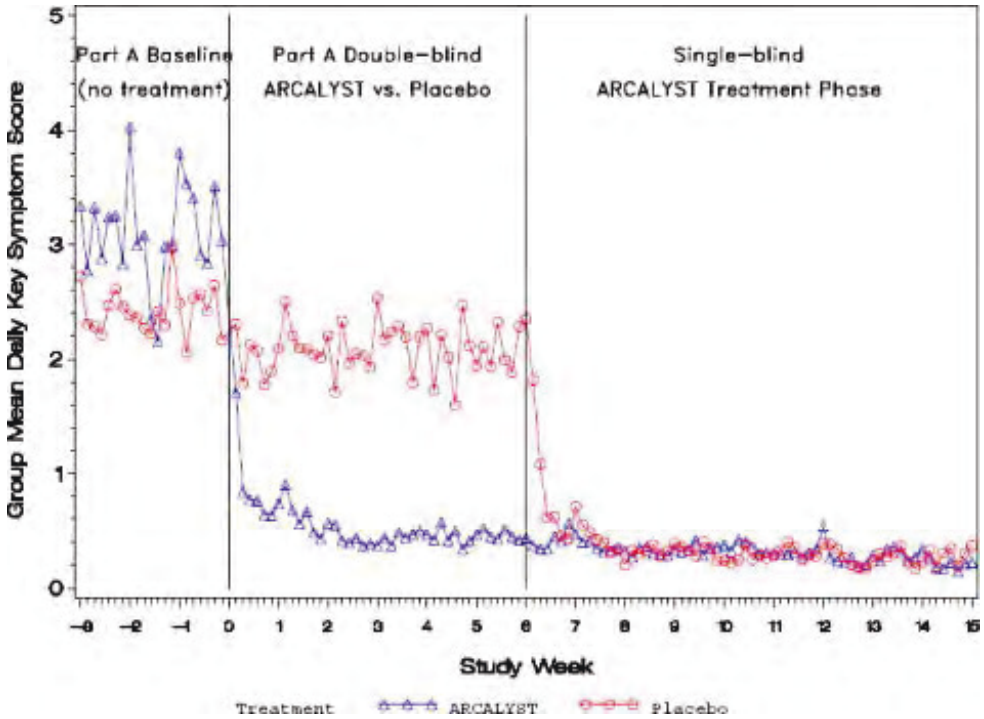
Period (Weeks 4 to 6)	2.1	0.5	Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment 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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U.S. License Number 1760
NDC 61755-001-01

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):

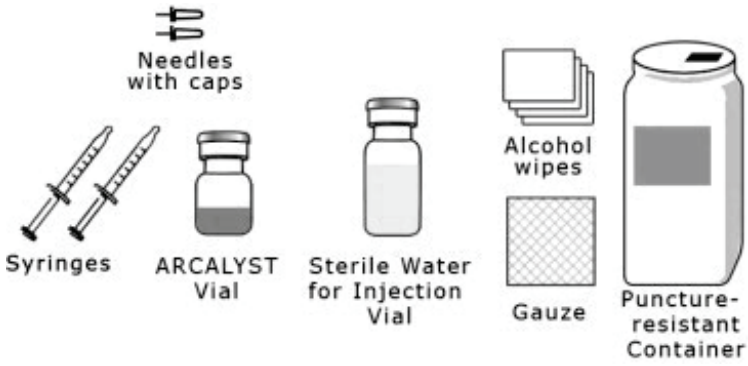


Figure 1

- 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

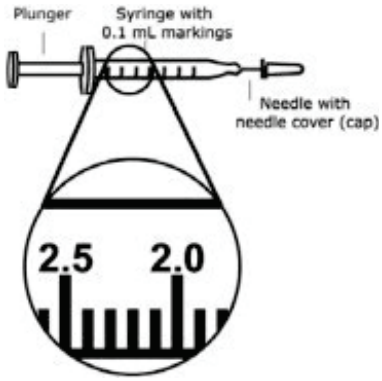


Figure 2

- 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).

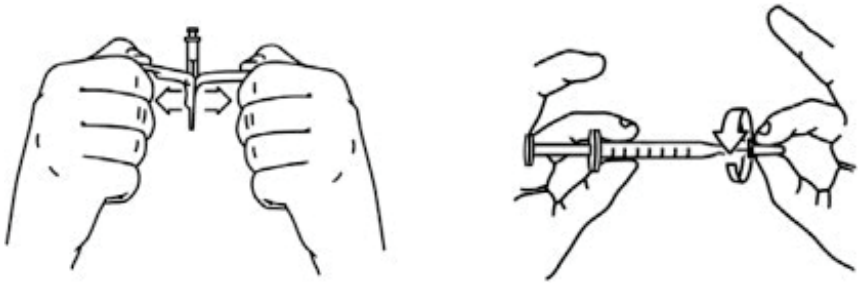


Figure 4

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).

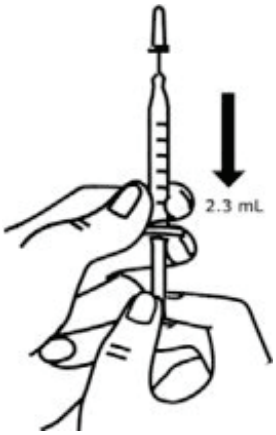


Figure 5

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).

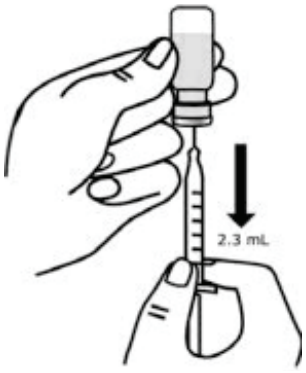


Figure 7

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).

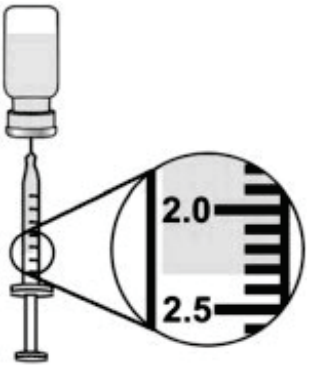


Figure 8

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).

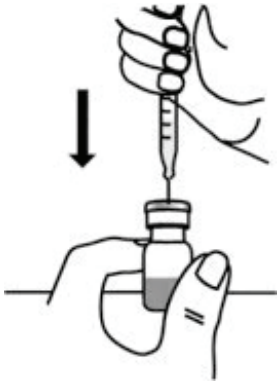


Figure 9

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.

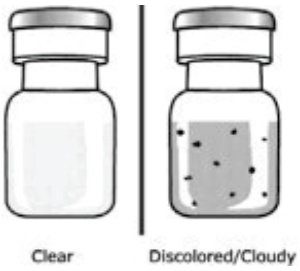


Figure 11

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).

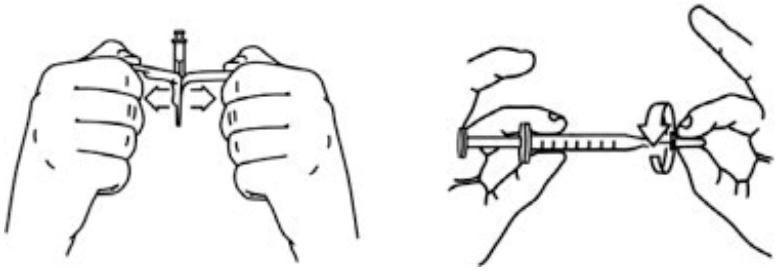


Figure 13

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).

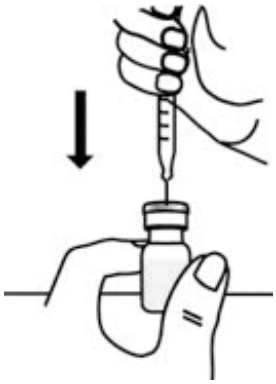


Figure 15

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).

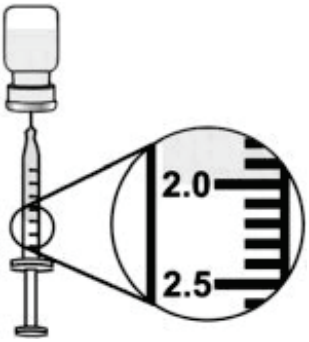


Figure 16

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.

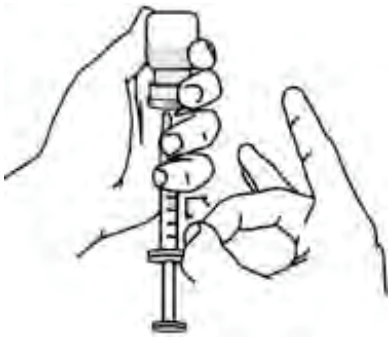


Figure 17

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)

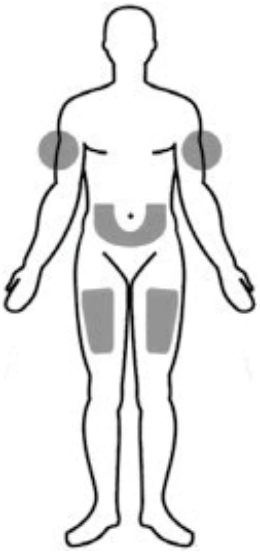


Figure 19

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).

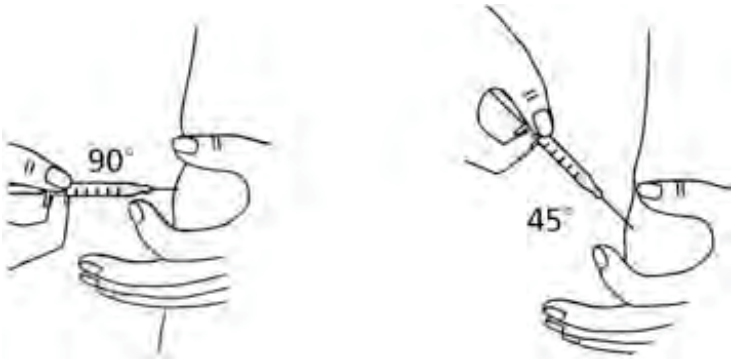


Figure 21

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).

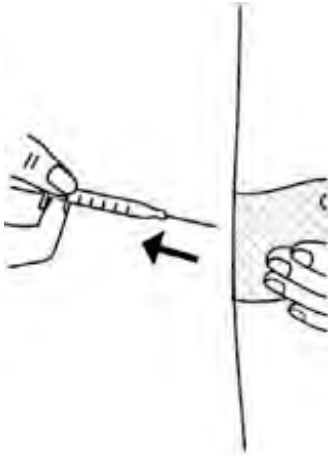


Figure 22

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:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
U.S. License Number 1760
NDC 61755-001-01

V 4.0

Principal Display Panel - Vial Carton

NDC 61755-001-01

Arcalyst®

(rilonacept)

Injection for Subcutaneous Use

220 mg sterile powder for reconstitution

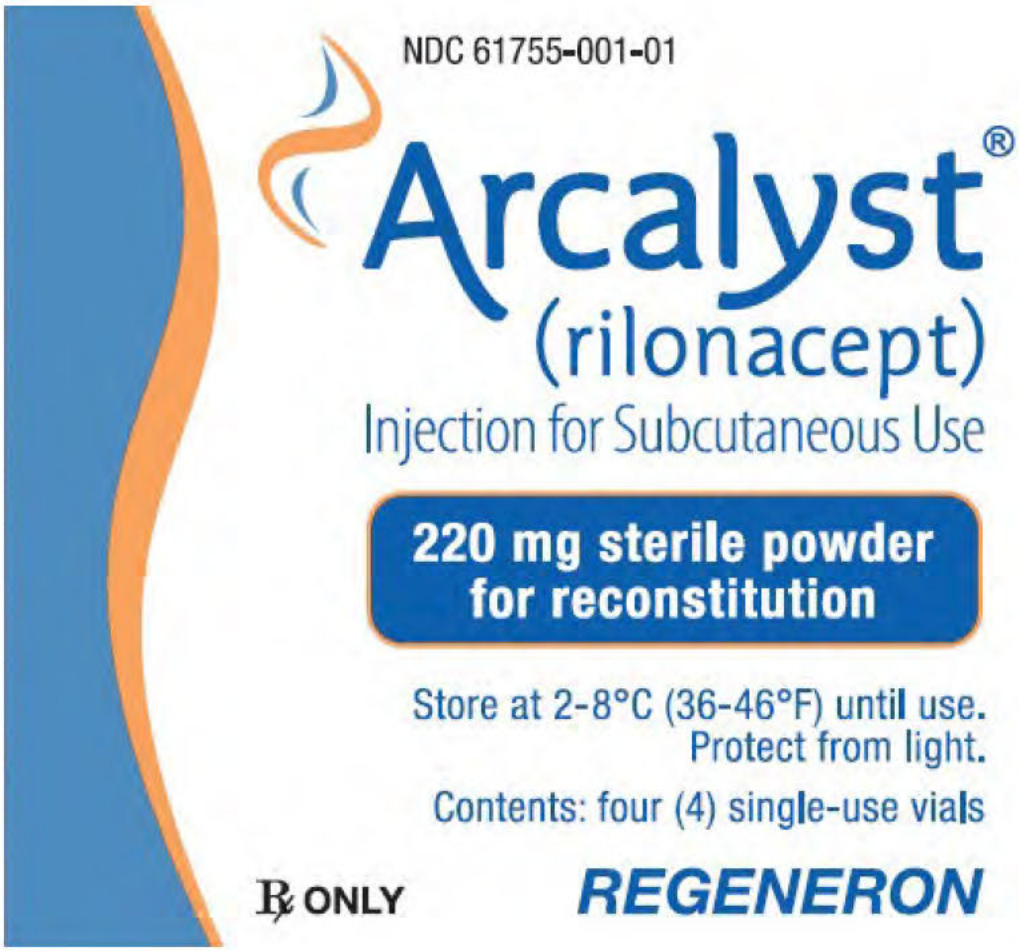
Store at 2-8°C (36-46°F) until use.

Protect from light.

Contents: four (4) single-use vials

Rx ONLY

REGENERON



ARCALYST

rilonacept injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61755 001

Route of Administration	SUBCUTANEOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
rilonacept (UNII: 8K80YB5GMG) (rilonacep UNII:8K80YB5GMG)	rilonacep	160 mg in 2 mL

Inactive Ingredients

Ingredient Name	Strength
Histidine (UNII: 4QD397987E)	
Arginine (UNII: 94ZLA3W45F)	
Polyethylene glycol 3350 (UNII: G2M7P15E5P)	
Sucrose (UNII: C151H8M554)	
Glycine (UNII: TE7660XO1C)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61755 001 01	4 in 1 CARTON	03/24/2008	
1		2 mL in 1 VIAL, SINGLE USE; Type 0: No a Combina ion Produc		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125249	02/27/2008	

Labeler - Regeneron Pharmaceuticals, Inc. (194873139)

Establishment

Name	Address	ID/FEI	Business Operations
Regeneron Pharmaceu icals, Inc.		945589711	ANALYSIS(61755 001) , API MANUFACTURE(61755 001) , LABEL(61755 001)

Appendix 3: Quality of Life Instrument

PROMIS Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global08	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Scale v1.2 – Global Health

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
Global08r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Global07r	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

Appendix 4: 11-point Numerical Rating Scale (NRS) for Assessment of Pericarditis Pain

Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point NRS will be used to measure the subject's level of pericarditis (chest) pain intensity (Dworkin et al 2005; Mannion et al 2007; Hawker et al 2011).

Subjects will be asked to select the score that best describes their average level of 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 pain on average in the last 24 hours

0	1	2	3	4	5	6	7	8	9	10