CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125249Orig1s049

Trade Name:	ARCALYST
Generic or Proper Name:	rilonacept
Sponsor:	Kiniksa Pharmaceuticals (UK), Ltd.
Approval Date:	March 18, 2021
Indication:	ARCALYST (rilonacept) is an interleukin-1 blocker indicated for: • Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS), and Muckle-Wells Syndrome (MWS) in adults and children 12 years and older. • Maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing 10 kg or more. • Treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

BLA 125249/S-049

SUPPLEMENT APPROVAL

Kiniksa Pharmaceuticals (UK), Ltd.
c/o Kiniksa Pharmaceuticals Corp.
Attention: Lisa Crockett, MS
Vice President, Regulatory Affairs
100 Hayden Avenue
Lexington, MA 02421

Dear Ms. Crockett:

Please refer to your supplemental biologics license application (sBLA), dated September 21, 2020, received September 21, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Arcalyst (rilonacept) lyophilized powder for reconstitution 220 mg vial.

This Prior Approval supplemental biologics application provides for the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years and older.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling **and** carton and container labeling submitted on March 16, 2021 as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 125249/S-049**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please call Maryam Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology, and Nephrology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or Medication Guide
  - Instructions for Use
- Carton and Container Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
03/18/2021 02:27:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125249Orig1s049

LABELING

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) for injection, for subcutaneous use
Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

Indications and Usage (1.2)	12/2020
Indications and Usage (1.3)	03/2021
Dosage and Administration (2.2)	03/2021
Dosage and Administration (2.3)	12/2020

INDICATIONS AND USAGE

ARCALYST (rilonacept) is an interleukin-1 blocker indicated for:

- Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS), and Muckle-Wells Syndrome (MWS) in adults and children 12 years and older (1.1, 14.1)
- Maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing 10 kg or more (1.2, 14.2)
- Treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years and older (1.3, 14.3)

DOSAGE AND ADMINISTRATION

Administer by subcutaneous injection (2.1)

- **CAPS, FCAS, MWS, and RP (2.2):**
  Adults:
  – Loading dose: 320 mg, delivered as two 160 mg (2 mL) injections.
  – Maintenance dose: 160 mg (2 mL) injection once weekly.
  Pediatric patients 12 years to 17 years:
  – Loading dose: 4.4 mg/kg, up to a maximum of 320 mg, delivered as 1 or 2 injections (not to exceed 2 mL/injection).
  – Maintenance dose: 2.2 mg/kg, up to a maximum of 160 mg (2 mL) injection, once weekly.
- **DIRA (2.3):**
  Adults and pediatric patients weighing 10 kg or more:
  – 4.4 mg/kg up to a maximum of 320 mg, delivered as 1 or 2 injections (2 mL/injection) once weekly.

DOSAGE FORMS AND STRENGTHS

For injection: 220 mg of lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Serious, life-threatening infections have been reported in patients taking ARCALYST. Do not initiate treatment with ARCALYST in patients with active or chronic infections. Discontinue treatment if a patient develops a serious infection. (5.1)
- Hypersensitivity Reactions: If a hypersensitivity reaction occurs, discontinue administration of ARCALYST and initiate appropriate therapy. (5.3)
- Immunizations: Avoid live vaccines. Update recommended vaccinations prior to initiation of therapy per current guidelines. (5.5)

ADVERSE REACTIONS

The most common adverse reactions reported by patients with CAPS and RP treated with ARCALYST are injection-site reactions and upper respiratory tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kiniksa at 1-833-KINIKSA (1-833-546-4572) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

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

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Cryopyrin-Associated Periodic Syndromes, Familial Cold Auto-Inflammatory Syndrome and Muckle-Wells Syndrome

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 pediatric patients 12 years and older.

1.2 Deficiency of IL-1 Receptor Antagonist

ARCALYST is indicated for the maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing at least 10 kg.

1.3 Recurrent Pericarditis

ARCALYST is indicated for the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and pediatric patients 12 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

ARCALYST is for subcutaneous use only.

2.2 Cryopyrin-Associated Periodic Syndromes, Familial Cold Auto-Inflammatory Syndrome, Muckle-Wells Syndrome and Recurrent Pericarditis

Adults: Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg each, administered on the same day at two different injection sites. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection.

Pediatric patients 12 years to 17 years: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum dose of 320 mg, administered as one or two subcutaneous injections, not to exceed single-injection volume of 2 mL per injection site. If the initial dose is given as two injections, administer on the same day at two different sites. 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 a once weekly dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to administer the dose, starting a new schedule based on this date.

2.3 Deficiency of IL-1 Receptor Antagonist

Adults: The recommended dose of ARCALYST is 320 mg, once weekly, administered as two subcutaneous injections on the same day at two different sites with a maximum single-injection volume of 2 mL. ARCALYST should not be given more often than once weekly.

Pediatric patients weighing 10 kg or more: The recommended dose of ARCALYST is 4.4 mg/kg (up to a maximum of 320 mg), once weekly, administered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. If the dose is given as two injections, administer both on the same day, each one at a different site.

When switching from another IL-1 blocker, discontinue the IL-1 blocker and begin ARCALYST treatment at the time of the next dose *[see Drug Interactions (7.1)]*.

2.4 Preparation for Administration

Reconstitute each single-dose vial of ARCALYST with 2.3 mL of preservative-free Sterile Water for Injection, USP, (supplied separately) prior to subcutaneous administration of the drug.

2.5 Administration

Using aseptic technique, withdraw 2.3 mL of preservative-free Sterile Water for Injection through a 18-gauge, 1- or 1½-inch needle attached to a 3-mL syringe and inject the preservative-free Sterile Water for Injection, USP, into the drug product vial for reconstitution. The needle and syringe used for reconstitution with preservative-free Sterile Water for Injection, USP, should then be discarded and should not be used for subcutaneous injections. After the addition of preservative-free Sterile Water for Injection, USP, reconstitute the vial contents 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 free from particulates. Prior to injection, inspect the reconstituted solution for any discoloration or particulate matter. Discard the solution if either are observed.

Using aseptic technique withdraw the recommended dose volume, up to 2 mL (160 mg), of the solution with a new 18-gauge, 1- or 1½-inch needle attached to a new 3-mL syringe. For the subcutaneous injection, replace the needle with a new 26 gauge, ½-inch needle. EACH VIAL SHOULD BE USED FOR A SINGLE DOSE ONLY. Discard the vial after withdrawal of drug.

After reconstitution, ARCALYST may be kept at room temperature, but keep it protected from light, and use the solution within three hours after reconstitution. Discard unused portions of ARCALYST.

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

3 DOSAGE FORMS AND STRENGTHS

For injection: 220 mg of rilonacept as a white to off-white, lyophilized powder for reconstitution in single-dose vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious 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 CAPS and RP patients on ARCALYST compared with placebo.

In the controlled portion of the CAPS study *[see Clinical Studies (14.1)]*, severe infection (bronchitis) was reported in one patient receiving ARCALYST. In an open-label extension study in CAPS, one patient developed bacterial meningitis and died *[see Adverse Reactions (6.1)]*.

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. **ARCALYST is not recommended for use with TNF inhibitors 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. Refer to current practice guidelines for evaluation and treatment of possible latent tuberculosis infections before initiating therapy with ARCALYST.

Treatment with ARCALYST should not be initiated in patients with an active or chronic infection. Discontinue ARCALYST if a patient develops a serious infection.

5.2 Risk of Malignancy

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

5.3 Hypersensitivity Reactions

Hypersensitivity reactions associated with ARCALYST occurred in clinical trials. If a hypersensitivity reaction occurs, discontinue ARCALYST and initiate appropriate therapy.

5.4 Lipid Profile Changes

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Increases in non-fasting lipid profile parameters occurred in patients treated with ARCALYST in clinical trials. Monitor patients' lipid profiles and consider lipid lowering therapies if needed, based on cardiovascular risk factors and current guidelines *[see Adverse Reactions (6.1)]*.

5.5 Immunizations

Since no data are available on the risks of secondary transmission of infection by live vaccines in patients receiving ARCALYST, avoid administration of live vaccines during treatment with ARCALYST.

No data are available on the effectiveness of vaccines in patients receiving ARCALYST. Since ARCALYST may interfere with normal immune response to new antigens, vaccines may not be effective 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 per current immunization guidelines, including pneumococcal vaccine and inactivated influenza vaccine.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Risk of Malignancy*[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Lipid Profile Changes *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

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

The data described herein reflect exposure to ARCALYST in over 2,000 patients who received at least one dose, including approximately 1700 exposed to 160 mg or more, of whom 151 patients were exposed for at least 6 months and 111 patients for at least one year. These included patients with CAPS and RP, patients with other diseases, and healthy volunteers.

CAPS

Approximately 60 patients with CAPS were 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 to17 years) were enrolled directly into the open-label extension phase of the trial.

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 in Patients with CAPS (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%)

DIRA

In a 2-year, open-label study, 6 pediatric patients with DIRA, 3 years to 6 years of age, received 2.2 to 4.4 mg/kg dose of ARCALYST once weekly *[see Clinical Studies (14.2)]*. The safety profile was generally consistent with that seen in patients with CAPS. The most common adverse reactions were upper respiratory infection (6 of 6), rash (5 of 6), otitis media (3 of 6), pharyngitis (3 of 6) and rhinorrhea (3 of 6).

RP

In the RP phase 3 study, a total of 86 patients received at least one dose of ARCALYST with a median treatment duration of 9 months *[see Clinical Studies (14.3)]*. Of the patients, 49 (57%) were female and 37 (43%) were male; 93% were White/Caucasians. The mean age was 44.7 years. Seven patients (8%) were aged 12-17 years old. No new adverse reactions were identified in this study.

Adverse Reactions of Special Interest

Injection-Site Reactions

In patients with CAPS or RP, 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.

Infections

During Part A in the CAPS study, the incidence of patients reporting infections was greater with ARCALYST (48%) than with placebo (17%). In Part B, randomized withdrawal, the incidence of infections was 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

Six serious infections were reported by four patients during the CAPS clinical program: *Mycobacterium intracellulare* infection; gastrointestinal bleeding and colitis; sinusitis and bronchitis; and *Streptococcus pneumoniae* meningitis *[see Adverse Reactions (6)]*.

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.

Changes in Hematologic Parameters Laboratory Changes

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.

Lipid Profile Changes

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.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. The data reflect the percentage of patients whose test results were positive for antibodies to the rilonacept receptor domains in specific assays. Additionally, 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 in other studies or to other products may be misleading.

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.

In the Phase 3 study of patients with RP there were no patients who tested positive for antibodies at baseline. At any point in time, 26 out of 86 (30%) subjects tested positive at any assessment and of these, 6 tested positive for neutralizing antibodies (NAb). At the last assessment, 10 subjects remained positive for anti-drug antibodies (ADA) and 1 subject remained positive for NAb. There was no correlation of antibody activity and either clinical effectiveness or safety.

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

Risk Summary

Rare pregnancy outcomes reported postmarketing and from clinical trials, with very limited use of ARCALYST in pregnant women, are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There may be risks to the mother and fetus associated with Cryopyrin Associated Periodic Syndromes (CAPS) *(see Clinical Considerations)*. In an animal reproduction study, subcutaneous administration of rilonacept to pregnant monkeys during the period of organogenesis was complicated by losses of drug exposure as the study progressed, due to anti-drug antibody formation at all doses, but a dose-related increase in exposure was still evident. There were no treatment-related effects on fetal survival or development of malformations with doses up to 11 times the maximum recommended human dose (MRHD). Increased incidences of lumbar ribs, a skeletal variation, were observed in fetuses at doses approximately 2 times the MRHD and higher that slightly exceeded incidences in both control animals and the historical control database (*see Data*). There were findings of multiple fusion and absence of the ribs and thoracic vertebral bodies and arches in one fetus of the only pregnant monkey with exposure to rilonacept during the later period of gestation associated with a dose approximately 6 times the MRHD (*see Data*). The relationship of these findings in a single fetus to drug treatment was unclear, as these findings were not evident in fetuses from pregnant monkeys that had higher exposures to rilonacept during the period of organogenesis associated with a dose approximately 11 times the MRHD.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and of miscarriage is 15–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased maternal levels of interleukin (IL)-1β, which induces inflammation that occurs in CAPS, may be associated with pre-term birth.

Data

Animal Data

In an embryo-fetal development study, pregnant cynomolgus monkeys received rilonacept at subcutaneous doses of 0, 5, 15 or 30 mg/kg given twice a week from gestation days 20 to 48. The study was complicated by losses of drug exposure as the study progressed, due to anti-drug antibody formation at all doses, but a dose-related increase in exposure was still evident. There were no treatment-related effects on fetal survival or development of malformations with doses up to 11 times the MRHD (on a mg/kg basis with maternal subcutaneous doses up to 30 mg/kg). Increased incidences of lumbar ribs, a skeletal variation, were observed in fetuses at doses approximately 2 times the MRHD and higher (on a mg/kg basis with maternal subcutaneous doses of 5 mg/kg and higher) that slightly exceeded incidences in both control animals and the

historical control database. There were findings of multiple fusion and absence of the ribs and thoracic vertebral bodies and arches in one fetus of the only pregnant monkey with exposure to rilonacept during the later period of gestation associated with a dose 6 times the MRHD (on a mg/kg basis with a maternal subcutaneous dose of 15 mg/kg). The relationship of these findings in a single fetus to drug treatment was unclear, as these findings were not evident in fetuses from pregnant monkeys that had higher exposures to rilonacept during the period of organogenesis associated with a dose approximately 11 times the MRHD (on a mg/kg basis with a maternal subcutaneous dose of 30 mg/kg). All doses of rilonacept reduced maternal serum levels of estradiol up to 64% compared to controls. In pre- and postnatal development studies in the mouse model using a murine analog of rilonacept (subcutaneous doses of 0, 20, 100 or 200 mg/kg), there was a small increase in the number of stillbirths in dams treated with 200 mg/kg three times per week.

8.2 Lactation

Risk Summary

There is no information on the presence of rilonacept in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARCALYST and any potential adverse effects on the breastfed child from ARCALYST or from the underlying maternal condition.

8.4 Pediatric Use

Cryopyrin-Associated Periodic Syndromes (CAPS) and Recurrent Pericarditis (RP)

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

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 reactions 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).

In the Phase 3 study RHAPSODY, 7 patients aged 12 years to 17 years were treated with ARCALYST subcutaneously with an initial loading dose of 4.4 mg/kg (up to a maximum of 320 mg) followed by 2.2 mg/kg (up to a maximum of 160 mg) weekly. These patients were treated for a median time of 15 weeks. There were no apparent differences in efficacy, safety or tolerability across age groups.

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)]*

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

Safety and effectiveness in pediatric patients with DIRA weighing 10 kg or more have been established *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.Safety and effectiveness of ARCALYST have not been established in pediatric patients weighing less than 10 kg for maintenance of remission of DIRA.

8.5 Geriatric Use

In the placebo-controlled clinical studies, 78 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 (6.1)]*. 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 studies have been conducted to evaluate the pharmacokinetics of rilonacept administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No studies have been conducted to evaluate 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-1R1) 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-dose 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, USP. 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 rilonacept (80 mg/mL), glycine (10 mg/mL), histidine (46 mM), L-arginine (50 mM), polyethylene glycol 3350 (30 mg/mL), and sucrose (20 mg/mL) at a pH of 6.5. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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.

DIRA is an auto-inflammatory, autosomal recessive disorder caused by loss of function mutations in the *IL1RN* gene, which encodes IL-1 receptor antagonist (IL-1ra), resulting in unopposed signaling of the proinflammatory cytokines IL-1α and IL-1β through the IL-1 receptor.

Interleukin-1 (IL-1) is a key cytokine that mediates the pathophysiology of many inflammatory processes, and it has been implicated as a causative factor in pericarditis. IL-1α and IL-1β bind to the universally expressed cell surface receptor, IL-1 Receptor type-1, triggering a cascade of inflammatory mediators. Pre-formed IL-1α is released by damaged/inflamed pericardial cells and may contribute to the maintenance and amplification of inflammation via activation of the NLRP3 inflammasome, which then augments the inflammatory response by production of IL-1β in a cascade amplification system.

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.

CRP is also an indicator of inflammation in DIRA. Maintenance of CRP reduction was observed in a clinical trial of pediatric patients with DIRA *[see Clinical Studies (14.2)]*.

CRP is also a recognized indicator of inflammation in pericarditis. Treatment with rilonacept was observed in a clinical trial with RP to be associated with resolution of acute pericarditis episodes, including rapid and sustained reduction in CRP, with a median time to normalization of 7 days *[see Clinical Studies (14.3)]*.

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.

The average trough levels of rilonacept were approximately 23 mcg/mL at steady-state, and the circulation half-life in vivo was approximately 7 days following a 320 mg loading dose and weekly subcutaneous doses of 160 mg for up to 36 weeks in patients with RP. Steady state appeared to be reached by approximately 2 weeks. No pharmacokinetic data are available in patients with hepatic or renal impairment.

No specific study was conducted to evaluate the effect of age, gender, or body weight on rilonacept exposure. Based on limited data obtained from the Phase 3 study RHAPSODY, steady state trough concentrations were similar between male and female patients. Age (26 to78 years) and body weight (50 to120 kg) did not appear to have a meaningful effect on trough rilonacept concentrations. The effect of race has not been assessed because of low numbers of non-Caucasian patients in the CAPS and RP programs, reflecting the epidemiology of these diseases.

In pediatric patients with DIRA (3 to 6 years of age and body weight 12.7 to 19.9 kg) who received weekly subcutaneous doses of 4.4 mg/kg of ARCALYST, the average steady-state trough levels ranged from 63.5 to 74.0 mg/mL during the period of 6 to 24 months from the start of treatment with ARCALYST.

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.

A murine analog of rilonacept had no effects on fertility and reproductive performance in male and female mice at subcutaneous doses up to 200 mg/kg three times per week.

14 CLINICAL STUDIES

14.1 Cryopyrin-Associated Periodic Syndromes, Familial Cold Auto-Inflammatory Syndrome and Muckle-Wells Syndrome

The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study (NCT00288704) with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS.

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

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

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

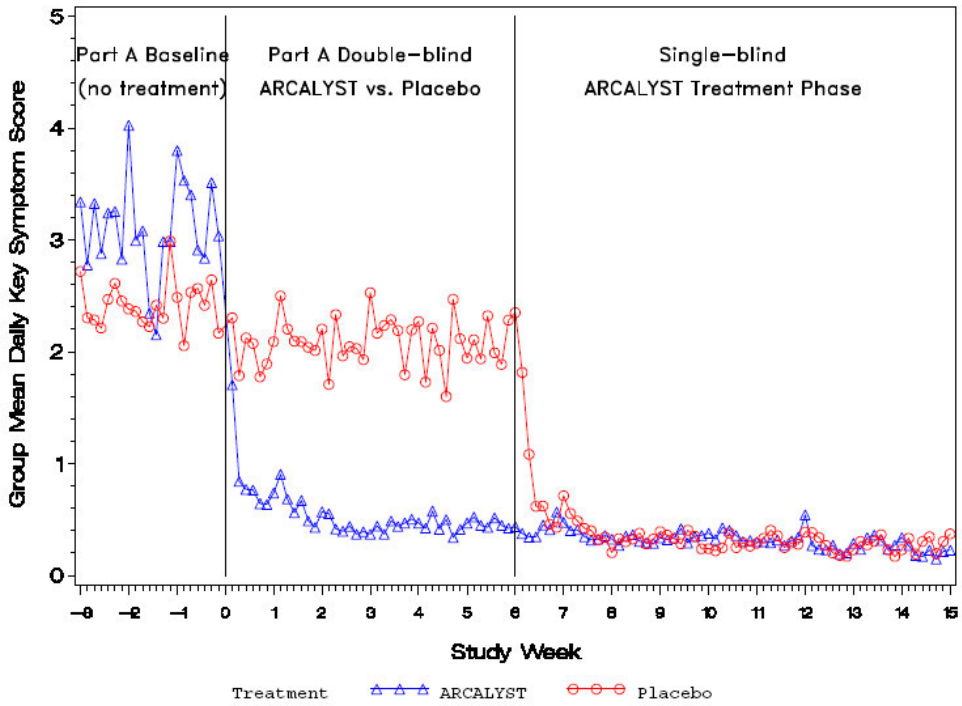
Table 2: Mean Symptom Scores

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

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

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

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



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

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

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

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

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

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

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

14.2 Deficiency of IL-1 Receptor Antagonist

The safety and efficacy of ARCALYST for the maintenance of remission of DIRA was demonstrated in a 2-year, open label study (NCT01801449) of 6 pediatric patients who previously experienced clinical benefit from daily injections of an IL-1 receptor antagonist, anakinra. The study population included patients with a loss-of-function *IL1RN* mutations. Patients had a median age at baseline of 4.8 years (range 3.3 to 6.2), and stopped anakinra treatment 24 hours before initiation of ARCALYST.

Remission was defined using the following criteria: diary score of < 0.5 (reflecting no fever, skin rash and bone pain), acute phase reactants (<0.5 mg/dL CRP), absence of objective skin rash, and no radiological evidence of active bone lesions.

Following an ARCALYST loading dose of 4.4 mg/kg subcutaneously, patients received a once-weekly maintenance dose of 2.2 mg/kg (up to a maximum 160 mg), and were assessed for remission and possible dose escalation. During the first 3 months of ARCALYST administration at the 2.2 mg/kg dose, five of 6 patients exhibited recurrence of pustular rash and therefore the dose was escalated to 4.4 mg/kg once-weekly (up to a maximum of 320 mg). One patient remained on the 2.2 mg/kg once-weekly dose.

All patients met the primary end point of the study, remission at 6 months and sustained the remission for the remainder of the 2-year study. No patient required steroid use during the study.

14.3 Recurrent Pericarditis

The efficacy and safety of ARCALYST was evaluated in the Phase 3 study RHAPSODY (NCT03737110), a double-blind, placebo-controlled, randomized withdrawal, multinational study. The study consisted of a 12-week run-in followed by a double-blind, placebo-controlled, randomized withdrawal period.

In the run-in period, adult patients received a loading dose of ARCALYST 320 mg followed by 160 mg weekly. Patients between 12 and 17 years of age received a loading dose of ARCALYST 4.4 mg/kg (up to 320 mg) followed by 2.2 mg/kg (up to 160 mg) weekly. During the run-in period, patients tapered and discontinued standard of care therapies.

In the withdrawal period, patients were randomized 1:1 to remain on ARCALYST 160 mg weekly or to receive placebo. The randomized withdrawal period continued until the pre-specified number of primary efficacy endpoint events (pericarditis recurrence) had accrued.

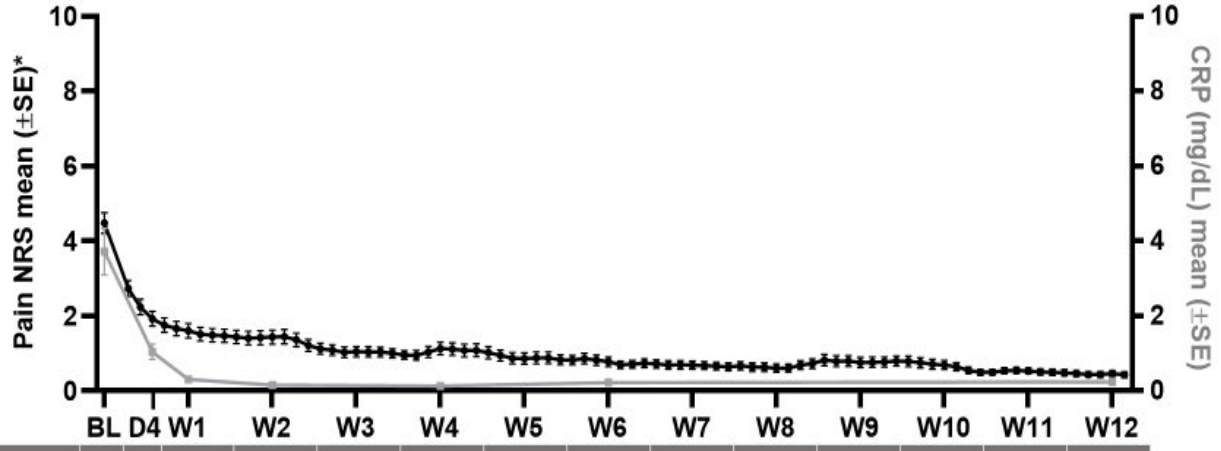
Patients recorded scores for pericarditis pain in a daily diary using the 0 to 10 NRS scale. Measurements of CRP, electrocardiograms, and echocardiograms were conducted at intervals during study visits and to assess pericarditis recurrence.

Patients who experienced pericarditis recurrence were eligible for open-label ARCALYST (bailout).

A total of 86 patients (mean age 45 years [range 13-78], 57% females) with symptomatic pericarditis recurrence were enrolled and received study treatment. Of these, 73 (85%) had a diagnosis of “idiopathic” pericarditis, and the remainder post-cardiac injury pericarditis. The mean duration of disease was 2.4 years with a mean of 4.4 pericarditis events per year including the qualifying pericarditis event (0-10 point Numerical Rating Scale [NRS] ≥ 4 and CRP ≥ 1 mg/dL). Mean qualifying NRS pain score was 6.2, and mean qualifying CRP level was 6.2 mg/dL.

During the run-in period, daily NRS pain scores and CRP levels decreased as shown in Figure 2.

Figure 2: Summary of Pain NRS and CRP Means



		BL	D4	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
CRP	# of Patients	85	79	82	81		79		82						81
	CRP Mean	3.7	1.0	0.30	0.15		0.13		0.22						0.24
Pain NRS	# of Patients	84		84	84	83	83	84	83	83	82	81	82	82	78
	Pain Mean	4.5		1.60	1.43	1.04	1.13	0.86	0.78	0.68	0.61	0.76	0.69	0.53	0.46

*Three-day rolling average was calculated based on non-missing values over each successive three-day interval.

Time to treatment response (NRS ≤ 2 and CRP ≤ 0.5 mg/dL) is shown in Table 4. The median time to treatment response was 5.0 days., All patients were required to taper off standard of care pericarditis medications before randomization, and median time to rilonacept monotherapy was 7.9 weeks during the run-in period.

Of the 86 patients enrolled , 41 (48%) were on treatment with corticosteroids (CS) at baseline (mean treatment duration of 20 weeks).

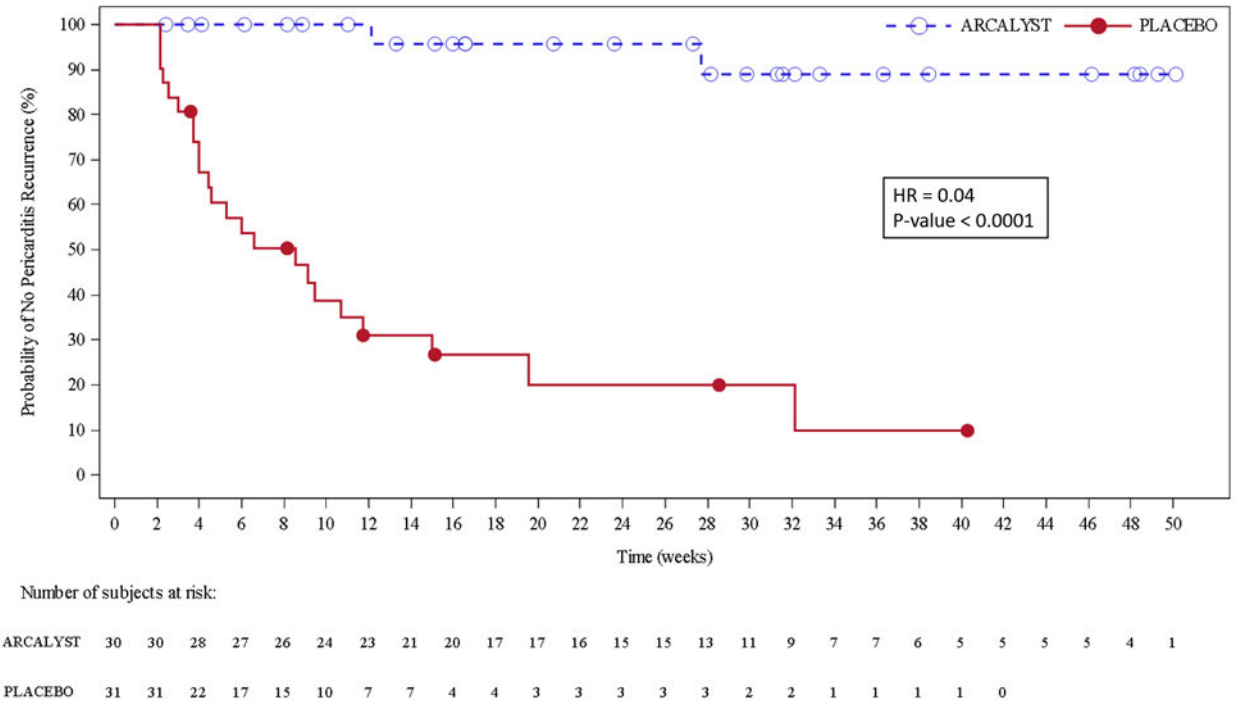
Table 4. Time to Treatment Response: Run-in Period

	ARCALYST (N=86)
Subjects with baseline NRS score >2 or CRP > 0.5 mg/dL	79
Subjects achieving treatment response	77 (97%)
Days to treatment response (median; 95% CI)	5 (4, 7)
Time to monotherapy (median; 95% CI)	8 (7, 8) weeks

The primary efficacy endpoint was time to first adjudicated pericarditis recurrence (based on pain, CRP and clinical signs) in the event-driven withdrawal period.[i]. Of 61 randomized, 23 patients (74%) in the placebo arm had a recurrence compared with 2 patients (7%) in the rilonacept arm who temporarily discontinued treatment for 1 – 3 doses. The median time-to-recurrence on rilonacept could not be estimated because too few events occurred and was 8.6 weeks (95% CI 4.0, 11.7) on placebo with a hazard ratio of 0.04 ($p < 0.0001$);Rilonacept reduced the risk of recurrence by 96% (Figure 3).

The two recurrence events in the rilonacept group happened in association with temporary interruptions of the trial-drug regimen, of one to three weekly doses. In the placebo group, all 23 patients who had pericarditis recurrence received bailout rilonacept, with resolution of the episodes.

Figure 3. Primary Efficacy Endpoint for RHAPSODY
Kaplan-Meier Curves for Time to Pericarditis Recurrence Based on ITT Analysis Set



Secondary efficacy endpoints were the proportion of patients with maintenance of clinical response, the percentage of trial days with none/minimal pericarditis pain (NRS ≤ 2) each measured at week 16 of the withdrawal period. Results are summarized in Table 5.

Table 5. Secondary Efficacy Endpoints for RHAPSODY

	ARCALYST n=21	Placebo n=20	Increase (%)	p-value
Number of patients who maintained response at Week 16	17	4	61	0.0002
Percentage of days with NRS ≤2	92	40	52	<0.0001

16 HOW SUPPLIED/STORAGE AND HANDLING

ARCALYST (rilonacept) for injection is supplied as a sterile, white to off-white, preservative-free, lyophilized powder in single-dose vials.

Each 220 mg vial of ARCALYST is supplied in a carton containing four vials (NDC 73604-914-04).

Store refrigerated at 2°C to 8°C (36°F to 46°F) in 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, protected from light *[see Dosage and Administration (2.5)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling labeling (Patient Information and Instructions for Use).

Assessment of Patient's or Caregiver's Administration of Arcalyst: 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, instruct them 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. If the total volume of dose needed is greater than 2 mL, provide instruction about how to divide the total dose and how to administer the 2 injections. Remind patients to discard vials with unused product. A sharps disposal container should be used for disposal of vials, needles and syringes. Instruct patients or caregivers in proper vial, syringe, and needle disposal, and should be cautioned against reuse of these items *[see Dosage and Administration (2.5)]*.

Injection-site Reactions: 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. Caution patients 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 *[see Adverse Reactions (6.1)]*.

Infections: Caution patients 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. Advise patients 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. Advise patients 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 *[see Warnings and Precautions (5.1)]*.

Vaccinations: Prior to initiation of therapy with ARCALYST review the vaccination history with adult and pediatric patients, parent(s), and/or caregiver relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ARCALYST *[see Warnings and Precautions (5.5)]*.

Manufactured by:

Kiniksa Pharmaceuticals (UK), Ltd.
London, UK W1S 4PZ
U.S. License Number 2236

1-833-KINIKSA (1-833-546-4572)
NDC 73604-914-04

Patient Information
ARCALYST® (ARK-a-list)
(rilonacept)
For Injection
For Subcutaneous Use

Read the Patient Information that comes with ARCALYST before you or your child start taking it and each time you or your child get a refill. There may be new information. This Patient Information leaflet does not take the place of talking with the healthcare provider about your or your child's medical condition or treatment.

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

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

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

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

You or your child should not take medicines that block tumor necrosis factor (TNF), such as Enbrel® (etanercept), Humira® (adalimumab), or Remicade® (infliximab), while you or your child are taking ARCALYST. You or your child 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 or your child's risk of getting a serious infection.

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

- 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. People with asthma may have an increased risk of infection.
- have diabetes or an immune system problem. People with these problems 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 or your child begin treatment with ARCALYST, talk with the healthcare provider about your or your child's vaccine history. Ask the healthcare provider whether you or your child should receive any vaccines, including the pneumonia vaccine and flu vaccine, before you or your child 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 is used to maintain control of symptoms of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and children weighing at least 22 pounds (10 kg).
- ARCALYST is used to treat Recurrent Pericarditis (RP) and reduce the risk of recurrence in adults and children 12 years and older.

It is not known if ARCALYST is safe and effective in children under 12 years of age.

It is not known if ARCALYST is safe and effective in children with DIRA weighing less than 22 pounds (10 kg).

What should I tell my or my child's healthcare provider before taking ARCALYST?

ARCALYST may not be right for you or your child. Before taking ARCALYST, tell your or your child's healthcare provider about all medical conditions, including if you or your child:

- are scheduled to receive any vaccines. You or your child should not receive live vaccines if you take ARCALYST. **See "What is the most important information I should know about ARCALYST?"**

- are pregnant or plan to become pregnant. It is not known if ARCALYST will harm your unborn child. Tell the healthcare provider right away if you become pregnant while taking ARCALYST.
- are breastfeeding or plan to breastfeed. It is not known if ARCALYST passes into breast milk. Talk to the healthcare provider about the best way to feed your or your child's baby during treatment with ARCALYST.

Tell the healthcare provider about all the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell the healthcare provider if you or your child take other medicines that affect the immune system, such as:

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

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

If you have any questions about any of this information, ask the healthcare provider.

How should I take ARCALYST?

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

- Take or give ARCALYST exactly as prescribed by the healthcare provider.
- ARCALYST is given by injection under the skin (subcutaneous injection) 1 time each week.
- ARCALYST should not be given more than 1 time each week.
- The healthcare provider will tell you how much ARCALYST to take or give and show you how to prepare and give the injection.
- Do not try to give ARCALYST injections until you are sure that you understand how to prepare and inject your dose. Call the healthcare provider or pharmacist if you have any questions, or if you would like more training.
- If you or your child take too much ARCALYST, call the healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ARCALYST?

ARCALYST can cause serious side effects, including:

- **See "What is the most important information I should know about ARCALYST?"**
- **Risk of Cancer.** Medicines that affect the immune system may increase the risk of getting cancer.
- **Allergic Reaction**. Stop taking or giving ARCALYST and call the healthcare provider or get emergency care right away if you or your child get any of the following symptoms of an allergic reaction while taking ARCALYST:
  - o rash
  - o swollen face
  - o trouble breathing
- **Changes in your blood cholesterol and triglycerides (lipids).** Your or your child's healthcare provider will do blood tests to check for these changes.

In people with CAPS and RP, the most common side effects of ARCALYST include:

- **Injection-site reactions including**: pain, redness, swelling, itching, bruising, lumps, inflammation, skin rash, blisters, warmth, and bleeding at the injection site.
- **Upper respiratory tract infections**
- **Joint and muscle aches in RP**

In people with DIRA, the most common side effects of ARCALYST include:

- **Upper respiratory infection**
- **Rash**
- **Ear infection**
- **Sore throat**
- **Runny nose**

These are not all the possible side effects of ARCALYST. Tell your or your child's healthcare provider if you or your child have any side effect that bothers you or does not go away. For more information, ask your or your child's healthcare provider or pharmacist. Call your or your child's healthcare provider 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 to protect from light.
- Store ARCALYST in the refrigerator between 36°F to 46°F (2°C to 8°C). Call your pharmacy if you have any questions.
- Refrigerated ARCALYST can be used until the expiration date printed on the vial and carton.
- ARCALYST may be kept at room temperature after mixing with Sterile Water for Injection, USP, and should be used within **3 hours** of mixing. Keep ARCALYST away from light.

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

General Information about the safe and effective use of ARCALYST.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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 symptoms that you have. It may harm them.
You can ask your healthcare provider or pharmacist for information about ARCALYST that is written for health professionals.

What are the ingredients in ARCALYST?
Active ingredient: rilonacept.
Inactive ingredients: glycine, histidine, L-arginine, polyethylene glycol 3350 and sucrose.

Manufactured by:
Kiniksa Pharmaceuticals (UK), Ltd.
London, UK W1S 4PZ
U.S. License Number 2236

Instructions for Use
ARCALYST® (ARK-a-list)
(rilonacept)
For Injection
For Subcutaneous Use

It is important that you read, understand and follow these instructions before you or your child start using ARCALYST so that you prepare and inject the medicine the right way.

Do not try to inject ARCALYST until you have been shown the right way to give the injections by your or your child's healthcare provider.

How do I prepare and give an ARCALYST injection?

Step 1: Setting up for an injection

1. Choose a table or other flat area to set up the supplies for your injection. Be sure the area is clean or clean it with an antiseptic or soap and water.
2. Wash your hands well with soap and water about 20 seconds, and dry with a clean towel.
3. Put the following supplies on the cleaned area for each injection (see Figure A):

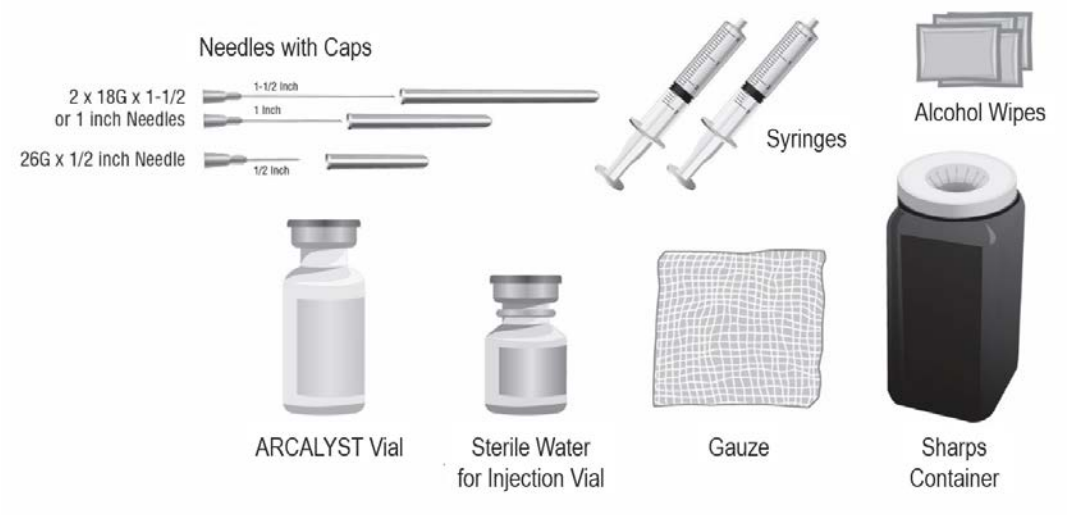


Figure A

Supplies needed to give your ARCALYST injection:

- 1 vial of ARCALYST (powder for mixing)

Additional supplies needed (available from the pharmacy):

- 1 vial of preservative-free Sterile Water for Injection, USP.
- 2 sterile, 3-milliliter (mL) disposable syringes with markings at each 0.1 mL (see Figure B):
  - 1 syringe for mixing ARCALYST
  - 1 syringe for injection

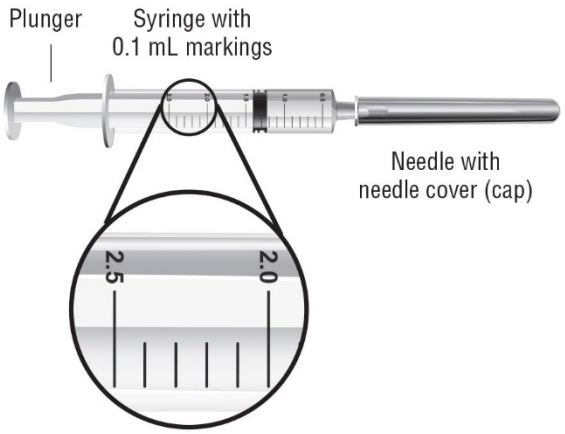


Figure B

- 2 sterile disposable needles (18-gauge, 1-inch or 1½-inch) and 1 sterile disposable needle (26-gauge, ½-inch) with needle covers
    - 1 18-gauge needle for transferring the Sterile Water for Injection, USP, to the rilonacept vial
    - 1 18-gauge needle for withdrawing the mixed solution
    - 1 26-gauge needle for injection
- 4 alcohol wipes
- 1 gauze pad
- 1 sharps disposal container for throwing away (disposing of) used needles, syringes, and vials

Note:

- Do not use Sterile Water for Injection, USP, 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 touch the rubber stopper, clean it with a new alcohol wipe.
- If you touch a needle or the needle touches any surface, throw away the entire syringe in the sharps disposal container and use 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 each syringe with the needle attached, in the sharps disposal container right after use.

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

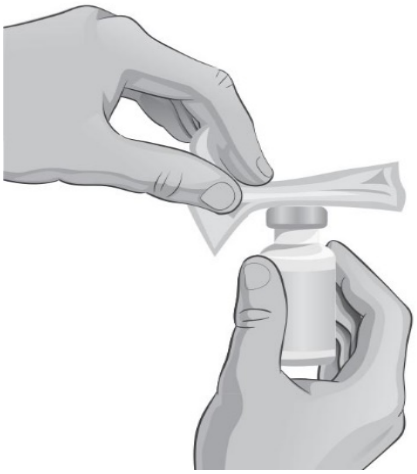


Figure C

5. Check the expiration date on the needle. Do not use the needle if the expiration date has passed. Contact your pharmacy if the expiration date has passed.
6. Open the wrapper that contains 1 of the 18-gauge needles 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 ARCALYST powder in the vial.
7. Check the expiration date on the syringe. Do not use the syringe if the expiration date has passed. Contact your pharmacy if the expiration date has passed.
8. Open the wrapper that contains the syringe by pulling apart the tabs (see Figure D).

9. Hold the barrel of the syringe with 1 hand and use your other hand to twist the 18-gauge needle with the cover onto the tip of the syringe until it fits firmly (see Figure E).

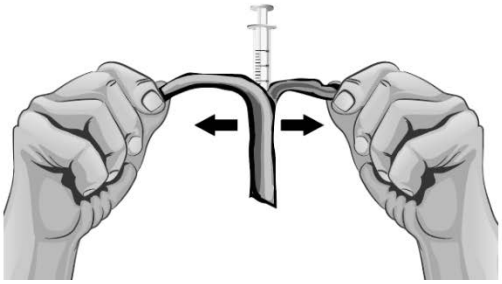


Figure D

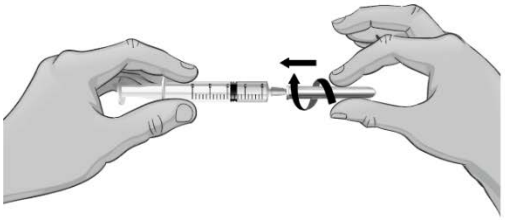


Figure E

10. Hold the syringe upright at eye level. With the needle cover still on the 18-gauge needle, pull back the plunger to the 2.3 mL mark to fill the syringe with air (see Figure F).

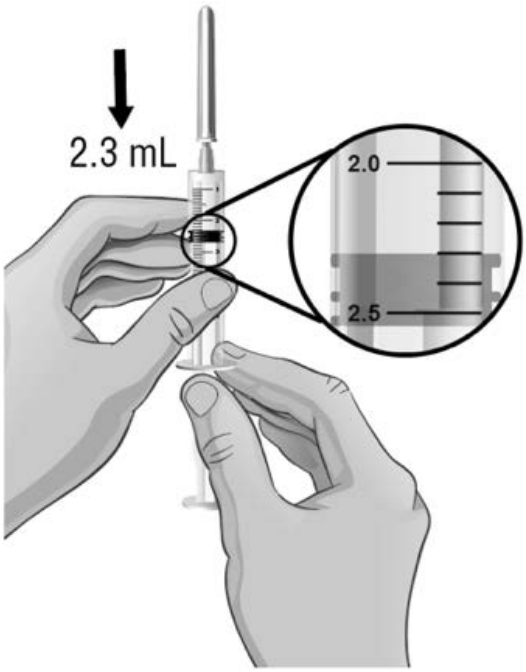


Figure F

11. Hold the syringe in 1 hand and 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 your medicine. Hold the Sterile Water for Injection, USP, 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 G).

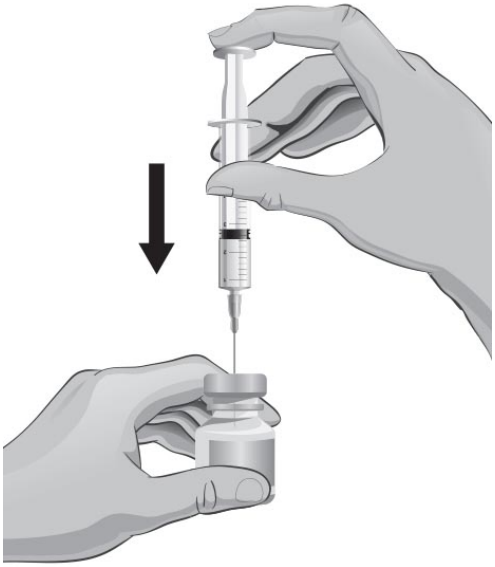


Figure G

12. Hold the vial in 1 hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up (see Figure H).
13. 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 for Injection, USP, from the vial (see Figure H).

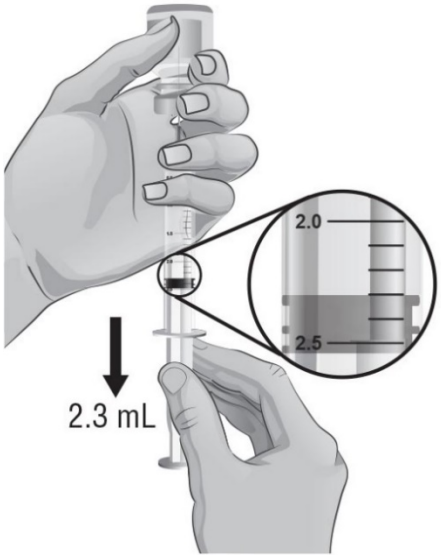


Figure H

14. Keep the vial upside down and gently tap the syringe with your fingers until any air bubbles rise to the top of the syringe.
15. 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.
16. After removing the air bubbles, check the syringe to be sure that the right amount of Sterile Water for Injection, USP, has been drawn into the syringe (see Figure I).

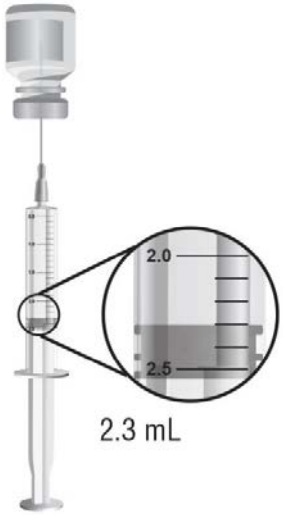


Figure I

17. Carefully remove the syringe with the 18-gauge needle from the Sterile Water for Injection, USP, vial. Do not touch the needle.

Step 3: Mixing ARCALYST

18. With 1 hand, hold the ARCALYST vial on a firm surface.
19. With the other hand, take the syringe with the 18-gauge needle that contains the Sterile Water for Injection, USP, and slowly insert the needle straight down through the rubber stopper of the ARCALYST vial.
20. Gently push the plunger in all the way to inject the Sterile Water for Injection, USP, into the vial aiming the stream of Sterile Water for Injection, USP, down the side of the vial into the powder (see Figure J).

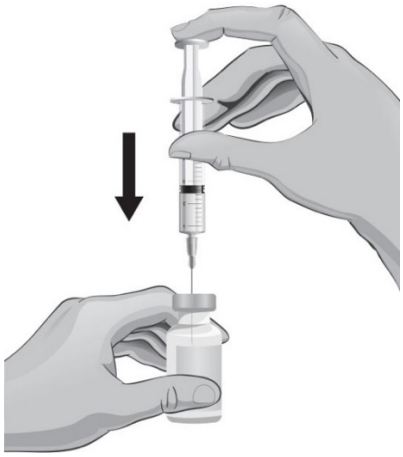


Figure J

21. Remove the syringe and needle from the rubber stopper and throw away the needle, syringe, and Sterile Water for Injection, USP, vial in the sharps disposal container. Do not try to put the needle cover back on the needle (see Figure K).

Figure K

22. Hold the vial containing the ARCALYST and Sterile Water for Injection, USP, sideways (not upright) as shown (see Figure L). Do not touch the rubber stopper. Quickly shake the vial back and forth (side-to-side) for about 1 minute.

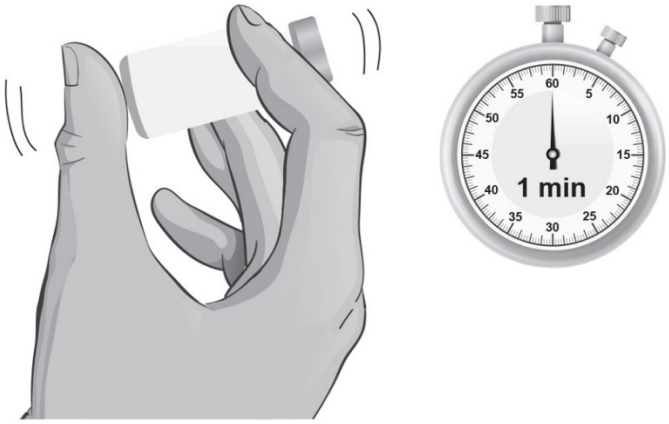


Figure L

23. Put the vial back on the table and let the vial sit for about 1 minute.
24. Check the vial for any particles or clumps of powder which have not dissolved.
25. 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.
26. Repeat Step 25 until the powder is completely dissolved and the solution is clear (see Figure M).

Figure M

27. 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 particles are in it.

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

28. ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **3 hours** of mixing. Keep ARCALYST away from light.

Step 4: Preparing the Injection

29. Hold the ARCALYST vial in 1 hand and wipe in 1 direction around the top of the ARCALYST vial with a new alcohol wipe with the other hand (see Figure N).

Figure N

30. Take a new sterile, disposable 18-gauge needle and attach it firmly to a new syringe without removing the needle cover (see Figures O and P).

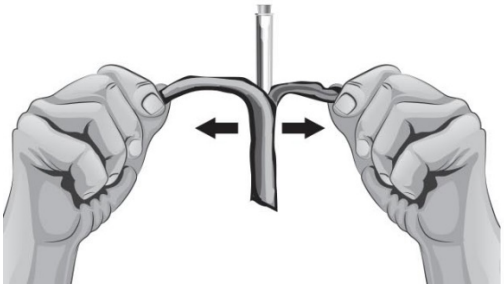


Figure O

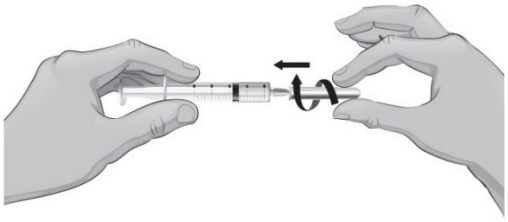


Figure P

31. To draw air into the syringe, hold the syringe upright 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 the healthcare provider has prescribed for you to inject (see Figure Q).

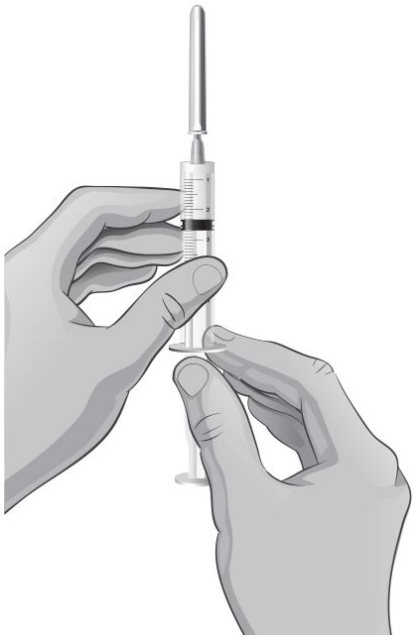


Figure Q

32. Hold the syringe in 1 hand and 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 asideand be careful not to touch the needle. Keep the ARCALYST vial on a flat firm surface and slowly insert the needle straight down through the rubber stopper. Push the plunger down and inject all of the air into the vial (see Figure R).

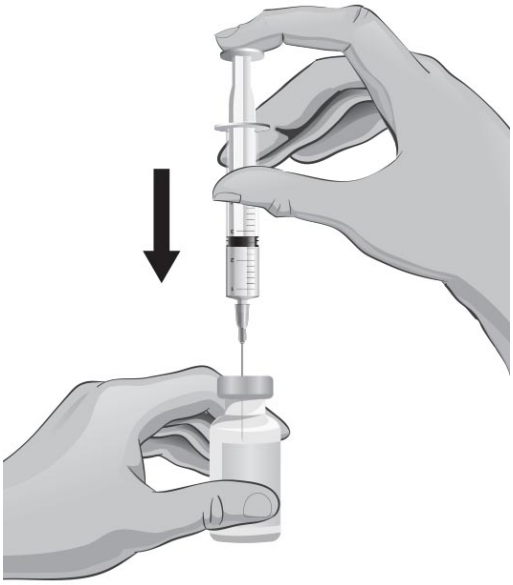


Figure R

33. Hold the vial in 1 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.
34. 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 or your child's healthcare provider (see Figure S).

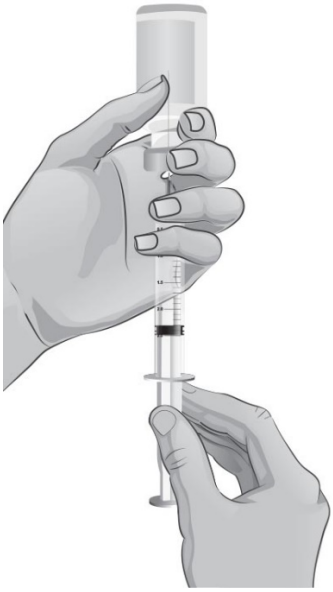


Figure S

Note: The maximum amount of medicine that you can withdraw from 1 vial of ARCALYST is 2 mL. If the amount of medicine you need to withdraw for your or your child's dose of ARCALYST is more than 2 mL, you will need to use 2 vials. The healthcare provider will tell you the right amount of medicine to withdraw from the 2 vials and how to give the 2 injections. **Always use new syringes and needles for each injection**.

35. 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 T).

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

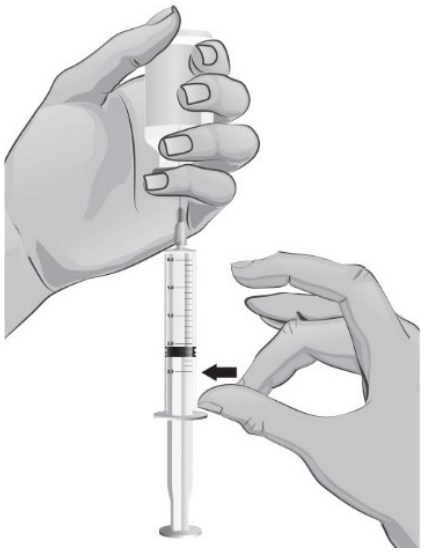


Figure T

36. To remove the air bubbles, slowly and gently push in the plunger so only the air is pushed through the needle.
37. Check to make sure that you have the amount of medicine prescribed by the healthcare provider in the syringe. Remove the syringe with the needle from the vial.
38. **You will now prepare to switch needles.**
39. To remove the 18-gauge needle and replace it with the new 26-gauge needle for injection, place the syringe with the 18-gauge needle and the needle cap on a flat surface (see Figure U1). **Use 1 hand** to slide the 18-gauge needle into the needle cap and **scoop upwards** to cover the needle (see Figure U2).
40. When the needle is covered, push the needle cap towards the syringe to fully attach it **with 1 hand** to prevent an accidental stick with the needle (see Figure U2). Twist off and remove the 18-gauge needle with the needle cap (see Figures U3 and U4).

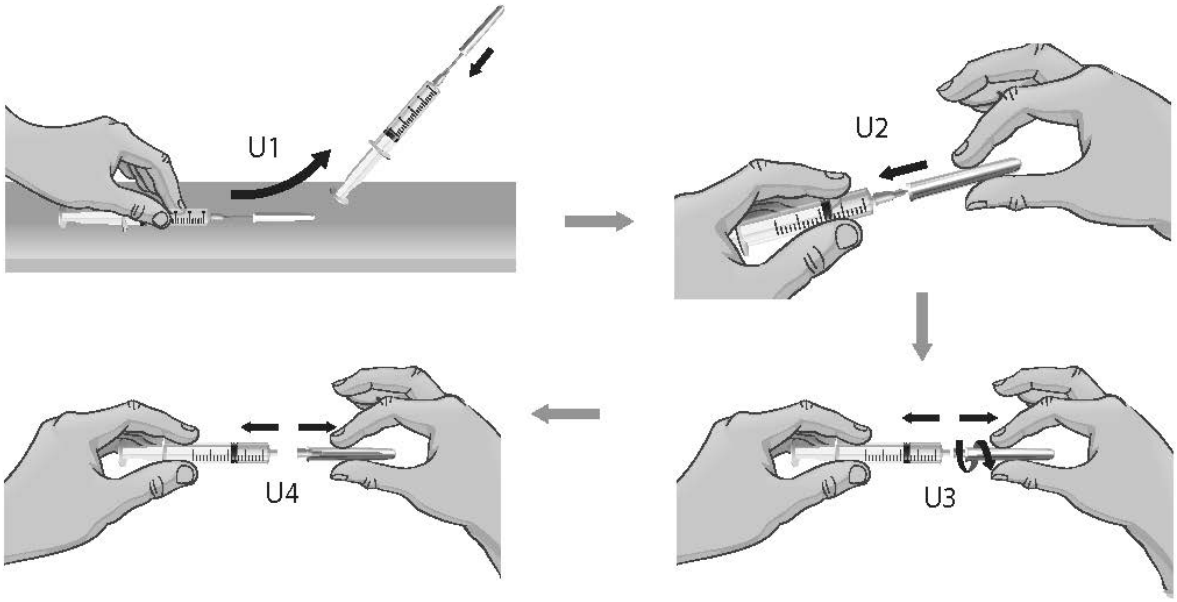


Figure U

41. Open a new sterile, disposable 26-gauge needle (see Figure V) and attach securely to the syringe without removing the needle cover (see Figure W).

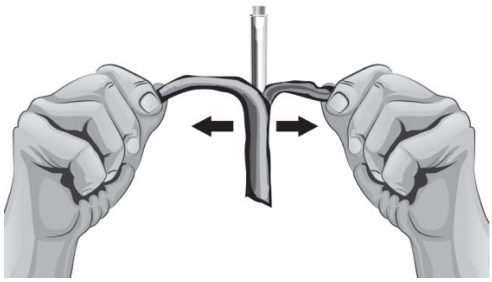


Figure V

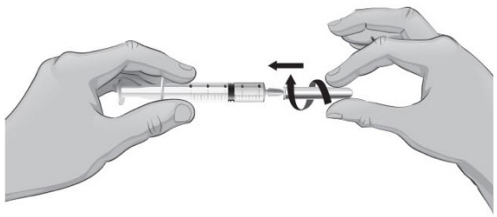


Figure W

42. Throw away the ARCALYST vial and 18-gauge needle that still has the needle cover attached to it in the sharps disposal container even if there is medicine left in the vial (see Figure X). Do not use any vial of ARCALYST more than 1 time.

Figure X

Step 5: Giving the Injection

43. ARCALYST is given by injection into the tissue directly under the skin (subcutaneous injection). Do not inject ARCALYST into any muscle, vein, or artery.

    You should change (rotate) the injection site each time you inject ARCALYST.

    If you need to use 2 vials and give 2 injections for your or your child's prescribed dose of ARCALYST, you should use 2 different injection sites.

Changing injection sites helps to prevent irritation and allows the medicine to be completely absorbed. Ask your or your child's healthcare provider if you have any questions about changing 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 or your child's 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 the left and right thighs. If you are giving the injection to your child or someone else, the upper left and right arms may also be used for injection (see Figure Y):

  Do not inject within a 2-inch area around the belly button.

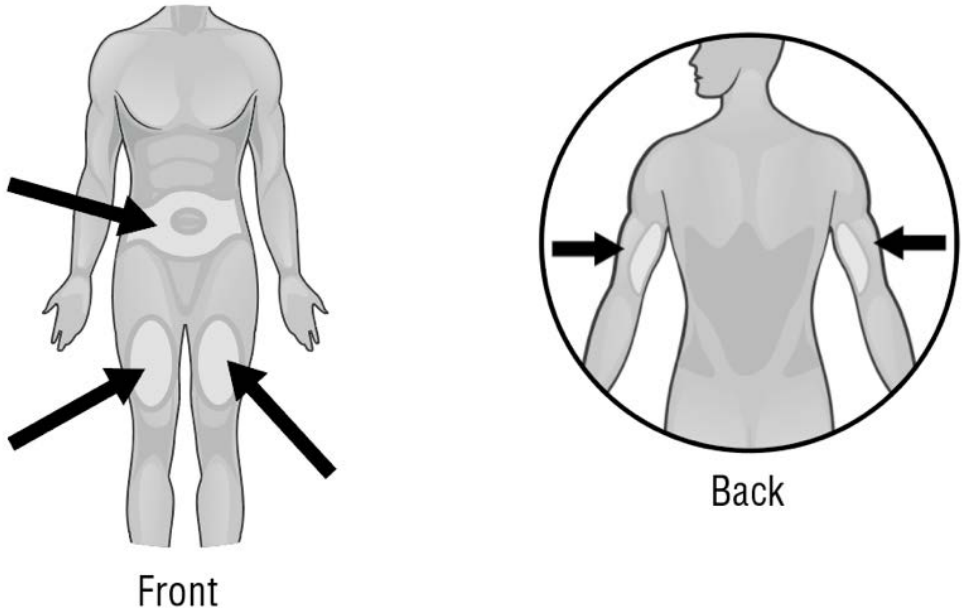


Figure Y

44. Choose the area for the injection. Clean the area in a circular motion with a new alcohol wipe. Begin at the center of the injection site and move outward. Let the alcohol air dry completely.
45. Remove the needle cover and hold the syringe in 1 hand like you would hold a pencil.
46. With the other hand gently pinch a fold of skin at the cleaned injection site (see Figure Z).

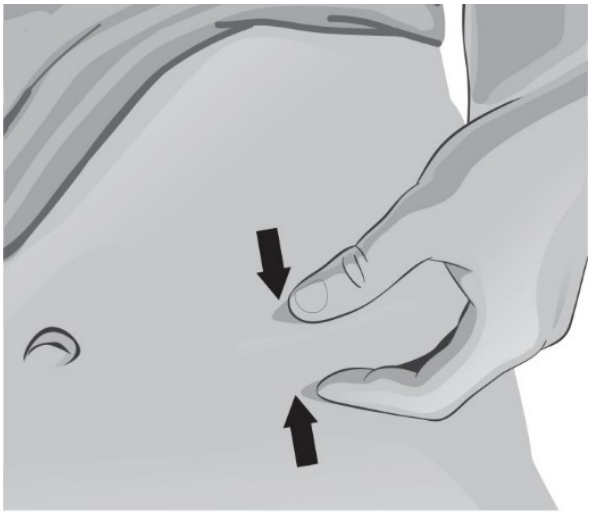


Figure Z

47. Use a quick “dart like” motion to insert the needle straight into the skin at a 90-degree angle (see Figure AA). Do not push down on the plunger while inserting the needle into the skin.

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

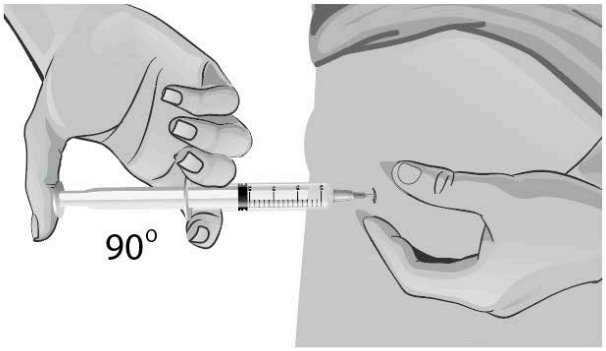


Figure AA

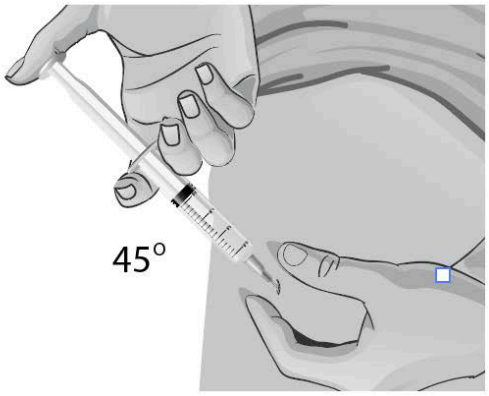


Figure BB

48. After the needle is completely in the skin, let go of the pinched skin.
49. With your free hand, hold the syringe near the bottom. Gently pull back the plunger. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle and throw away (discard) the syringe and needle in the sharps disposal container. Start over with “**Step 1: Setting up for an injection**” using new supplies (syringes, needles, alcohol swabs, gauze pad, new vials of ARCALYST and Sterile Water for Injection, USP).
50. If no blood comes into the syringe, 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.
51. Pull the needle out of the skin and hold a gauze pad over the injection site for several seconds (see Figure CC).

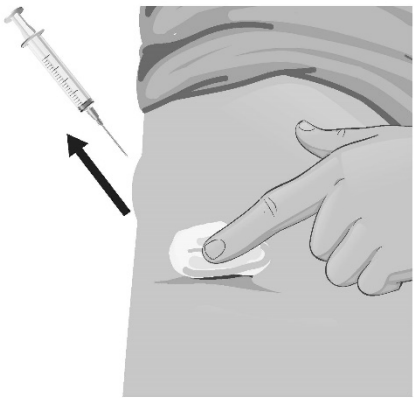


Figure CC

52. Do not replace the needle cover. Throw away the vials, used syringes and needles in an FDA-cleared sharps disposal container (see Figure DD). **Do not** throw away vials, needles, or syringes in the household trash or recycle.

    If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,

- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

Figure DD

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

- **Do not** reuse or share your syringes with other people.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.
- **Do not** recycle your used sharps disposal container.

53. Keep the sharps disposal container out of the reach of children.
54. Used alcohol wipes can be thrown away in the household trash.

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

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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KINIKSA

Manufactured by:

Kiniksa Pharmaceuticals (UK), Ltd.
London, UK W1S 4PZ
U.S. License Number 2236
NDC 73604-914-04

For more information about ARCALYST, call 1-833-KINIKSA (1-833-546-4572), or visit www.ARCALYST.com.

Revised: 03/2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125249Orig1s049

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Executive Summary

Application Type	351(a) sBLA
Application Number(s)	125249 / SN145
Priority or Standard	Priority
Submit Date(s)	21 SEP 2020
Received Date(s)	21 SEP 2020
Filing Date	20 NOV 2020
Review Completion Date	Primary Review: 15 FEB 2020; CDTL Memo: 26 FEB 2020
PDUFA Goal Date	21 MAR 2021
Division/Office	Division of Cardiology & Nephrology / OCHEN
Division Director	Norman Stockbridge MD, PhD
CDTL	Fred Senatore MD, PhD, FACC
Reviewer Name(s)	Clinical: Fred Senatore MD, PhD, FACC / Clair Ji, PhD Statistics: Dali Zhou, PhD
Established/Proper Name	Rilonacept
(Proposed) Trade Name	ARCALYST®
Applicant	Kiniksa Pharmaceuticals GmbH
Dosage Form(s)	Lyophilized Powder/sterile water vials and syringes for self-administration
Applicant Proposed Dosing Regimen(s)	Loading dose: 160 mg (2 mL) x 2 subcutaneous Maintenance Dose: 160 mg (2 mL) subcutaneous once weekly
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4)
BLA Submission	\\CDSESUB1\evsprod\BLA125249\0145

Materials Reviewed		
Reviews		
#	**Discipline (Date)**	**Reviewers**
1	Clinical/Statistics Primary Review sBLA 125249 reviews	Dr. Dali Zhou Dr. Claire Ji Dr Fred Senatore
Consults		
1	COA	Dr. Onyekachukwu Illoh Dr. Susan Pretko Dr. Elektra Papadopoulos
2	DMEPA	Dr. Maximilian Straka Dr. Hina Mehtra

Executive Summary

Brief History of the Review Process Leading to the Regulatory Action

Pericarditis

Pericarditis has been characterized as acute (few days to 3 weeks), incessant (> 4-6 weeks but less than three months without remission), recurrent (acute pericarditis with a symptom-free interval of 4-6 weeks or longer followed by symptoms and signs compatible with the original pericarditis), and chronic (lasting greater than 3 contiguous months).

The etiology of more than 80% of diagnosed acute pericarditis remains unknown after a standard diagnostic approach. Even though pericarditis is often presumed to be precipitated by a virus, the mechanisms that perpetuate inflammation and lead to recurrence are poorly understood. The hallmark presentation is chest pain, mimicking a myocardial infarction. The chest pain sometimes worsens by inspiration and improves by sitting up and leaning forward (distinguishing feature compared to the chest pain of myocardial infarction where there is no position-related or respiratory cycle pain dependency). Characteristic electrocardiograms can distinguish pericarditis (concave ST-segment elevation across all coronary artery territories) from myocardial infarction (convex ST-segment elevation focused on the territory of the infarct related artery). The clinical presentation also includes elevated biomarkers of inflammation: sedimentation rate, white blood cell count, and C-reactive protein (CRP).

There are no approved medications for the treatment of any form of pericarditis. The key standard of care treatments include aspirin and ibuprofen (1-3 weeks for acute pericarditis; weeks to months for recurrent pericarditis), and colchicine (3 months for acute pericarditis, at least 6 months for recurrent pericarditis). Other off-label treatments for recurrent pericarditis, each prescribed for months in duration, include steroids, anakinra, azathioprine, methotrexate, mycophenolate mofetil and rilonacept.

Recurrent pericarditis results in a compromised quality of life, but has an overall good long-term prognosis (i.e., no risk of mortality and no significant risk of an evolving constrictive pericarditis).

Rilonacept

Rilonacept is a recombinant fusion protein that binds to Interleukin-1α or Interleukin-1β, thus preventing interaction of these interleukins with their cell-surface receptors. Inhibition of this interleukin pathway produces an anti-inflammatory effect.

Rilonacept was approved in 2008 for the treatment of Cryopyrin-Associated Periodic Syndromes, including Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome. A BLA for rilonacept for treatment of gout flares received a complete response in 2012 because of a small therapeutic effect in the pivotal trial's intention-to-treat population (mild gout) deemed by the Arthritis Advisory Committee to not be representative of the patient population likely to be prescribed rilonacept (severe gout).

Development of Rilonacept for the Indication of Recurrent Pericarditis

The development of rilonacept for recurrent pericarditis began in 2017 with the design of RHAPSODY (***R***ilonacept In***h***ibition of Interleukin-1 *a*lpha and beta for Recurrent ***P***ericarditis: a Pivotal ***S***ymptomatology and ***O***utcomes Stu***dy***). This was a phase 3, multi-center, multi-national, double-blind, placebo-controlled, randomized-withdrawal study with an open label extension. The trial consisted of: 1) a 4-week screening period; 2) a 12-week single blind run-in (RI) period; 3) a double-blind, placebo-controlled, randomized withdrawal (RW) period for a duration dependent upon achieving 22 adjudicated recurrent pericarditis events; and 4) a long-term extension (LTE) period of up to 2 years **(Figure 1**). Rilonacept was self-administered or administered by the assistance of a health care provider subcutaneously once weekly.

Subjects were required to be diagnosed with recurrent pericarditis for eligibility to participate in the trial (acute pericarditis, 1st episode of recurrence, and 2nd episode of recurrence serving as the qualifying event for enrollment). The qualifying recurrent pericarditis event required at least 1 day of pericardial pain ≥ 4 on a numerical rating scale (NRS) for pain ranging from 0-10 (**Figure 2**) and a CRP level ≥ 1.0 mg/dL within 7 days prior to first administration of rilonacept. Both the NRS and CRP criteria were not required to be satisfied on the same day within the 7 day qualification period. Further, inclusion criteria required that at least one of the pericarditis episodes prior to screening had met at least 2 of the 4 clinical findings: 1) pericarditis chest pain; 2) pericardial rub; 3) new widespread ST-segment (concave) elevation or PR-segment depression on ECG; or 4) pericardial effusion (new or worsening).

The RI period involved weaning subjects from baseline medications while concomitantly administering rilonacept, until the treatment consisted of rilonacept monotherapy. Responders to rilonacept monotherapy, defined as no or minimal pain (NRS ≤ 2.0) and a CRP level < 0.5 mg/dL, continued to the RW period where subjects were randomized 1:1 to receive continued rilonacept or placebo.

The primary efficacy endpoint was defined as the time from randomization to the date of the first pericarditis recurrence for each subject. Each potential endpoint was dichotomously adjudicated (yes or no) by an independent committee using a pre-specified algorithm based on the following: 1) required levels of pain (NRS ≥ 4); 2) required CRP level ≥ 1.0 mg/dL; and 3) supportive clinical data (e.g. ECG, echocardiography, physical examination). There were a total of 24 data elements per subject available to the adjudication committee for ascertainment of recurrent pericarditis. Clinical judgement was used by the adjudication committee based on the totality of the evidence presented in each adjudication, rather than reliance on the categorical presence of pre-specified data elements in the absence of clinical judgement.

There were three secondary endpoints the applicant planned to be included in the label:

1. Proportion of subjects who maintained a clinical response at Week 16 of the RW period.
2. Percentage of days with no or minimal pericarditis pain in the first 16 weeks of the RW period.
3. (b) (4)

(b) (4)

Figure 1: RHAPSODY Trial Design

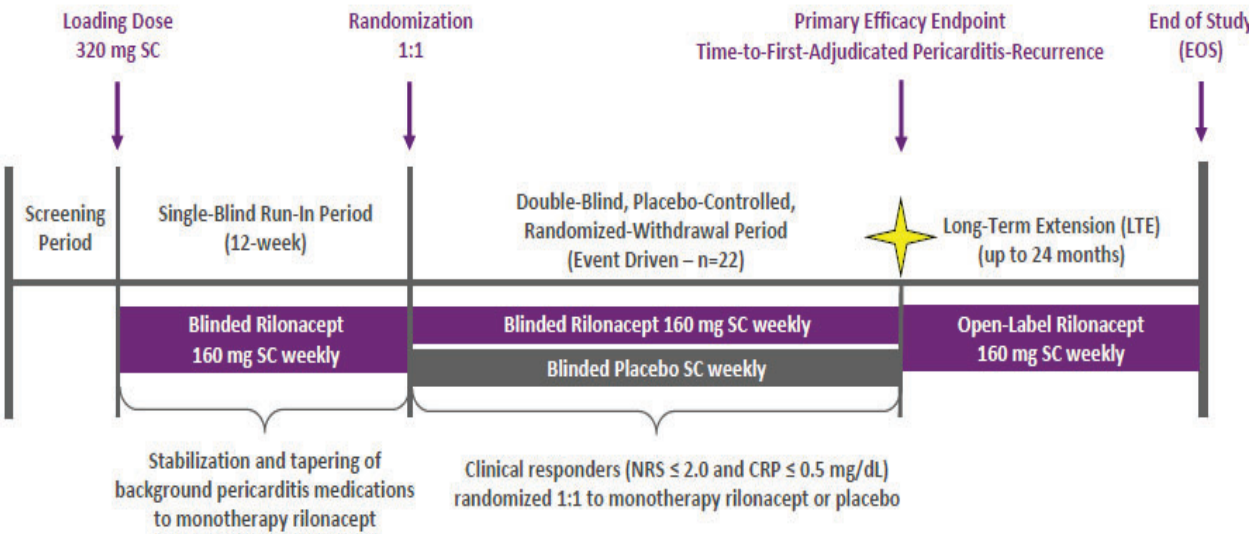
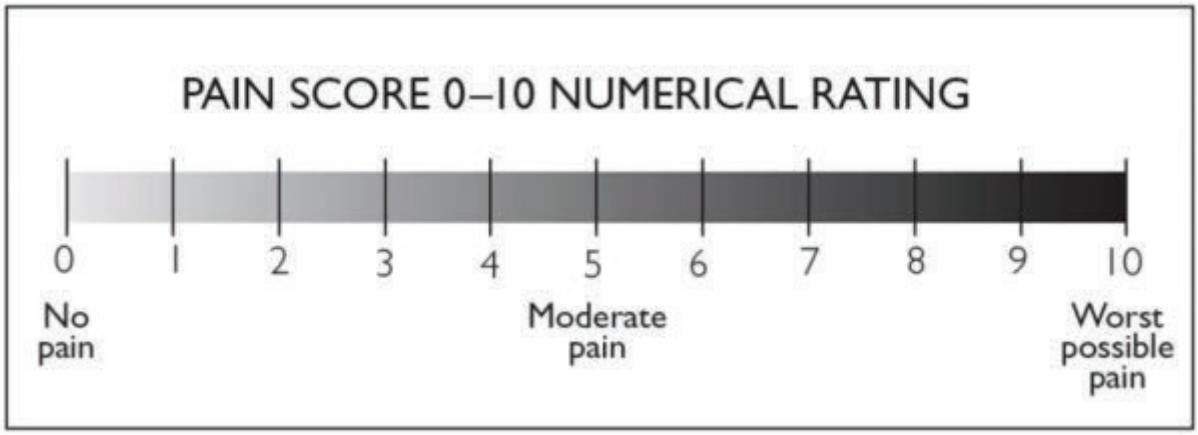


Figure 2: Numerical Pain Scale for Ascertainment of the Primary Efficacy Endpoint.



RHAPSODY Results

The trial was conducted in 46 centers in 4 countries: USA (24 sites), Australia (7 sites), Israel (11 sites) and Italy (4 sites).

There were no issues with product quality, clinical microbiology, pharmacology / toxicology, or clinical pharmacology. The Office of Scientific Investigation was not consulted because no single site or region of the world uniquely influenced the outcome of the study to warrant either a routine or for-cause audit.

The intention-to-treat population was approximately 48% - 52% male/female. The mean age was 46.4 years, 92% Caucasian, 7% black; 39 of 61 subjects in the RW period came from the USA. The mean pre-RI period baseline qualifying NRS score was 6.3 (standard deviation 1.8) and the mean pre-RI period baseline qualifying CRP level was 6.2 mg/dL (standard deviation 6.7 mg/dL).

The mean number of pericarditis episodes at enrollment was 4.4 (standard deviation 4.3). Of the 86 subjects in the RI period, approximately 92% were on baseline medications for recurrent pericarditis, including 80% on colchicine and 49% on steroids. In the RW period, 30 subjects were randomized to continued rilonacept and 31 subjects were randomized to placebo.

The primary endpoint occurred in 2 of 30 subjects in the rilonacept arm and 23 of 31 subjects in the placebo arm during the RW period. The review team assessed the NRS as capable of distinguishing moderate pain (required prior to the RI period and for the adjudicated diagnosis of recurrent pericarditis) from minimal/no pain (requisite definition of responder). From all the clinical data elements used to support the adjudication, the adjudication packages showed the diagnosis of recurrent pericarditis to be predominately based on the NRS and the CRP level with little support from ancillary clinical features (e.g., ECG, echocardiographic findings, physical exam).

The median time to recurrence of pericarditis was 8.6 weeks in the placebo arm but was not

estimable in the rilonacept arm because of the low event rate. The hazard ratio (95% CI) calculated from Cox proportional hazard model was 0.04 (0.01, 0.18), with a p value of < 0.0001 from the log rank test showing a statistically significant result in comparing the distribution of time to recurrence of pericarditis between the two arms.

The effectiveness of rilonacept was consistent across all pre-specified subgroups: use and duration of steroids at baseline, age group (18-64 years, 65-78 years), gender, region (USA, non-USA), number of pericarditis episodes at enrollment (< 5, ≥ 5), and anti-drug antibody status.

The demonstrated efficacy was durable (effective for the duration of treatment) but of limited persistence (cessation of treatment precipitated further recurrence of pericarditis within weeks). The mean exposure to rilonacept was 6 months. For this patient population, a clinical decision to treat patients with rilonacept indefinitely may be reasonable, but long term effects of rilonacept are not known in this patient population.

The design of RHAPSODY did not accommodate demonstration of rilonacept as first line treatment for pericarditis (acute or recurrent). Further, the pivotal trial did not evaluate a rapid switch from standard-of-care to rilonacept monotherapy because of weaning requirements (50% of the subjects were on steroids) and pre-planned weaning from standard of care therapy (NSAIDS, colchicine). However, the available data did not contraindicate the use of rilonacept as 1st line treatment.

Similar to most cardiovascular clinical trials, patient under-representation (i.e., paucity of Black and Latino patients) was apparent in this trial, especially when the majority of participants came from the USA. Consequently, effectiveness in these populations are have not been documented in this trial.

There was no observable rilonacept-associated safety risk except for injection-site reactions. A hypothetical risk for cancer due to rilonacept's immunosuppressive mechanism of action and a small imbalance of cancer rates in the rilonacept vs the placebo arms in the gout pivotal clinical trial has otherwise not been borne out. However, the currently approved label includes a warning about this potential risk which is adequate for conveying the risk.

The benefit of rilonacept therapy in reducing myocardial infarction-mimicking pain in each episode of recurrent pericarditis was weighed against the risk of injection-site reactions and the unsubstantiated potential for cancer. The review team assessed the benefit as outweighing the risk.

Conclusion

RHAPSODY was a well-controlled and adequately performed phase 3 clinical trial. The data from the trial met the evidentiary standard pursuant to §21 CFR 314.126 to support an indication to treat (as demonstrated in the RI period) and to prevent (as demonstrated in the RW period) recurrent pericarditis.

Treatment with rilonacept should continue for 6 months for recurrent pericarditis, but clinical judgement should be used for optimal timing and duration of treatment.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FORTUNATO F SENATORE
03/16/2021 08:28:53 AM

NORMAN L STOCKBRIDGE
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125249Orig1s049

CLINICAL REVIEW(S)

CLINICAL and STATISTICAL REVIEW

Application Type	351(a) sBLA
Application Number(s)	125249 / SN145
Priority or Standard	Priority
Submit Date(s)	21 SEP 2020
Received Date(s)	22 SEP 2020
Filing Date	20 NOV 2020
Review Completion Date	Primary Review: 15 FEB 2020; CDTL Memo: 26 FEB 2020
PDUFA Goal Date	21 MAR 2021
Division/Office	Division of Cardiology & Nephrology / OCHEN
Reviewer Name(s)	Clinical: Fred Senatore MD, PhD, FACC / Claire Ji, PhD Statistics: Dali Zhou, PhD
Established/Proper Name	Rilonacept
(Proposed) Trade Name	ARCALYST®
Applicant	Regeneron
Dosage Form(s)	Lyophilized Powder/sterile water vials and syringes for self-administration
Applicant Proposed Dosing Regimen(s)	Loading dose: 160 mg (2 mL) x 2 subcutaneous Maintenance Dose: 160 mg (2 mL) subcutaneous once weekly
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4)
BLA Submission	\\CDSESUB1\evsprod\BLA125249\0145

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Glossary

AC	advisory committee
ADA	Anti-Drug Antibody
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRT	clinical review template
CSR	clinical study report
CS	corticosteroid
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOE	Level of Evidence
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent to treat
NAb	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
OCS	Office of Computational Science
ODD	Orphan Drug Designation
OPQ	Office of Pharmaceutical Quality
ORT	Oral Rescue Therapy
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGA-PA	Physician Global Assessment of Pericarditis Activity
PGI-PS	Patient Global Impression of Pericarditis Severity
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RI	Run-In period
RW	Randomized-Withdrawal period
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

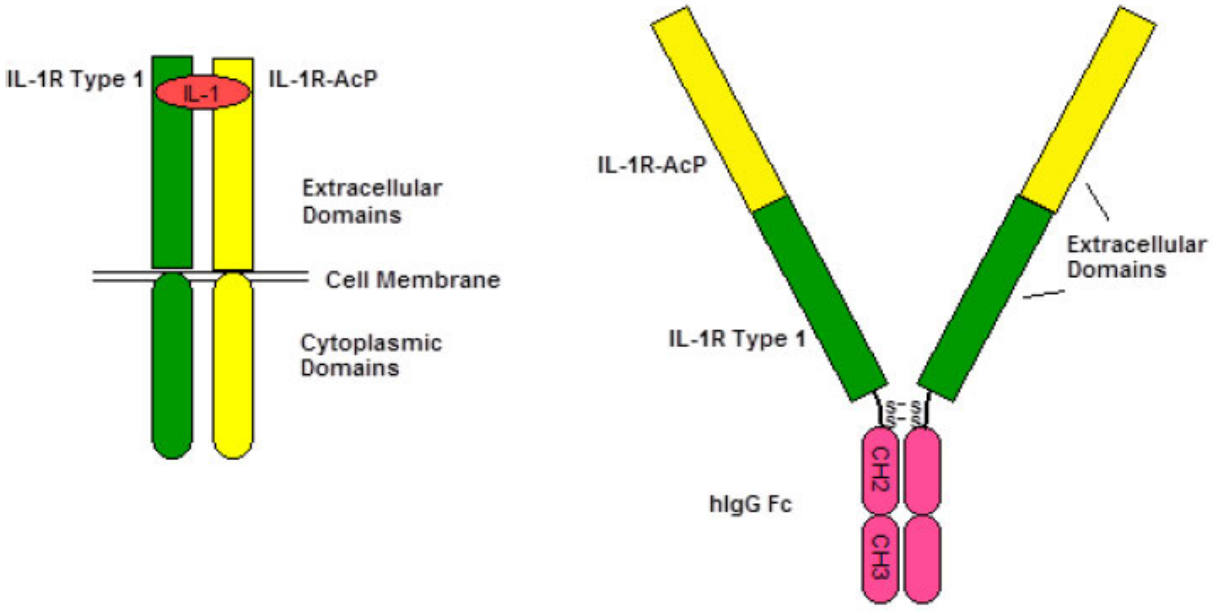
1.1. Product Introduction

Rilonacept is a recombinant fusion protein consisting of an extracellular domain and an intracellular (cytoplasmic) domain. The extracellular domain consists of two units; each unit contains two subunits required for interleukin 1 (IL-1) signaling: the IL-1 type 1 receptor (IL-1R1) and the IL-1 receptor accessory protein (IL-1R-AcP). The intracellular domain is the Fc portion of human immunoglobulin G (IgG)1 (Figure 1).

Rilonacept is created by fusing the sequences encoding for IL-1R-AcP, IL-IR1, and Fc without intervening linker sequences.

Rilonacept is reported to act as a soluble decoy receptor that binds to IL-1α or IL-1β, thus preventing their engagement with the cell-surface receptors for IL-1 and consequently inhibiting IL-1 activity (Klein et al, 2020).

Figure 1: Schematic Representation of Rilonacept



Source: IND-136896 pre-BLA Top Line Briefing Package

1.2. Conclusions on the Substantial Evidence of Effectiveness

RHAPSODY, the placebo-controlled randomized-withdrawal trial designed to demonstrate the effectiveness of rilonacept, produced results that met the statutory evidentiary standard pursuant to §21 CFR 314.126 for the treatment of recurrent pericarditis.

Recurrent pericarditis occurred in 2 of 30 subjects in the rilonacept arm and 23 of 31 subjects in the placebo arm. These statistically significant results were clinically meaningful based on pain relief as evaluated by a numerical rating scale and corroborated by C-reactive protein levels (i.e., marker of inflammation).

At baseline, enrolling subjects were required to have experienced an initial event of acute pericarditis and at least two subsequent recurrences (the last recurrence serving as the qualifying event for enrollment in the RHAPSODY trial). As there is no drug approved for recurrent pericarditis, consenting subjects were on off-label treatment (80% on colchicine, 67% on NSAIDS, and approximately 50% on corticosteroids) at baseline. From baseline pain levels and CRP levels, it can be reasonably inferred that the off-label standard of care for pericarditis was not effective in resolving the qualifying recurrence. The pivotal trial data showed that rilonacept treatment for recurrent pericarditis resolved the pain that subjects experienced while on off-label standard of care treatment. Rilonacept treatment was durable (effective while on treatment) but had limited persistence (cessation of treatment precipitated further recurrence of pericarditis within weeks). The demonstrated limited persistence raised the question of how long patients should be treated. The average exposure was 6 months and data for up to 2-years of long-term treatment is pending. For this patient population, a clinical decision to treat patients with rilonacept indefinitely may be reasonable, but long-term effects of rilonacept is currently not known in this patient population.

The design of RHAPSODY did not accommodate demonstration of rilonacept as first line treatment for pericarditis (acute or recurrent). Further, the pivotal trial did not accommodate an evaluation of a rapid switch from standard-of-care to rilonacept monotherapy because of weaning requirements with half of the ITT population on steroids as well as the pre-specified weaning process of standard treatment (e.g., NSAIDS, colchicine). The label should state these facts but leave to clinical judgment the optimal use of rilonacept with respect to when to treat and duration of treatment.

As in most cardiovascular clinical trials, the RHAPSODY trial suffered from under-representation of Black and Latino patients, thus rendering non-conclusive the effectiveness

of rilonacept in these populations.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Benefit

Recurrent pericarditis occurred in 2 of 30 subjects in the rilonacept arm and 23 of 31 subjects in the placebo arm. These results were deemed clinically meaningful based on pain relief as evaluated by a numerical rating scale and corroborated by C-reactive protein levels (i.e., marker of inflammation). The results were shown to be durable (effective for the duration of treatment) but of limited persistence (cessation of treatment precipitated further recurrence of pericarditis within weeks). The mean exposure to rilonacept was 6 months. For this patient population, a clinical decision to treat patients with rilonacept indefinitely may be reasonable, but long-term effects of rilonacept are not known in this patient population pending long-term (up to 2 years) safety data availability.

Risk

During the mean 6-month exposure, there were no deaths. The most common adverse events were injection site reactions (34%) and infections (34%), none of which were SAEs.

There was a concern about rilonacept causing cancer because of its immunosuppressive action. During the evaluation for a gout indication that led to non-approval mainly for a low therapeutic effect and a trial population unlikely to be the target of prescription in clinical practice, there was a small numerical increase in cancer events in the rilonacept arm (0.4%) compared to placebo (0%) considered real by the Arthritis Advisory Committee.

Following approval of rilonacept in 2008 for cryopyrin-associated periodic syndrome (CAPS), including familial cold autoinflammatory syndrome and Muckle-Wells Syndrome, approximately 365 patients were exposed to rilonacept between 2008 and 2018 in the post-market setting. Thirty-one SAEs were reported between 2011-2020. The most frequent SAEs were infections and infestations (system of organ class, or SOC, 19 cases), followed by surgical/medical procedures (SOC, 7 cases), pneumonia (preferred term, or PT, 4 cases), and CAPS (PT, 4 cases). There was one report of breast cancer and one report of non-serious squamous cell carcinoma during this post-market time period.

Benefit-Risk Evaluation

The benefit associated with reducing the incidence of recurrent pericarditis is weighed against the risk of injection-site reactions, non-serious infections, and the hypothetical potential for cancer not substantiated from the existing safety database. Recurrent pericarditis that is usually

as painful as that associated with a myocardial infarction, results in a compromised quality of life but has an overall good long-term prognosis (i.e., no risk of mortality and no significant risk of an evolving constrictive pericarditis). The benefit of reducing the pain accompanying each episode of recurrent pericarditis is assessed as outweighing the discomfort of an injection site reaction.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pericarditis has been characterized as acute, incessant, recurrent and chronic. For all types of pericarditis, symptoms and signs include: chest pain (sometimes pleuritic) with improvement by sitting up and leaning forward, pericardial friction rub on auscultation, widespread concave upward ST-segment elevation and/or PR-segment depression on ECG, new or worsening pericardial effusion (echocardiography), evidence of pericardial inflammation on imaging (CT, MRI), and elevated markers of inflammation (sedimentation rate, white blood cell count, and C-reactive protein). • Acute pericarditis can last for a few days to 3 weeks. Incessant pericarditis lasts 4-6 weeks but less than 3 months without remission. Recurrent pericarditis is defined as a documented first attack of acute pericarditis with a symptom free interval of 4-6 weeks or longer, and evidence of subsequent recurrence documented by recurrent symptoms/signs compatible with pericarditis. Chronic pericarditis lasts for greater than 3 months. • Recurrent pericarditis affects about 20%--50% of all patients with	The clinical context of the proposed rilonacept indication is the treatment of recurrent pericarditis, defined as a return of original symptoms / signs of an initial event that follows a symptom-free interval of 4-6 weeks or longer.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	a first treatment for pericarditis. Lower rates have been reported in patients who received colchicine in the first or subsequent episode of pericarditis. The risk of recurrence is especially high in those treated with corticosteroids, as well as in those with multiple recurrences and those where the etiology of pericarditis is not known.	
Current Treatment Options	• No drug has been approved by the FDA for the treatment of pericarditis of any type. • In acute pericarditis, the treatment paradigm includes aspirin, ibuprofen, or colchicine. • In recurrent pericarditis, treatment includes longer durations of aspirin, ibuprofen, colchicine, as well as indomethacin, prednisone, anakinra, methotrexate, azathioprine, mycophenolate mofetil, IVIG and rilonacept. The level of evidence (LOE) for aspirin, ibuprofen, and colchicine was rated as A (indicates data derived from multiple randomized clinical trials or meta-analyses). The LOE for indomethacin and prednisone was rated as B (data derived from a single randomized clinical trial or large non-randomized studies [≥ 100 subjects]). The LOE for azathioprine, anakinra, and IVIG was rated as C (consensus of expert opinion/ data from small studies, retrospective studies, or registries). Evidence for rilonacept was not documented.	Rilonacept may be the first drug / biologic approved for the treatment of recurrent pericarditis. The current off-label standard of care relies on publications and data that were not formally reviewed by the FDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Evidence • RHAPSODY was a well-controlled and adequately performed clinical trial. The effectiveness of rilonacept demonstrated in RHAPSODY met the standard of evidence required to approve rilonacept for the treatment of recurrent pericarditis. • Recurrent pericarditis occurred in 2 of 30 subjects in the rilonacept arm and 23 of 31 subjects in the placebo arm. These results were statistically significant and were deemed clinically meaningful based on pain relief as evaluated by a numerical rating scale and corroborated by C-reactive protein levels (i.e., marker of inflammation). Uncertainties • Rilonacept treatment for recurrent pericarditis was shown to be durable (effective for the duration of treatment) but had limited persistence (cessation of treatment precipitated further recurrence within weeks). This raised the question of how long patients should be treated. The average exposure was 6 months. For this patient population, a clinical decision to treat patients with rilonacept indefinitely may be reasonable, but long-term effects of rilonacept are not known in this patient population. • The RHAPSODY trial was not designed to show evidence supporting the use of rilonacept as first line treatment for pericarditis (acute or recurrent). Further, RHAPSODY did not evaluate a rapid switch from standard-of-care to rilonacept monotherapy because of weaning requirements (50% of the subjects were on steroids) and pre-planned	• Rilonacept effectively reduced the incidence of recurrent pericarditis in patients with at least two recurrent episodes. • Rilonacept was durable but had limited persistence. • The pivotal trial was not designed to show rilonacept as 1st line therapeutic agent, but the available data has not contraindicated its use as 1st line treatment. • There was no data supporting a rapid switch from standard-of-care to rilonacept monotherapy. • Effectiveness in Black and Latino patients could not be determined due to under-representation in the pivotal trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weaning from standard of care therapy (NSAIDS, colchicine). However, the available data did not rule out use of rilonacept as 1st line treatment. • Similar to most cardiovascular clinical trials, patient under-representation (i.e., paucity of Black and Latino patients) is apparent in this trial, especially when the majority of participants came from the USA. Consequently, effectiveness in these populations are undetermined.	
Risk and Risk Management	• There was no observable rilonacept-associated risk except for injection-site reactions and non-serious infections. • A hypothetical risk for cancer due to rilonacept's immunosuppressive mechanism of action and a small imbalance of cancer rates in the rilonacept vs the placebo arms in a gout clinical program has otherwise not been borne out.	The risk of rilonacept appears to be focused on injection-site reactions and non-serious infections.

1.4. Patient Experience Data

This sBLA is based on patient experience data: Numerical Rating Scale for pain.

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
	X	□	Patient reported outcome (PRO)	Sec 9.5.3.5 Sec 11.4.3.6
		□	Observer reported outcome (ObsRO)	
	X	□	Clinician reported outcome (ClinRO)	Sec 9.5.3.5 Sec 9.8.1.1
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Pericarditis has been characterized as acute, incessant, recurrent and chronic. For all types of pericarditis, symptoms and signs include: chest pain (sometimes pleuritic) and improved by sitting up and leaning forward, pericardial friction rub on auscultation, widespread concave upward ST-segment elevation and/or PR-segment depression on ECG, new or worsening pericardial effusion (echocardiography), evidence of pericardial inflammation on imaging (CT, MRI), and elevated markers of inflammation (sedimentation rate, white blood cell count, and C-reactive protein).

Acute pericarditis can last for a few days to 3 weeks. Incessant pericarditis lasts 4-6 weeks but less than 3 months without remission. Recurrent pericarditis is defined as a documented first attack of acute pericarditis with a symptom free interval of 4-6 weeks or longer, and evidence of subsequent recurrence documented by recurrent symptoms/signs compatible with pericarditis. Chronic pericarditis lasts for greater than 3 months.

The etiology of more than 80% of diagnosed acute pericarditis remain unknown (idiopathic) after a standard diagnostic approach (Brucato et al., 2018). Even though pericarditis is often presumed to be precipitated by a virus, the mechanisms that perpetuate inflammation and lead to recurrence are poorly understood.

Large epidemiologic studies on pericarditis are not available and are difficult to organize because the diagnosis is mostly clinical. However, in an observational study from an Italian urban area of 220,000 inhabitants, pericarditis incidence was reported in 27.7 cases per 100,000 person-years; and data from a Finnish national registry demonstrated a standardized incidence rate of hospitalizations for acute pericarditis of 3.32 per 100,000 person-years. Overall, pericarditis accounts for 0.2% of all hospital cardiovascular admissions and is in approximately 5% of patients with nonischemic chest pain in emergency departments in North America and Western Europe. The incidence of pericarditis in postmortem studies ranges from 1% to 6% (Lombardi, 2017).

Recurrent pericarditis affects about 20%--50% of all patients with a first treatment for pericarditis. Lower rates have been reported in patients who received colchicine in the first or subsequent episode of pericarditis. The risk of recurrence is especially high in those treated with corticosteroids, as well as in those with multiple recurrences and those where the etiology of pericarditis is not known (Imazio et al., 2016).

Similar to acute pericarditis, most cases of recurrent pericarditis are idiopathic, but the pathogenesis is presumed to be immune-mediated or auto-inflammatory (Table 1). This

presumption is supported by detection of autoantibodies in patients with idiopathic recurrent pericarditis (Imazio et al., 2016). Other etiologies of recurrent pericarditis are infectious (mostly viral), systemic / autoinflammatory disease, and neoplastic pericardial disease.

Despite a compromising quality of life, patients with idiopathic recurrent pericarditis have an overall good long-term outcome without mortality and without a significant risk of an evolving constrictive pericarditis (Imazio et al., 2017)

Table 1: Etiology of Recurrent Pericarditis

Etiology of Recurrent Pericarditis	Frequency
Idiopathic	>70%
Infectious, especially viral	Up to 33%
Systemic inflammatory disease/pericardial injury	5-10%
Autoinflammatory Disease	5-10%
Neoplastic pericardial disease	5%
Inadequate treatment of index pericarditis episode	Unknown

Source: Imazio et al., 2016

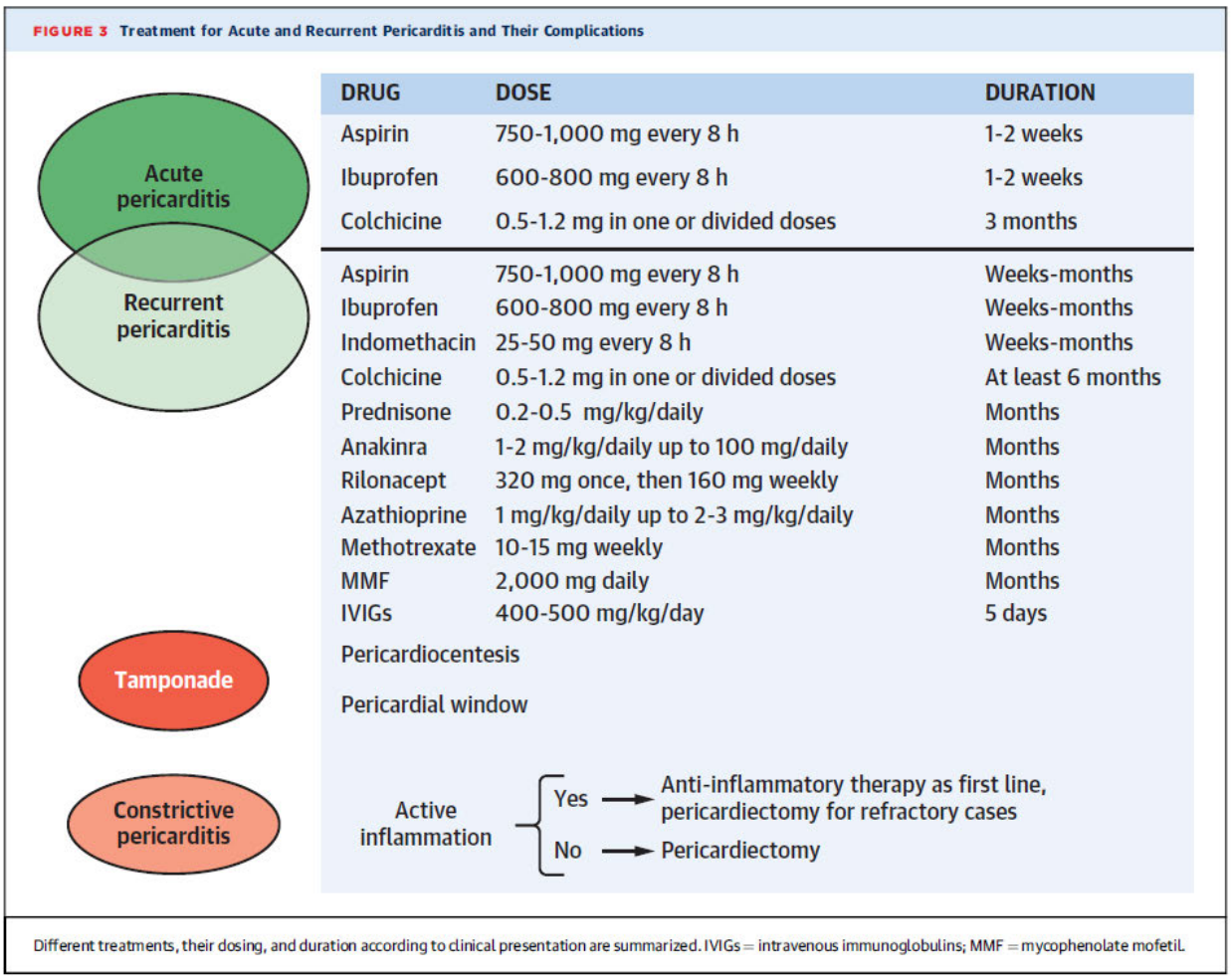
2.2. Analysis of Current Treatment Options

No drug has been approved by the FDA for the treatment of pericarditis of any type.

The current treatment for acute and recurrent pericarditis is shown in Table 2. In acute pericarditis, the treatment paradigm includes aspirin, ibuprofen, or colchicine. In recurrent pericarditis, treatment includes longer durations of aspirin, ibuprofen, colchicine, as well as indomethacin, prednisone, anakinra, methotrexate, azathioprine, mycophenolate mofetil, IVIG and rilonacept. The level of evidence (LOE) for aspirin, ibuprofen, and colchicine was rated as A (indicates data derived from multiple randomized clinical trials or meta-analyses). The LOE for indomethacin and prednisone was rated as B (data derived from a single randomized clinical trial or large non-randomized studies [≥ 100 subjects]). The LOE for azathioprine, anakinra, and IVIG was rated as C (consensus of expert opinion/ data from small studies, retrospective

studies, or registries) (Imazio, 2016). Evidence for rilonacept was not documented.

Table 2: Treatment for Acute and Recurrent Pericarditis



Source: Chiabrando et al., 2020.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ARCALYST® (rilonacept) was approved by the FDA on 27 FEB 2008 for the treatment of Cryopyrin-Associated Periodic Syndromes, including Familial Cold Autoinflammatory Syndrome

and Muckle-Wells Syndrome in adults and children 12 years of age and older. In adults ≥ 18 years of age, treatment initially begins with two 2-mL subcutaneous injection of 160 mg on the same day at two different sites. Maintenance dosing continues with a once weekly injection of 160 mg administered as a single 2-mL subcutaneous injection. A key warning includes interference with the immune system, thus leaving subjects susceptible to life-threatening infections. Key precautions include instructions to discontinue treatment if a serious infection develops, to not initiate treatment in patients with active or chronic infections, and to not administer concomitant live vaccines.

Rilonacept was not approved to prevent gout flares during initiation of uric-acid lowering therapy in adult patients with gout (b) (4) . The proposed dosage for the gout indication was 80 mg or 160 mg SC once weekly for 16 weeks.

A meeting was convened with the Arthritis Advisory Committee (AAC) on 08 MAY 2012 to evaluate the benefit/risk profile from the BLA supplement. The AAC was divided on whether the efficacy data supported approval for the proposed indication (6 yes, 5 no). The no-voters expressed concern that the indicated population was not representative of the population in which this product would be used (patients with more severe gout and for longer duration of illness), and that efficacy data lacked context versus other available treatment alternatives (i.e., colchicine and NSAIDS were prohibited although tolerated in the evaluated patient population). Further, the AAC agreed that 16 weeks may not have been an adequate duration of treatment for all patients. Regarding safety, the panel voted against the adequacy of the safety database (3 yes, 8 no). The committee voted 11-0 against approval.

(b) (4)

(b) (4)

3.2. Summary of Pre-submission/Submission Regulatory Activity

- 29 SEP 2017: Kiniksa submitted IND 136896 for rilonacept (KPL-914) for the treatment of recurrent idiopathic pericarditis. The development program consisted of 2 studies in patients with symptomatic recurrent pericarditis: 1) KPL-914-C001, an Open-Label Pilot Study, and 2) KPL-914-C002, a Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study with an Open Label Extension. Dosology in both studies included a subcutaneous loading dose (160 mg x 2) followed by weekly self-administered subcutaneous dosing (160 mg). Analgesics were allowed as rescue medication. The primary endpoint was C-reactive protein levels and pericarditis symptoms using an 11-point numerical rating scale.
- 02 NOV 2017: Sponsor was notified of permission to proceed with a key non-hold comment to exclude subjects taking high-dose steroids.
- 17 JUL 2018: EOP2 meeting took place where the FDA agreed that the ongoing single phase 3 trial could support a supplemental application.
- 21 NOV 2019: Rilonacept was granted breakthrough designation.
- 04 MAR 2020: At a Type-B meeting, the sponsor proposed to close the 24-week randomized withdrawal period as soon as at least 22 adjudicated events have been accrued. Thus, closure would occur before all subjects have completed the 24-weeks. The rationale for this proposal was 22 events will generate sufficient power (assuming a HR 0.244, 1-sided alpha 0.025, 90% power). Originally, closure of the 24-week randomized withdrawal period would have occurred after at least the 22nd adjudicated recurrent pericarditis event and after all subjects have been treated in the 24-week period. The Division agreed to this proposal provided that the interim results would not have influenced the decision to amend the protocol. In response to a separate question, the Division agreed that restriction of the Integrated Summary of Safety to the recurrent pericarditis population was acceptable.
- 16 APR 2020: Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 360bb), rilonacept was granted orphan-drug designation (ODD) for the treatment of recurrent pericarditis.
- 31 JUL 2020: In a teleconference, the sponsor reported top-line results from the pivotal trial (RHAPSODY). The Division of Cardiology & Nephrology (DCN) indicated that the topline data would support a supplemental BLA. DCN also agreed that there was a good case for priority review to be decided after the sBLA submission.
- 25 AUG 2020: At a Type B teleconference meeting, DCN accepted the sponsor's proposal for the 120-day safety update to include > 105 unique subjects exposed, 50-60 subjects with 6 months exposure, and 20-25 subjects with 1- year exposure. DCN agreed

with the content and format of the electronic datasets as well as the proposed table of contents. Based on the ODD, DCN agreed that rilonacept was exempt from PREA requirements.

3.3. Foreign Regulatory Actions and Marketing History

- 10 JUL 2007: Rilonacept was granted orphan designation (EU/3/07/456) by the European Commission to Regeneron UK, Limited, UK for the treatment of cryopyrin-associated periodic syndromes such as Familial Cold Urticaria Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multisystem Inflammatory Disease (also known as Chronic Infantile Neurological Cutaneous Articular Syndrome).
- 23 OCT 2009: Rilonacept was approved by the EMA for the indications under orphan designation.
- 24 OCT 2012: Rilonacept was withdrawn at the request of the sponsor Regeneron. Orphan designation was rescinded simultaneous to the withdrawal of marketing authorization (https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307456). In a public statement from the EMA press office (EMA/695977/2012), the reason for the sponsor's voluntary withdrawal of marketing authorization was commercial. The product was reportedly never on the market in any country of the European Community (https://www.ema.europa.eu/en/documents/public-statement/public-statement-rilonacept-regeneron-withdrawal-marketing-authorisation-european-union_en.pdf).

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI was not consulted for this supplemental BLA. No individual sites impacted the outcome of the trial based on sensitivity analyses.

4.2. Product Quality

No issues.

4.3. Clinical Microbiology

No issues.

4.4. Nonclinical Pharmacology/Toxicology

No issues.

4.5. Clinical Pharmacology

No issues.

4.6. Devices and Companion Diagnostic Issues

No issues.

4.7. Consumer Study Reviews

No issues.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

One pivotal clinical trial served as the source of evidence of efficacy (KPL-914-C002). A pilot study (KPL-914-C001) was added to the pivotal trial to serve as an additional source for safety evaluation (Table 3).

Table 3: Listing of Clinical Trials Relevant to BLA-125429

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
KPL-914-C002	03737110	Phase 3, multi-center, double-blind placebo-controlled randomized withdrawal study with an open label long-term extension.	Adults 320 mg (2x160 mg) SC at baseline, then 160 mg/week SC Pediatric 4.4 mg/kg (2x2.2 mg/kg, max 160 mg each dose) at baseline, then 2.2 mg/kg/week SC (max 160 mg SC)	Time to pericarditis recurrence, defined as time from randomization to date of first pericarditis recurrence for each subject.	Run-in period: 12-week single-blind. Double-blind withdrawal period: duration defined when 22 recurrent pericarditis events occurred. Long-term extension: up to 24 months.	86 enrolled/79 completed/15 continuing long-term extension at time of data cut-off.	Patients with a diagnosis of recurrent idiopathic pericarditis (RIP).	# Centers 46 # Countries 4 (USA, Australia, Israel, and Italy).
Studies to Support Safety								
KPL-914-C001	03980522	Phase 2 open-label single-active arm pilot study. Study divided in 5 parts: *Parts* *1*: RIP at least one previous recurrence,	Adults Load: 320 mg (2x160 mg) SC at baseline, then 160 mg/week SC Pediatric Load: 4.4 mg/kg (2x2.2 mg/kg,	Parts 1, 2, 4 Variability of CRP and 11-point Numerical Rating Scale for pericardial pain. Parts 3 and 5 -Disease activity	-Treatment period: 2 to 6 week: up to 6 doses (Day 0, Week # 2, 3, 4, 5, 6). -Long-term extension: 18 weeks.	25 enrolled/23 completed in extension. Parts *1*: 12 (11 completed in extension). *2*: 3 (3 completed in	Patients with a diagnosis of RIP or post pericardiotomy syndrome (PPS).	# Centers 14 # Countries 1 (USA)

		symptomatic, elevated CRP. *2*: RIP at least one previous recurrence, symptomatic, CRP not elevated, MRI confirmed. *3*: RIP at least two previous recurrences, steroid dependent and not meeting criteria for a flare. *4*: PPS at least one previous recurrence, elevated CRP. *5*: PPS at least two previous recurrences, steroid dependent and not meeting criteria for a flare.	max 160 mg each dose) at baseline, then 2.2 mg/kg/week SC (max 160 mg SC)	after steroid taper.		extension). *3*: 6 (5 completed in extension). *4*: 1 (1 completed in extension). *5*: 3 (3 completed in extension).		

Source: BLA Package: Clinical Summary (module 2.7), CSRs of both studies (module 5)

5.2. Review Strategy

The applicant's efficacy analysis was confirmed by the review team statistician via re-analysis. Safety evaluation was based on: 1) integration of trial KPL-914-C002 and the pilot study KPL-914-C001; and 2) safety data from the gout (b) (4)

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. KPL-914-C002: RHAPSODY (*R*ilonacept In*h*ibition of Interleukin-1 *a*lpha and beta for Recurrent *P*ericarditis: a Pivotal *S*ymptomatology and *O*utcomes Stu*dy*)

6.1.1. Study Design

Overview and Objective

The primary objective was to assess the efficacy of rilonacept in subjects with recurrent pericarditis. The secondary objective was to assess the safety of rilonacept in the same patient population.

Dosology

The rilonacept dose in the RHAPSODY trial was the same as that currently approved for the Cryopyrin-Associated Periodic Syndromes: 320 mg SC load (4.4 mg/kg in subjects 12←→18 years, inclusive) followed by once weekly SC doses at 160 mg (2.2 mg/kg in subjects 12←→18 years, inclusive). There was no dose-response study to ascertain the optimal dose for this proposed indication. The dose chosen for RHAPSODY was assumed to be effective as demonstrated in other inflammatory conditions for which rilonacept was approved.

Trial Design

RHAPSODY was a Phase 3, multicenter, double blind, placebo controlled, randomized withdrawal study with an open-label extension (Figure 2). The trial was conducted at 46 centers in 4 countries (USA, Australia, Israel, and Italy), totaling 46 principal investigators and 138 sub-investigators. There were 24 sites in the USA (24 investigators, 66 sub-investigators); 7 sites in Australia (7 investigators, 21 sub-investigators), 11 sites in Israel (11 investigators, 33 sub-investigators); and 4 sites in Italy (4 investigators, 18 sub-investigators) See appendix 13.3 for a complete list of investigators.

The trial consisted of: 1) a 4-week screening period; 2) a 12-week single blind run-in (RI) period; 3) a double-blind, placebo-controlled, randomized withdrawal (RW) period for a duration dependent upon achieving 22 adjudicated recurrent pericarditis events; and 4) a long-term extension (LTE) period of up to 2 years.

In the single-blind 12-week RI period, rilonacept was administered SC once weekly to all subjects. The dose was 320 mg (2 SC injections of 160 mg each) followed by a 160 mg SC once weekly throughout the RI period. Once weekly doses were either self-administered by the subject or by a health care provider in an outpatient visit. The RI period was subdivided into a 1-week stabilization period, a 9-week weaning period, and a 2-week monotherapy period.

In the 1-week stabilization period, blinded rilonacept was administered in addition to standard-of-care (SOC) pericarditis therapy.

In the 9-week weaning period, subjects were weaned from background SOC therapy while blinded rilonacept treatment continued. The weaning of NSAIDs, corticosteroids, and colchicine were tapered according to guidelines in the Pharmacy Manual. In this trial, aspirin was considered to be an NSAID. In general, corticosteroids were weaned starting at week 1 of the RI period and withdrawn at the end of the 9-week period. NSAIDs and colchicine were weaned starting at week 4 of the run-in period and withdrawn at the end of the 9-week period.

In the 2-week monotherapy period, subjects who were successfully weaned from SOC therapy continued to receive rilonacept monotherapy for 2 weeks.

Subjects on rilonacept monotherapy who achieved a clinical response were randomized 1:1 to rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects $\geq$ 12 and < 18 years old) SC once weekly or matching placebo SC once weekly in the RW period. A clinical response was defined as an 11-point Numerical Rating Scale (NRS) $\leq$ 2.0 and CRP < 0.5 mg/dL. Subjects were blinded to the time of transition from the RI period to the RW period (i.e., they were unaware of the duration of the RI period).

The following information request was submitted to the Applicant in the 74-day letter:
Regarding trial design, you stated that subjects were blinded to the time of transition from the 12-week single *blind run-in period (RI) to the double-blind randomized withdrawal (RW) period. The RI was comprised of distinct periods: a 1-week stabilization period, a 9-week weaning period, and a 2-week rilonacept monotherapy period. Subjects who responded to rilonacept monotherapy were then randomized to the RW period. Based on this design, it is not clear who was blinded and how the subjects would not have known the transition between the RI and the RW period. We would appreciate a clarification.*

The Applicant responded as follows:

"At the beginning of a Run-in (RI) Period, eligible subjects were informed that they would receive rilonacept treatment to allow for tapering of background standard-of-care (SOC) pericarditis medications. Subjects eligible for participation in the RW Period (i.e., who successfully met Clinical Response criteria, including NRS ≤2, CRP ≤0.5, had tapered off of all background SOC treatments, and completed 2 weeks of rilonacept monotherapy without experiencing a recurrence) were randomized to rilonacept or placebo at the RI Week 12/RW Baseline Visit). However, subjects were not informed of the duration of the run-in period or when they were going to be transitioned to the Randomized Withdrawal (RW) Period; they were simply told that at some point in the trial they had a 50/50 chance of receiving placebo. To support that objective, the drug supply provided to patients during the RI and RW periods was identical (blinded) so as to blind that transition point to the subjects. The investigators, however, who were aware of the 12-week duration of the run-in period, as they had to assess eligibility for randomization were strictly and consistently instructed and reminded not to alert the subjects in any way of the Week 12 assessment or randomization decision. Therefore, "single blind" for the RI Period refers to the subjects-only being blinded to the time of their transition from active (but blinded) rilonacept in the RI period to randomized, double-blind (rilonacept or placebo) treatment in the RW period."

We also requested the IFCs that were not originally provided in the BLA but were available upon request. A review of the US Master Adult Informed Consent Forms version 1.0 (05 OCT 2018) and version 5.0 (11 MAR 2020) showed that the precise time of randomization to the RW period was not specified, consistent with the intent by the applicant to not alert the subject to the transition time from RI to RW, thus maintaining the single-blind.

The NRS is shown in Figure 3. An NRS $\leq$ 2 signifies a range from no pain to three ordinal scale categories below that categorized as moderate pain (i.e., NRS score of 5). An episode of recurrent pericarditis required recurrence of pain to an NRS level $\geq$4 and an elevated CRP based on adjudication criteria described in the next session (Adjudication Process). The recurring pain was defined as typical of pericarditis associated with or without supportive evidence of

pericarditis (Clinical Study Report Synopsis-CTD 5.3.5.1)

During the event-driven double-blind RW period, clinic visits occurred monthly for 6 months, and every two months thereafter. At the announced end of the double-blind period following the achievement of 22 adjudicated events, subjects underwent an end-of-randomized-withdrawal visit.

At these visits, subject status evaluation included concomitant medications, CRP level (measured at a central lab), study drug compliance review, assessment of pericarditis recurrence and adverse event reporting. Echocardiography, 12 lead ECG, and quality of life assessments occurred at month 6 and at the end-of-randomized-withdrawal visit. The 11-point NRS score for pericardial pain was measured daily (see schedule of events in Appendix 13.4).

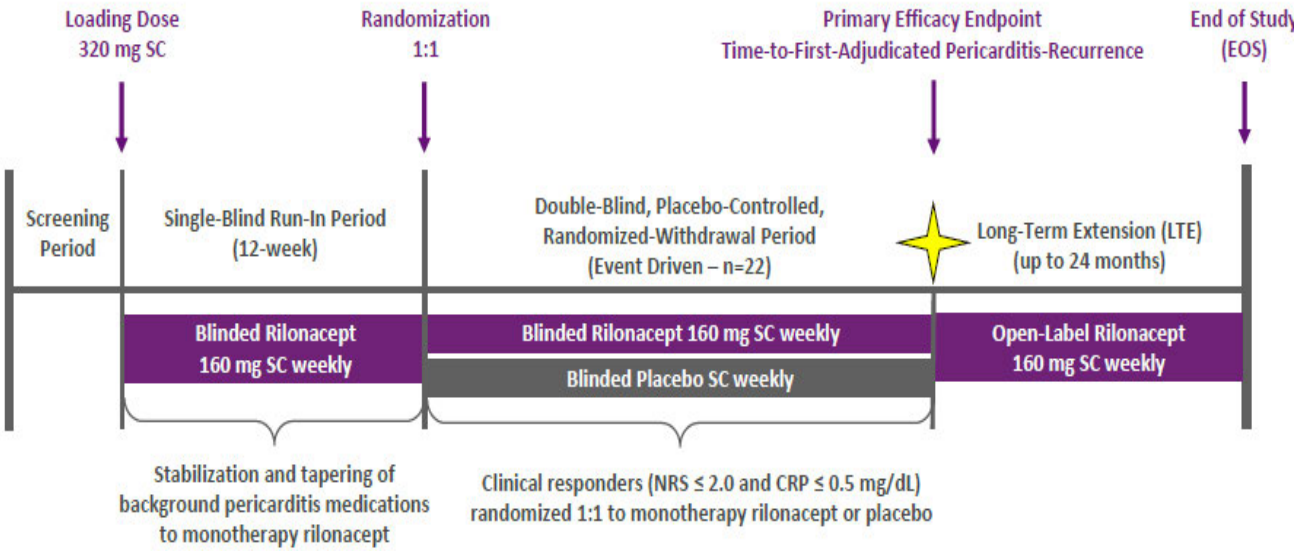
Management of suspected recurrent pericarditis (Figure 4) in the RW period required assessment of NRS and CRP. If NRS was $\geq$ 4 and CRP was $\geq$ 1.0 mg/dL, the subject was provided oral rescue therapy (ORT). ORT comprised of analgesics first, then NSAIDs, then colchicine and /or bailout with rilonacept. If either NRS or CRP did not meet the qualifying values, they were assessed for ability to be observed without ORT. If able to have ORT withheld, the subject continued on blinded study drug. If unable to have ORT withheld, the subject was provided with ORT in addition to continued blinded study drug. The evaluation for potential recurrent pericarditis included protocol specified ECG, echocardiography, and physical exam (i.e. friction rub). If symptoms progressed, the subject was diagnosed with recurrent pericarditis.

At the time of terminating the RW period when the requisite number of adjudicated endpoint events occurred, all subjects still taking study drug had the option to continue treatment with open-label rilonacept in the LTE period or to withdraw from the study.

Subjects who completed the RI period and had met the definition of a clinical response but were not yet randomized to the RW period at the time when it ended had the option to enter the LTE directly or to withdraw from the study. Treatment in LTE will continue until the earliest of the following occurs:

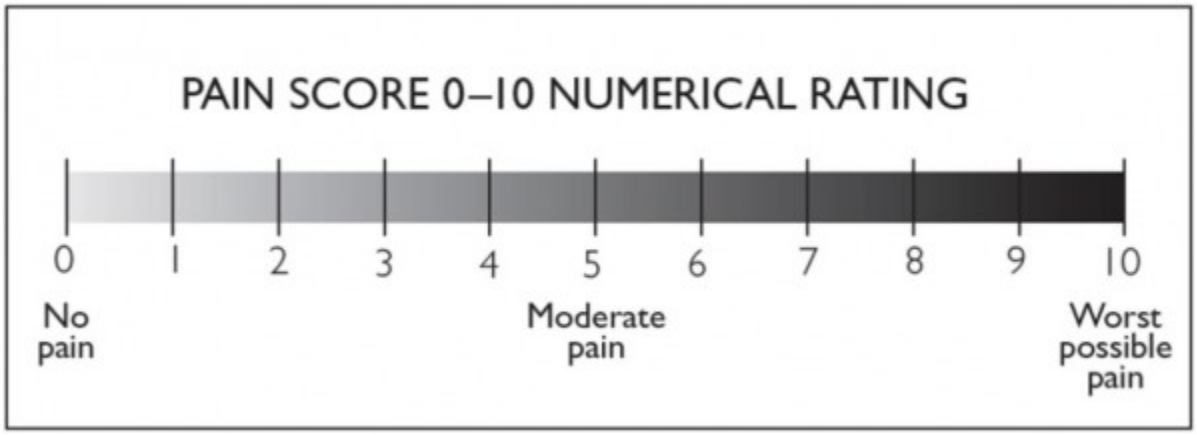
- Rilonacept is approved for commercial use or is available for reimbursement to treat pericarditis in the region.
- The subject has received 24 months of treatment in the LTE or the investigator and subject decided to continue in the study off-treatment.

Figure 2: RHAPSODY Trial Design



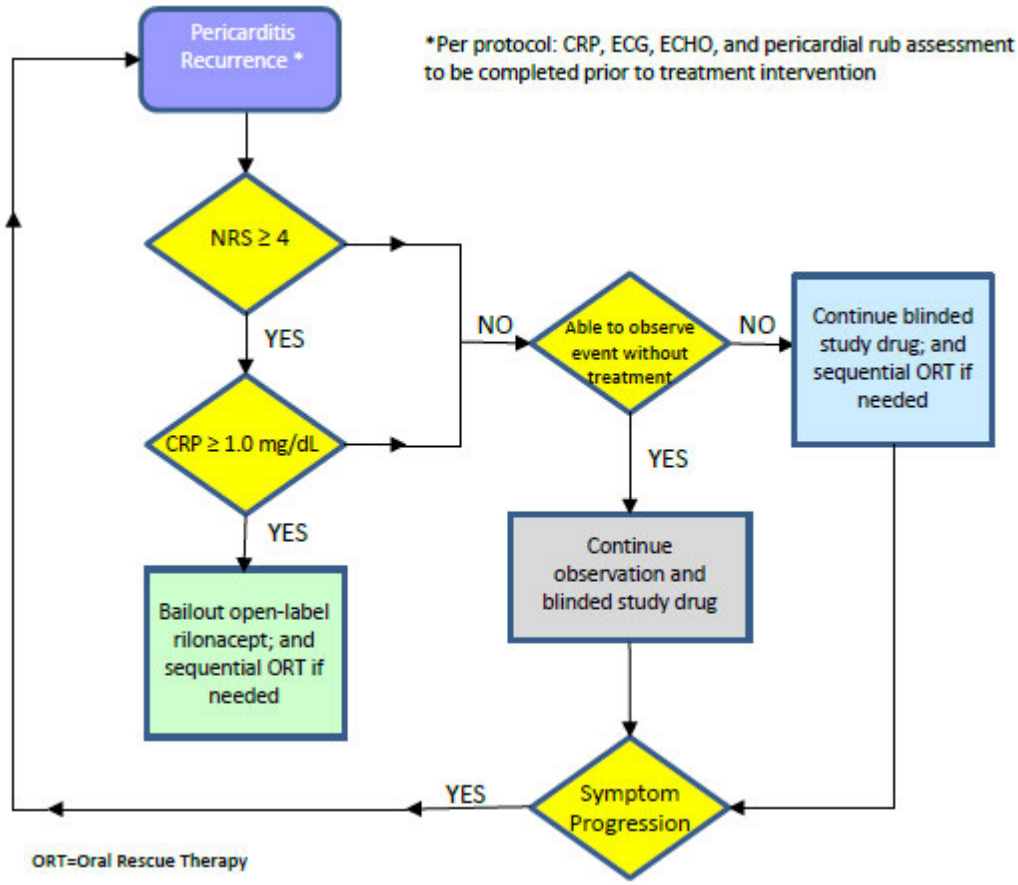
Source: Briefing Package, Type B Meeting 23 JUL 2020

Figure 3: Numerical Rating Score



Source: https://www.aci.health.nsw.gov.au/networks/eci/clinical/ndec/pain-any-nmg

Figure 4: Management of Suspected Pericarditis Recurrence in the Double-Blind Period



Source: Applicant's CSR-Figure 2

Study Structure

[redacted] (b) (4) was the contract research organization tasked with clinical monitoring and central lab safety analyses. [redacted] (b) (4) [redacted] (b) (4) was responsible for echocardiographic and MRI data. [redacted] (b) (4) was responsible for patient-centered outcome data.

Adjudication Process

The Clinical Events Committee (CEC) tasked with endpoint adjudications is from [redacted] (b) (4) [redacted] (b) (4)

Based on the [redacted] (b) (4) (Appendix A: Clinical Event Definition), the CEC voted on the existence of the primary efficacy endpoint from a subject's data package (*yes, no, more*

information is needed) using the following definitions:

1. Re-appearance or worsening of typical pericarditis pain (with at least one NRS recording ≥ 4) AND elevated CRP (≥1.0 mg/dL) either on the same day or separated by no more than 7 days, OR
2. Re-appearance or worsening of typical pericarditis pain (with at least one NRS recording ≥ 4) AND abnormal CRP (> 0.5 mg/dL) either on the same day or separated by no more than 7 days AND at least one supportive evidence of pericarditis (*see below**), OR
3. Re-appearance or worsening of typical pericarditis pain (but no NRS recording ≥ 4) AND elevated CRP (≥1.0 mg/dL) not attributable to other causes AND at least 1 supportive evidence of pericarditis (*see below**).

**Supportive Evidence of Pericarditis*

- *Increased WBC count greater than the upper limit of normal.*
- *Fever > 38°C.*
- *Presence of pericardial rub.*
- *ECG changes consistent with pericarditis.*
- *New or worsening pericardial effusion on echocardiogram.*
- *New or worsening pericardial inflammation on MRI or other imaging modality.*

An information request was sent to the Applicant in the 74-day letter. Adjudication criterion # 1 appeared to not require supportive clinical evidence or ruling out attribution to other causes even though the NRS re-elevation assumed a typical pericarditis pain the subject already experienced. Adjudication criterion # 3 appeared to not require a temporal relationship between NRS and CRP (presumably because supportive clinical evidence would have sufficed for the diagnosis). As an RCT with a blinded adjudication committee, it was unlikely that bias was produced. However, there was a question of reduced specificity. The Applicant was asked why criterion # 1 did not require supportive clinical evidence or ruling out attribution to other etiologies. The applicant was also asked to include any evidence that CRP, a non-specific biomarker, sufficiently supported a diagnosis of pericarditis in the absence of other supportive evidence if not separated by NRS criteria by more than 7 days. The applicant was asked to provide a list of subjects in each arm who were positively adjudicated, and the specific criteria cited by the adjudication committee.

The Applicant responded by stating the CEC was not required to identify which factors were determinative in the adjudication. The dataset submitted to the independent blinded adjudicators included echocardiograms which had been centrally read by other blinded readers along with ECGs, laboratory result documents, vital signs, and the Investigator's assessment of pericardial rub.

Documentation to support an adjudication per event were:

- Discharge Summary/Letter (if hospitalized) or other clinical summaries.
- Clinical description of the event (including symptom onset/duration, diagnostic workup including workup for alternate causalities, and treatment).
- Pericarditis pain Level (daily record from patient and visits/phone calls).
- Local CRP reports from screening, randomization and time of recurrence.
- All central CRP values (provided in Patient Profile).
- ECG tracings from randomization and time of recurrence (may include site interpretations).
- All available local and central Echo results/reports (RI Baseline, Randomization, RW Week 24, time of recurrence, end-of-randomized-withdrawal).
- Presence or absence of pericardial rub (full physical at screening visit and abbreviated physical at RI baseline and RI Week 12 and any other clinical assessments of pericardial rub).
- Pericarditis Recurrence Assessment Form (if available).

The adjudication listing provided by the Applicant upon our request is shown in Appendix 13.4. The individual subjects adjudicated as having recurrent pericarditis were primarily based on criterion # 1. ECG tracings and the presence of a pericardial friction rub were mostly negative (pericardial friction rubs are usually not heard on auscultation to rule out pericarditis). The adjudication process was carried out in a manner consistent with the prespecified adjudication charter.

Study Endpoints

The primary efficacy endpoint was the clinical event of adjudicated recurrent pericarditis, defined as the time from randomization to the date of the first pericarditis recurrence for each subject.

Secondary endpoints included the following:
Key secondary endpoints

- Proportion of subjects who maintained a clinical response at Week 16 of the RW period.
- Percentage of days with no or minimal pericarditis pain in the first 16 weeks of the RW period. No or minimal pain was defined as ≤2 on the 11-point NRS.
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGI-PS) at week 16 of the RW period. The PGI-PS (Patient Global Impression of Pericarditis Symptoms) is a single-item measure that uses a 7-point rating scale ranging from absent (no recurrent pericardial symptoms) to very severe (recurrent pericarditis symptoms that cannot be ignored).

Additional secondary endpoints

- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period.
- Time to pericarditis pain NRS ≥4 in the RW period.
- Time to CRP level ≥1 mg/dL. This was for elevation of CRP for which no other cause other than pericarditis was identified.
- Time to pericardial rub.
- Time to widespread ST-segment elevation or PR-segment depression on ECG, whichever occurred first.
- Time to new or worsening pericardial effusion on ECHO.
- Change in category of ECHO pericardial effusion size at Week 24 and end of RW based on central labs.
- Change over time in CRP levels during the RI and RW periods and in the LTE.
- Change over time in the subject's assessments of pericarditis pain (weekly average) during the RW period and in the LTE.
- Proportion of subjects with absent or minimal pericarditis activity based on the PGA-PA over time during the RW period, during the RI period, and during the LTE period.
- Change over time in SF-36 (Physical and Mental Component Scores and domain scores) during the RW period, RI period, and LTE period.
- Changes in SF-6D (6 domain scores and utility index) during the RW period, RI period, and the LTE period.
- Change in EQ-5D-5L (Euro-Quality of Life) during the RW period, RI period, and LTE period. The levels of the first 5 questions were converted to an index value. Change from baseline in each one of the 7 values constituted an endpoint.
- Change in subject's sleep quality assessed with the ISI during the RW period, RI period, and LTE period. Change in ISI total score, which is the sum of the 7 items over time.
- Change in ISI categories during the RW period, RI period, and LTE period.
- Cumulative number (percentage) of subjects who received sequential ORT, corticosteroids, or bailout rilonacept for pericarditis every 4 weeks cumulatively in the RW period.
- Proportion of subjects using ORT (analgesics, NSAIDs, and/or colchicine) for pericarditis in the first 24 weeks.
- Time to pain response. Pain response was defined as a rolling average of NRS score of 2 or less on 3 consecutive days.
- Time to treatment response, defined as time from first dose to the first day of pain response (defined above) and CRP ≤0.5 mg/dL within 7 days before or after pain response. Treatment response day will be the first day that the above criterion is met. Whether pain response occurs before or after CRP ≤0.5 mg/dL, the response day will be the day of pain response.

- Time to CRP normalization (≤0.5 mg/dL).
- Time to rilonacept monotherapy.
- Number (percentage) of subjects with normalization of CRP at RI Week 12.
- Change from baseline in pericarditis pain at RI Week 12 and over time.
- Change from baseline in CRP level at RI Week 12 and over time.
- Proportion of subjects with resolution of ECHO and ECG abnormalities (yes/no) at RI Week 12.
- Percentage of days with no or minimal pain (NRS ≤2) while on treatment.
- Number (percentage) of subjects who were off background pericarditis medication on or before Weeks 4, 8, 10, and 12.

Inclusion Criteria

Subjects must have met all of the following criteria to be enrolled in the study:

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

  *(pericarditis pain ≥4 and CRP ≥1 mg/dL were not required to be present on the same day)
- Had received NSAIDs and/or colchicine and/or corticosteroids (in any combination), if used, at stable dose levels (or at least not increased) for at least 3 days prior to and including RI baseline (first administration of study drug), and changes in medications made within this time period (e.g., 1-time use of NSAIDs) were not anticipated, in the

opinion of the investigator, to significantly alter assessments of baseline disease activity.

- If using NSAIDs and/or colchicine and/or corticosteroids at the time of RI baseline (first administration of study drug), was willing and able, in the opinion of the investigator, to taper and discontinue those medications within the 9-week tapering time in the RI period of the study while continuing rilonacept treatment.
- Female subjects must have been:
    - Postmenopausal, defined as at least 12 months after the cessation of menses (without an alternative medical cause) OR
    - Incapable of pregnancy OR
    - Permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation or having a male partner with vasectomy as affirmed by the subject OR
    - If of childbearing potential, must have agreed to use a highly effective method of contraception during the study and for 3 months after the last study drug administration (e.g., hormonal contraceptives associated with inhibition of ovulation, intrauterine device [IUD], intrauterine hormone-releasing system [IUS], or sexual abstinence)
- If male and sexually active, must have had documented vasectomy or must practice birth control and not donate sperm during the study and for 3 months after the last study drug administration.
- Up-to-date with all immunizations, in agreement with current local immunization guidelines for immunosuppressed subjects, before RI baseline (first administration of study drug).
- Able to adequately maintain a daily subject diary according to protocol.
- Able to adhere to the study visit schedule and understand and comply with the other protocol requirements.
- Agreed to refrain from making any new, major lifestyle changes that may affect pericarditis symptoms (e.g., changing exercise pattern) from the time the ICF was signed through the end of the double-blind RW period.

Exclusion Criteria

Subjects meeting any of the following criteria were excluded from the study:

- Diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis; or systemic autoimmune diseases with exception of Still's disease.
- Pregnant, breastfeeding, or planning a pregnancy or fathering a child during the study or within 3 months after the last study drug administration.

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

- Received immunization with a live (attenuated) vaccine within 12 weeks before screening or was expected to receive live (attenuated) vaccine during the study or within 12 weeks after the last study drug administration.
- History of positive or intermediate results for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening.
- Estimated glomerular filtration rate <30 mL/min.
- History of malignancy of any organ system within the past 5 years before screening (other than a successfully treated non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
- 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.
- Had a serious infection, been admitted to the hospital for an infection, treated with oral antibiotics for a documented infection within 2 weeks of RI baseline (first administration of study drug), or treated with IV antibiotics for an infection within 8 weeks of RI baseline.
- Had an organ transplant.
- Screening laboratory test results meeting any of the following criteria:
    - Hemoglobin level <10.0 g/dL
    - WBC count <3.0 × 103/μL
    - Neutrophil count <1.5 × 103/μL
    - Platelet count <100 × 103/μL
    - Total bilirubin level >1.5 × the upper limit of normal (ULN) unless the test results are consistent with those for Gilbert's syndrome
    - Aspartate aminotransferase or alanine aminotransferase values >2 × ULN
- In the investigator's opinion, had a history of alcoholism or drug/chemical abuse within 2 years before screening.
- Known hypersensitivity to ARCALYST (rilonacept) or to any of its excipients.
- Received an investigational drug during the 30 days (or 5 half-lives, whichever is longer) before screening or was planning to receive an investigational drug (other than that administered during this study) or use an investigational device at any time during the study.
- In the investigator's opinion, had any other medical condition that could adversely affect the subject's participation or interfere with study evaluations. This included significant concomitant illnesses such as, but not limited to, cardiac, renal, neurological, endocrinological, metabolic, pulmonary, gastrointestinal, or psychiatric diseases.
- In the opinion of the investigator, was not likely to be compliant with the study protocol.
- In the opinion of the investigator, should not participate in this study.

Statistical Analysis Plan

Sample size estimation was based on the assumption that the time to adjudicated first pericarditis recurrence followed an exponential distribution. The median time to recurrence in the placebo arm was assumed to be 8 weeks based on rilonacept washout pharmacokinetics at steady state. The hazard ratio was assumed to be 0.244. Given a 1-sided significance level of 2.5% median time to event, a minimum of 22 adjudicated pericarditis recurrence events was required to achieve 90% power. Thus, 50 subjects were randomized (25 subjects per arm). Assuming a 10% drop-out rate between the RI period and the RW period, approximately 56 subjects were planned to be enrolled.

There were two stratification variables at randomization:

- Stratification variable 1: oral CS use at RI baseline,
- Stratification variable 2: diagnosis of recurrent idiopathic pericarditis at RI baseline.

When a stratum has ≤5 events of interest in a log-rank test or all subjects in the stratum had the same response in a CMH test, Stratification 2 would be pooled. If the same situation still exists after pooling, the analysis would be done without stratification.

A gatekeeping procedure in combination with Hochberg's procedure was applied to test the primary and major secondary endpoints to control the overall 1-sided type I error rate at 0.025 level. If the primary endpoint was significant, the first key secondary endpoint would be tested at 1-sided alpha of 0.025. If both the primary endpoint and the first key secondary endpoint were significant, the second and the third key secondary endpoints would be tested with Hochberg's procedure at overall 1-sided alpha=0.025.

For primary analysis, only CEC-confirmed pericarditis recurrence was considered as an event. Primary endpoint was analyzed using log rank test on ITT analysis set, stratified by randomization strata. The hazard ratio between the two groups and the corresponding Wald 95% CI were calculated based on Cox proportional-hazards model with treatment as covariate, stratified by randomization strata.

Secondary analyses were based on the Week 16 analysis set, defined as all subjects randomized at least 16 weeks before data cutoff.

- The first key secondary endpoint, proportion of subjects who maintained clinical response (weekly average of daily pericarditis pain on the 11-point NRS ≤2.0 and CRP level ≤0.5 mg/dL, and on monotherapy of randomized study drug at Week 16) at Week 16 of the RW period, was analyzed using CMH test, stratified by the stratification variables at randomization. Subjects who had recurrence, discontinued double-blinded treatment, lost to follow-up, and used bailout rilonacept or rescue medications (ORT or corticosteroid) before Week 16 were considered as non-responders. If either weekly average of NRS or CRP

was missing at week-16 assessment, the subject was considered as a non-responder.

- The second key secondary endpoint, percentage of days with pain NRS ≤2 in the first 16 weeks post randomization, was analyzed using ANCOVA with treatment, stratification variables at randomization, and RI baseline NRS score category (NRS≤2 vs. NRS>2) as covariates. NRS assessments after treatment termination were included. NRS assessments while on rescue medications for pericarditis were considered not meeting the criterion. Receiving each administration of bailout rilonacept would disqualify for meeting NRS ≤2 for 7 days. Missing values were counted as 0 day meeting the criterion.
- The third key secondary endpoint, proportion of subjects with absent or minimal pericarditis symptoms (based on the7-point PGIPS) at Week 16 of the RW period, was analyzed using CMH test, stratified by the stratification variables at randomization. Subjects who did not have the assessment due to early termination or other reasons were considered as non-responders. Subjects who took rescue medications at the Week 16 assessment or used bailout rilonacept on or before Week 16 were also considered as non-responders.

Subgroup analyses for the primary efficacy endpoint were performed by the following variable for the RW period:

- Oral CS use at baseline (RI baseline, i.e., beginning of RI period): yes or no
- Diagnosis of recurrent idiopathic pericarditis (RI baseline): yes or no
- Type of pericarditis: idiopathic, post pericardiotomy syndrome, Dressler's syndrome, and Still's disease. Other type will not be included in the subgroup analysis due to the small sample size.
- Age group: 12 - <18, 18 - <65, and 65 – (maximum age in ITT analysis set) [Analysis for the pediatric group (12- <18) may not be performed if the sample size is too small.]
- Gender: males vs. females
- Race: Caucasian vs. non-Caucasian
- Region: USA vs. non-USA
- Number of pericarditis episodes at enrollment (including index and qualifying episodes): <5 vs. ≥5
- ADA status: ADA positive at any assessment, ADA positive with neutralizing antibody at any assessment, and ADA negative at every assessment.

Protocol Amendments

The original protocol (Version # 1) was finalized 25 SP 2018. There were 2 protocol amendments.

Amendment # 1 (Protocol Version # 2) was finalized 12 APR 2019. Amendment # 1 featured: 1) revision of one criterion for study drug discontinuation (deletion of the discontinuation requirement for any serious adverse event); 2) addition of a baseline PK drug level measurement; 3) removal of a 10 subject limit in a cardiac MRI substudy; 4) revision of the full physical examination text (change the genitourinary exam from mandatory to per clinical judgement; 5) correction of minor inconsistencies among various documents: protocol synopsis, protocol text, informed consent and the investigator brochure; and 6) updating of applicant study contacts.

Amendment # 2 (Protocol Version # 3) of the protocol was finalized 10 MAR 2020. The key changes were as follows: 1) expanding the number of planned enrolled subjects from 75 to 100; 2) removing the requirement for 50 subjects to have completed 24 weeks in the RW period in order to trigger the primary analysis; this substantially reduced the period of double-blind placebo treatment for those randomized to placebo and who did not experience a recurrence event; 3) at the time of RW period closure for having met the number of subjects experiencing the primary endpoint, all subjects still in the RI period who met the definition of clinical responder were allowed to transition to the LTE period and continue rilonacept treatment; and 4) prolongation of the LTE period to up to 2 years, with reduced frequency of in-clinic assessments from every 8 weeks to every 12 weeks and simplified home assessments, as well as the ability to discontinue treatment with the security of bailout rilonacept in the event of a future recurrence. The LTE period was expected to bridge the period between the end of the RW period and anticipated approval of rilonacept.

In addition to protocol amendments, protocol-specific clinic visits were replaced by remote visits due to the Covid-19 epidemic. Remote visits consisted of site-to-subject phone calls and home trial services, including visiting nurses (all countries) and echocardiography (USA only) and ECGs (USA only). Some assessments could not be completed remotely (physical exams, MRI, ECGs (out of USA) and echocardiography (out-of-USA). Study drug was shipped directly to the subjects' home to avoid interruption of study drug treatment. Visit windows were extended to allow study assessments to be performed over several days due to increased logistical coordination and scheduling challenges. A total of 50 subjects were impacted by Covid-19 mediated protocol changes (36 in USA, 8 in Italy, 5 in Israel, and 1 in Australia).

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant stated that the RHAPSODY trial was conducted in compliance with Good Clinical Practice, including archiving of essential documents. The case study report was written in compliance with the International Council for Harmonization (ICH) E3 Guideline. The BLA package review concluded compliance with 21 CFR 312.50 to 312.70 (responsibilities of sponsors and investigators), as well as 21 CFR Part 50 (protection of human subjects) and 21 CFR Part 56 (IRBs).

Financial Disclosure

Of 46 principal investigators and 138 sub-investigators in KPL-914-C002 (RHAPSODY), three had financial disclosures described as significant payments of other sorts (Table 4).

Table 4: List of RHAPSODY Investigators with Financial Disclosure

Site Number	Site Name	Investigator	Role	Dates of Participation	Subjects enrolled (% of total enrolled)
(b) (6)			Principal Investigator	(b) (6)	
			Principal Investigator		
			Sub-Investigator		

Source: CTD 1.3.4 Financial Disclosure.

(b) (6):

- Kiniksa Pharmaceuticals, Ltd. and (b) (6) entered an Investigator Initiated Non-Interventional Research Study Agreement, effective (b) (6), in which (b) (6) was named as Co-Investigator. This was a (b) (6) (b) (6) The total value of this contract was $127,120, of which Kiniksa has paid $100,000 between the dates of (b) (6) and (b) (6).

- Kiniksa Pharmaceuticals, Ltd. and (b) (6) entered a Research Agreement, effective (b) (6), in which (b) (6) was named as Co-Investigator. This (b) (6)," was

intended to test [redacted]. The total value of this contract was $455,000, of which Kiniksa has paid $210,000 between the dates of [redacted].

- Kiniksa Pharmaceuticals, Ltd. and [redacted] entered an Investigator-Initiated Clinical Trial Agreement, effective [redacted], for execution of the clinical study entitled, [redacted] served as a Sponsor-Investigator of this study. The total value of this contract was $30,000.00, of which Kiniksa has paid $5,000 on [redacted].

[redacted]:

- Kiniksa Pharmaceuticals, Ltd. and [redacted] entered a project agreement, effective [redacted], for execution of the [redacted]. This [redacted] pericarditis patients treated at [redacted] to address an existing gap in the literature. [redacted] served as Investigator of this study. The total value of this contract was $300,000, which was paid in full on [redacted].

[redacted]:

- Kiniksa Pharmaceuticals, Ltd. and [redacted] entered an Investigator Sponsored Study Agreement, effective [redacted], for execution of the clinical study entitled, [redacted] served as a [redacted] of this study. The total value of this contract was $205,000, of which Kiniksa has paid $55,000 between the dates of [redacted].

Analysis from a site-specific tool showed that [redacted] enrolled a significant number of subjects, and the [redacted] showed a much higher treatment effect than other sites. A sensitivity analysis was performed by removing [redacted] site and re-analyzing the primary efficacy endpoint data. The results showed no impact on the outcome of the trial, thus attenuating the need for an audit. Further, the clinical endpoints, although partly based on a subjective parameter, were independently and blindly adjudicated, thus reducing the potential for bias.

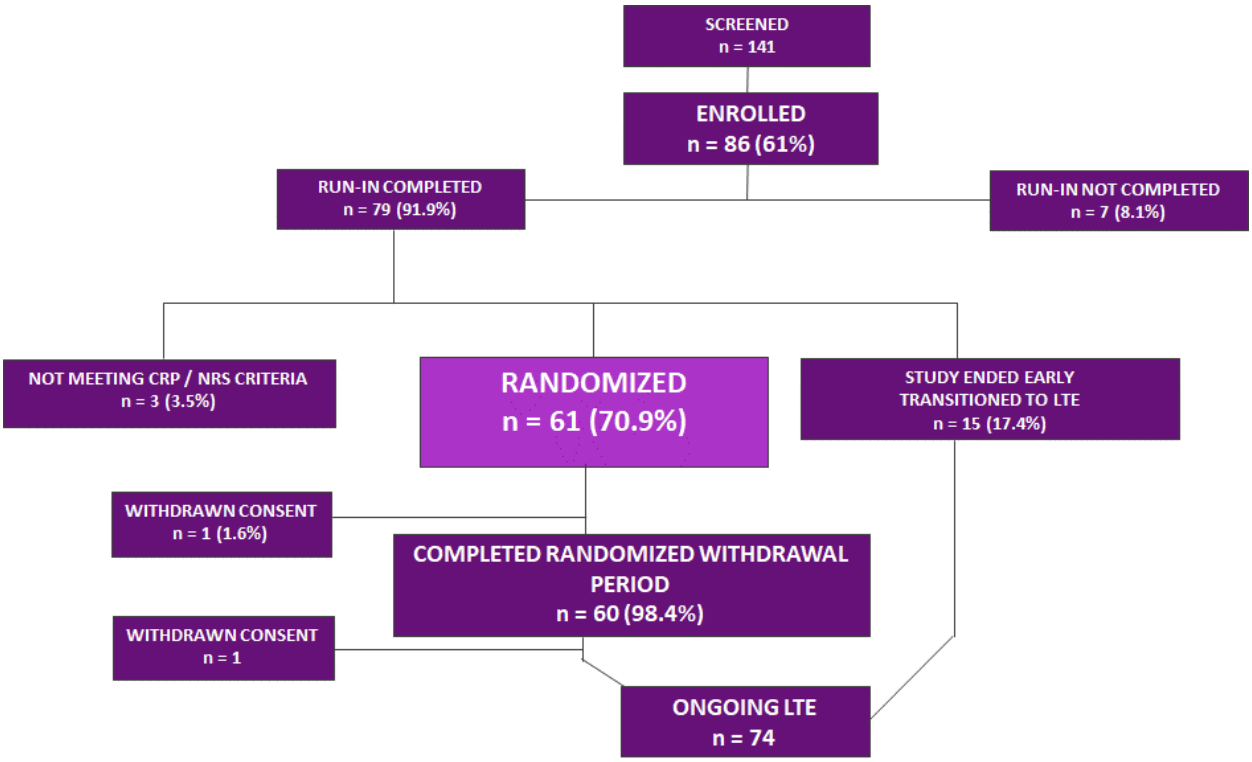
In summary, there were no observed issues based on financial disclosures; the outcome of the study was not altered by removing the [redacted].

Patient Disposition

The RHAPSODY trial subject disposition is shown in Figure 5. A total of 141 subjects were screened; 86 were enrolled; 79 completed the RI period; 61 were randomized; and 60 completed the RW period. Of the 18 subjects who completed the RI period but who were not randomized (79 RI completers minus 61 randomized), 15 ended the study early and were transitioned to the LTE period and 3 did not demonstrate a clinical response (i.e., did not meet CRP / NRS criteria). Of the 61 subjects who were randomized, 1 subject from placebo group withdrew consent. Of the 60 subjects who completed the RW period, 1 withdrew consent prior to transitioning into the LTE period. The remaining 59 subjects plus the early LTE transitioned subjects (total 74) continued in the ongoing LTE period.

From the safety dataset, the mean duration of exposure to rilonacept was 24 weeks.

Figure 5: RHAPSODY Trial Subject Disposition



Source: Applicant's figure in CSR-section 10.1, verified by statistical reviewer.

Protocol Violations/Deviations

The applicant reported an overall protocol violation rate of 77% with no impact on data interpretation (Table 5). Treatment compliance did not appear to be an issue. However, the Applicant reported an overall 54% incidence of protocol violations described as "missing

endpoint assessment".

Reviewer Comment: An information request was submitted in the 74-day letter regarding missing endpoint assessment. This is addressed in the data quality and integrity section of this review.

Table 5: RHAPSODY Protocol Violations

	Number of Subjects (%)			
	Run-In Period*	Randomized Withdrawal Period		
		Rilonacept	Placebo	Total
	N=86	N=30	N=31	N=61
Subjects with at least 1 protocol violation	52 (60)	21 (70)	26 (84)	47 (77)
Disclosure of randomization timing	0	0	3 (10)	3 (5)
Exclusion Criteria	12 (14)	0	0	0
Inclusion Criteria	1 (1)	1 (3)	0	1 (2)
Missing endpoint assessment*	15 (17)	14 (47)	19 (61)	33 (54)
Other	1 (1)	0	0	0
Study procedure/assessment	30 (35)	13 (43)	5 (16)	18 (30)
Study treatment admin/dispense	9 (10)	0[a]	2 (7)[b]	2 (3)
Treatment Compliance	2 (2)	2 (7)	2 (6)	4 (7)
Visit scheduling	15 (17)	8 (27)	14 (45)	22 (36)

Source: CSR Table 14.1.5, verified by statistical reviewer.
* potential issue: protocol violations in the RI period also include violations during screening
[a]Different from applicant's table value 1(3.3).
[b]Different from applicant's table value 1(3.2).

Demographic characteristics are shown in Table 6Error! Reference source not found.. The subjects in the RW period were similarly divided between male and female. The average age at RW baseline for the ITT population was 46.4 years (standard deviation 15.1 years). The population was mostly white (92%) and the majority of the subjects came from the USA (64%). The demographic characteristics were balanced between the two arms of the RW period.

Reviewer Comment: Patient under-representation is apparent in this trial, especially when the majority of participants came from the USA.

Table 6: Demographic Characteristics in RHAPSODY

Demographic Parameters	Placebo-controlled Withdrawal Period		
	Rilonacept (N= 30) n (%)	Placebo (N= 31) n (%)	Total (N= 61) n (%)

Sex			
Male	14 (46.7)	15 (48.4)	29 (47.5)
Female	16 (53.3)	16 (51.6)	32 (52.5)
Age			
Mean years (SD)	48.0 (15.7)	44.8 (14.5)	46.4 (15.1)
Median (years)	51	48	49
Min, max (years)	17, 71	16, 67	16, 71
Age Group (n, %)			
12 -17 years	1 (3.3)	2 (6.5)	3 (4.9)
18 -64 years	24 (80)	27 (87.1)	51 (83.6)
65 -78 years	5 (16.7)	2 (6.5)	7 (11.5)
Mean BMI (SD)	28.2 (6.6)	29.3 (8.9)	28.7 (7.7)
Race			
White	28 (93.3)	28 (90.3)	56 (91.8)
Black or African American	1 (3.3)	3 (9.7)	4 (6.6)
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other[1]	1 (3.3)	0	1 (1.6)
Ethnicity (n, %)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	30 (100)	31 (100)	61 (100)
Region			
United States	19	20	39
Italy	5	7	12
Israel	4	4	8
Australia	2	0	2
TOTAL	30	31	61

Source: applicant's CSR Table 14.1.2.1, verified by statistical reviewer.
[1] Not specified.

Baseline pericarditis characteristics are shown in Table 7Error! Reference source not found.. A majority (85%) of the baseline recurrent pericarditis events were classified as idiopathic. The mean number of recurrent pericarditis episodes per year prior to enrollment was 4.4 (standard deviation 4.3). The recurrent pericarditis event that qualified the subject for enrollment occurred approximately 12 days prior to enrollment. Approximately 34% of the qualifying recurrent pericarditis events had a pericardial effusion. These baseline characteristics were balanced between the two arms in the RW period.

Table 7: Pericarditis Baseline Characteristics, Duration and Frequency of Recurrence

	Run-In	Randomized Withdrawal		
		Rilonacept	Placebo	Total
	N=86	N=30	N=31	N=61
	n (%)	n (%)	n (%)	n (%)
Type of Recurrent Pericarditis				
Idiopathic	73 (84.9)	26 (86.7)	26 (83.9)	52 (85.2)
Post-pericardiotomy syndrome	12 (14.0)	3 (10.0)	5 (16.1)	8 (13.1)
Dressler	1 (1.2)	1 (3.3)	0	1 (1.6)
Mean duration of pericarditis, years, SD	2.4 (3.1)	3.1 (4.4)	1.9 (2.1)	2.5 (3.5)
Mean # Episodes per year (SD)	4.4 (4.9)	4.4 (5.2)	4.3 (2.9)	4.4 (4.3)
Mean time since beginning of qualifying episode, days (SD)	12.5 (8.7)	11.9 (6.2)	11.9 (7.8)	11.9 (7.0)
	n (%)	n (%)	n (%)	n (%)
Pericardial Effusion for qualifying episode				
Yes	33 (38.4)	10 (33.3)	11 (35.5)	21 (34.4)
No	53 (61.6)	20 (66.7)	20 (64.5)	40 (65.6)

Source: applicant's CSR Table 14.1.2.2, verified by statistical reviewer.

The mean baseline qualifying NRS score was 6.3 (standard deviation 1.8) on an 11-point scale (i.e., moderate pain). The mean baseline qualifying CRP was 6.3 (standard deviation 6.2) mg/dL (Table 8Error! Reference source not found.). The mean qualifying NRS score was equally balanced between the two arms in the RW period. The mean qualifying CRP was slightly higher in the rilonacept arm (6.6 mg/dL, standard deviation 7.3 mg/dL) compared to the placebo arm (6.0 mg/dL, standard deviation 5.1 mg/dL), but not considered significant.

Table 8: Mean Baseline Qualifying NRS and CRP

	Run-In	Randomized Withdrawal		
		Rilonacept	Placebo	Total
	N=86	N=30	N=31	N=61
Mean Qualifying NRS Score (SD)	6.2 (1.8)	6.4 (1.7)	6.3 (1.9)	6.3 (1.8)
Mean Qualifying	6.2 (6.7)	6.6 (7.3)	6.0 (5.1)	6.3 (6.2)

CRP mg/dL (SD)				

Source: applicant's CSR Table 14.1.2.2, verified by statistical reviewer.

Qualifying episode and baseline concomitant medications are shown in Table 9Error! Reference source not found.. At qualifying episode, 80% were receiving colchicine; 67% were receiving NSAIDS; and 49% were receiving corticosteroids. Concomitant use of pericarditis medications at RI Baseline were similar to that at qualifying episode with 76% receiving colchicine; 61% receiving NSAIDS; and 48% receiving corticosteroids.

Table 9: Qualifying Episode and Baseline Medications

	Run-In	Randomized Withdrawal		
		Rilonacept	Placebo	Total
	N=86	N=30	N=31	N=61
Qualifying Episode Medications				
	n (%)	n (%)	n (%)	n (%)
	81 (94.2)	28 (93.3)	30 (96.8)	58 (95.1)
Analgesics	10 (11.6)	5 (16.7)	3 (9.7)	8 (13.1)
• Non-opioid	8 (9.3)	4 (13.3)	2 (6.5)	8 (13.1)
• Opioid	5 (5.8)	4 (13.3)	1 (3.2)	6 (9.8)
NSAIDS	58 (67.4)	20 (66.7)	19 (61.3)	39 (63.9)
• Aspirin	4 (4.7)	0	3 (9.7)	3 (4.9)
• Other	54 (62.8)	20 (66.7)	16 (51.6)	36 (59.0)
Colchicine	69 (80.2)	27 (90.0)	26 (83.9)	53 (86.9)
Corticosteroids	42 (48.8)	14 (46.7)	14 (45.2)	28 (45.9)
• Oral	42 (48.8)	14 (46.7)	14 (45.2)	28 (45.9)
• IM/IV	1 (1.2)	0	0	0
Other	4 (4.7)	3 (10.0)	1 (3.2)	4 (6.6)
Baseline Medications				
	n (%)	n (%)	n (%)	n (%)
	79 (91.9)	26 (86.7)	30 (96.8)	56 (91.8)
Analgesics	7 (8.1)	4 (13.3)	2 (6.5)	6 (9.8)
Non-opioid	6 (7.0)	3 (10.0)	2 (6.5)	5 (8.2)
Opioid	4 (4.7)	4 (13.3)	0	4 (6.6)
NSAIDS	52 (60.5)	17 (56.7)	18 (58.1)	35 (57.4)
Aspirin	4 (4.7)	0	3 (9.7)	3 (4.9)
Other	48 (55.8)	17 (56.7)	15 (48.4)	32 (52.5)
Colchicine	65 (75.6)	25 (83.3)	25 (80.6)	50 (82.0)

Corticosteroids	41 (47.7)	13 (43.3)	14 (45.2)	27 (44.3)
Oral	41 (47.7)	13 (43.3)	14 (45.2)	27 (44.3)
IM/IV	0	0	0	0
Other	4 (4.7)	3 (10.0)	1 (3.2)	4 (6.6)

Source: applicant's CSR Table 14.1.2.2 verified by statistical reviewer.

The baseline duration and mean dose of corticosteroids used by subjects prior to enrollment in the trial (i.e., prior to RI) are shown in Table 10. Of the approximately 50% of the subjects in the RI period who were on corticosteroids at baseline, the majority of those subjects (59%) received corticosteroids for a duration of less than 4 weeks at a mean dose of 16 mg per day. Approximately 20% of those subjects received corticosteroids for a duration of 4←→26 weeks at a mean dose of 22 mg/day; 22% of those subjects received corticosteroids for a duration of ≥ 26 weeks at a mean dose of 14 mg/day. The number of subjects receiving corticosteroids in each of these time brackets were evenly distributed between the arms of the RW period. However, the corticosteroid dose was noticeably higher in the placebo arm compared to the rilonacept arm for each time bracket: 17 mg vs 9 mg (< 4 weeks duration); 24 mg vs 12 mg (4←→ 26 weeks duration); 21 mg vs 15 mg (≥ 26 weeks duration). Although corticosteroid use for pericarditis is clinically associated with a higher rate of recurrence, the differential dose in each time bracket between the arms is of unknown clinical significance.

Table 10: Duration and Mean Dose of Steroid Treatment Before Enrollment in Trial

	Run-In	Randomized Withdrawal		
		Rilonacept	Placebo	Total
	N=41	N=13	N=14	N=27
Duration and Dose of Steroid Treatment before enrollment				
< 4 weeks, n (%)	24 (58.5)	8 (61.5)	9 (64.3)	17 (63.0)
Mean Dose (mg/day) SD	16.0 (12.1)	9.4 (7.1)	17.1 (11.6)	13.5 (10.2)
4←→26 weeks, n (%)	8 (19.5)	3 (23.1)	2 (14.3)	5 (18.5)
Mean Dose (mg/day) SD	21.5 (13.7)	11.6 (7.2)	23.6 (9.5)	16.4 (9.6)
≥ 26 weeks, n(%)	9 (22.0)	2 (15.4)	3 (21.4)	5 (18.5)
Mean Dose (mg/day) SD	14.0 (9.4)	15.0 (7.1)	20.7 (9.0)	18.4 (7.9)

Source: applicant's CSR Table 14.1.2.3, verified by statistical reviewer.

Concomitant Medications, and Rescue Medication Use

During the RI period, the number of subjects receiving background anti-pericarditis medications

was reduced from 92% at baseline to 3% at week 12 (Table 11). The majority of subjects at baseline were on an average of 2 of 4 categories of anti-pericarditis medications: analgesics, corticosteroids, NSAID, and colchicine. The reduction in the number of subjects receiving anti-pericarditis medications during the RI period was irrespective of the number of treatment categories.

Table 11: Concomitant Pericarditis Medications Over Time in the Run-In Period

RI Period (Baseline and Week #)					
	Baseline	Week 4	Week 8	Week 10	Week 12
N	86	83	81	80	79
Background Pericarditis Medication	n*(%)	n*(%)	n*(%)	n*(%)	n*(%)
-Not receiving background meds	7 (8.1)	15 (18.1)	49 (60.5)	71 (88.8)	77 (97.5)
-Receiving background meds	79 (91.9)	68 (81.9)	32 (39.5)	9 (11.3)	2 (2.5)
>3 categories	1 (1.2)	1 (1.2)	0	0	0
3 categories	24 (27.9)	11 (13.3)	2 (2.5)	0	0
2 categories	39 (45.3)	31 (37.3)	9 (11.1)	4 (5.0)	1 (1.3)
1 category	15 (17.4)	25 (30.1)	21 (25.9)	5 (6.3)	1 (1.3)
-analgesics only	1 (1.2)	1 (1.2)	1 (1.2)	0	0
-corticosteroid only	6 (7.0)	9 (10.8)	8 9.9)	1 (1.3)	0
-NSAID only	4 (4.7)	3 (3.6)	2 (2.5)	1 (1.3)	0
-colchicine only	4 (4.7)	12 (14.5)	9 (11.1)	2 (2.5)	0
-other	0	0	1 (1.2)	1 (1.3)	1 (1.3)

Source: applicant's CSR Table 14.1.4.3.2, verified by statistical reviewer
Note: *The percentages are based on number of subjects still on treatment at each timepoint.

Efficacy Results-Primary Endpoint

The primary event of recurrent pericarditis occurred in 2 subjects in the rilonacept arm and 23 subjects in the placebo arm during the RW period (Table 12Error! Reference source not found.). The median time to recurrence of pericarditis was 8.6 weeks in the placebo arm, but not estimable in the rilonacept arm because of low event rate (Table 13Error! Reference source not found.).The hazard ratio (95% CI) calculated from Cox proportional hazard model was 0.04 (0.01, 0.18), with a p value of < 0.0001 from the log rank test showing a statistically significant result in comparing the distribution of time to recurrence of pericarditis between the two arms. According to the strata pooling rule specified in SAP, since one stratum had ≤ 5 events of

interest, stratification variable 2: diagnosis of recurrent idiopathic pericarditis at RI baseline was pooled in calculating hazard ratio and p-value.

Table 12: Recurrent Pericarditis Categories in the Randomized Withdrawal Period

	RW Period	
Pericarditis Recurrence Categories, n(%)	Rilonacept (N=30)	Placebo (N=31)
Number of Subjects with recurrent pericarditis	2 (6.7)	23 (74.2)
-recurrence without receiving ORT, CS or bailout	2 (6.7)	22 (71.0)
-recurrence after receiving ORT/CS	0	1 (3.2)
-recurrence after receiving bailout	0	0
Number of subjects censored (without recurrence)	28 (93.3)	8 (25.8)

Source: applicant's CSR Table 14.2.1.1 verified by statistical reviewer
ORT = Oral Rescue Therapy comprised of analgesics first, then NSAIDs, then colchicine; CS = corticosteroids; Bailout = treatment with rilonacept.

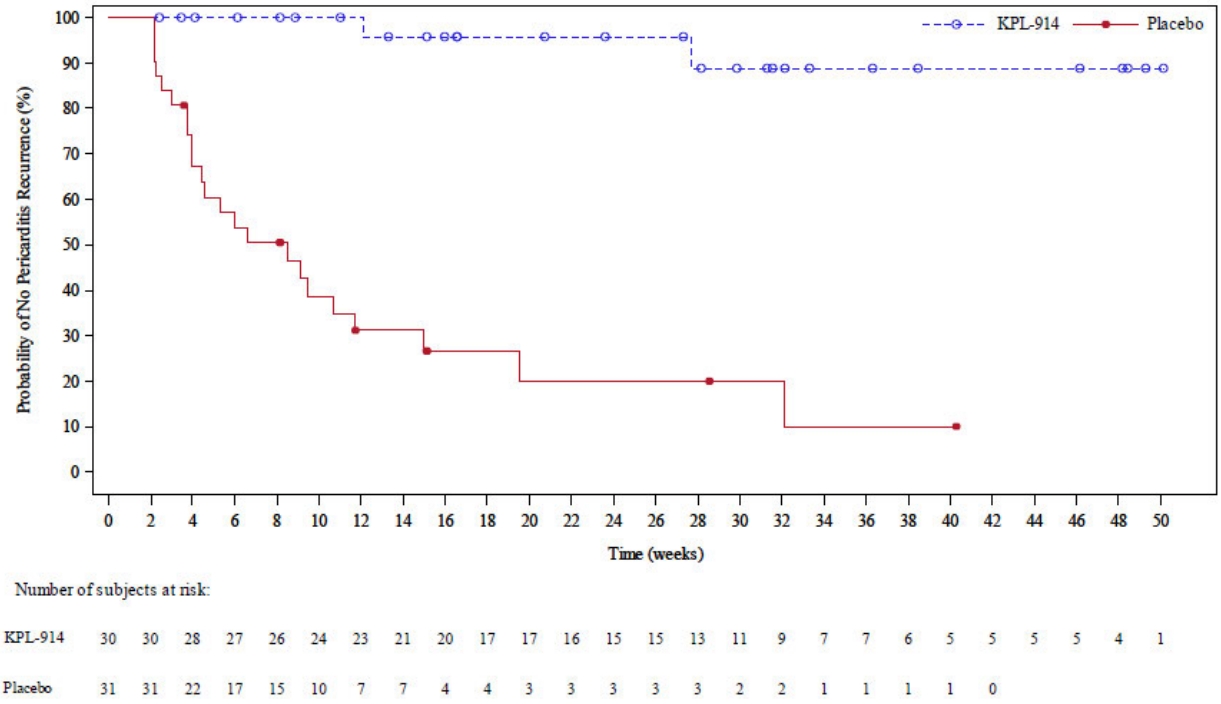
Table 13: Time to Recurrence of Pericarditis in the Randomized Withdrawal Period

Time to Recurrence (weeks)	RW Period	
	Rilonacept (N=30)	Placebo (N=31)
25th percentile, 95% CI	NE*	3.7 (2.1, 5.3)
Median, 95% CI		8.6 (4.0, 11.7)
75th percentile, 95% CI		19.6 (9.1, NE)
HR (rilonacept vs placebo), 95% CI, 2-sided p-value	0.04 (0.01, 0.18), p < 0.0001	

Source: applicant's CSR Table 14.2.1.1, verified by statistical reviewer
*Not estimable due to small sample size (only two events were observed in this arm).
HR and 95%CI are calculated based on a Cox proportional-hazards model with treatment as covariate and stratified by oral corticosteroid use at run-in baseline. Two-sided p-value is from the log-rank test stratified by oral corticosteroid use at run-in baseline.

The plot of Kaplan-Meier curves (Figure 6Error! Reference source not found.) showed the two curves started to separate at around week 2 of RW period, and demonstrated a precipitous drop in the probability of no-recurrence in the placebo arm of the RW period.

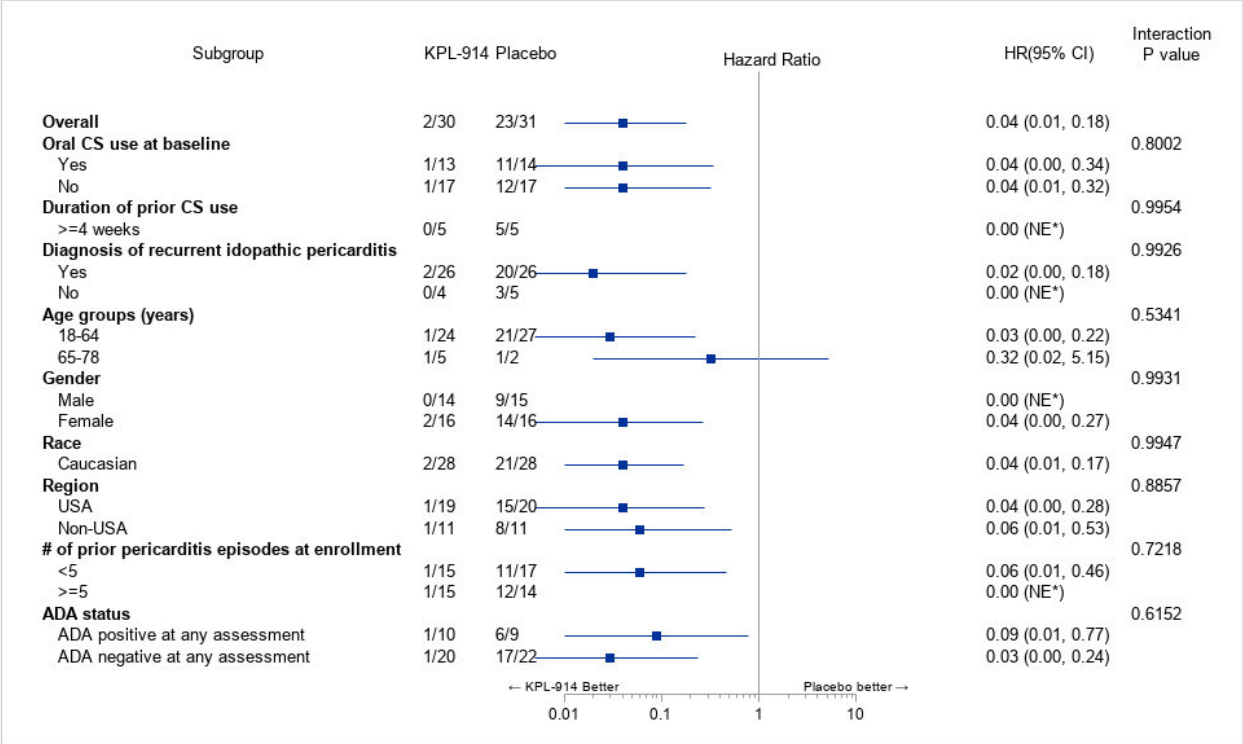
Figure 6: Kaplan-Meier Curve for Time to Recurrent Pericarditis (ITT Analysis Set)



Source: applicant's CSR Figure 14.2.1.1 verified by statistical reviewer.

Shown in Figure 7, the efficacy evaluation for the primary endpoint of the following pre-specified subgroups were performed: use of corticosteroids at RI baseline, diagnosis of recurrent idiopathic pericarditis at RI baseline, etiology of recurrent pericarditis, age groups, gender, region, number of pericarditis episodes at enrollment, and ADA status. Additional analysis on duration of prior corticosteroid use ≥4 weeks at baseline was also performed. The effectiveness of rilonacept was consistent across all evaluated subgroups. Note that due to low event rate, some subgroups had wider or non-estimable confidence intervals. The interaction test for homogeneity did not suggest any heterogeneity with respect to the treatment effect of rilonacept across the subgroups. Under-representation of Black and Latino patients resulted in inability to assess the effectiveness of rilonacept in these populations.

Figure 7: Forrest Plot for Time to Recurrent Pericarditis



Source: generated by statistical reviewer.
Hazard ratios and 95%CIs are based on cox proportional hazards model with randomization stratification factors. Interaction p-values (two-sided) are based on cox proportional hazards model including treatment, subgroup and a subgroup by treatment interaction term as fixed effects, with randomization stratification factors.
*Due to low event rate, these confidence intervals were not estimable.
Note: Since the "Yes" category of diagnosis of recurrent idiopathic pericarditis subgroup is exact the same group of subjects with the "idiopathic" category of etiology of recurrent pericarditis subgroup, thus the results were combined, and the figure did not show both results.

The main data element leading to a positive adjudication was the NRS scale (pre-RI baseline moderate pain to minimal or no pain at the end of the RI period, and back to moderate pain for the diagnosis of recurrent pericarditis during the RW period). The CEC cited adjudication criterion # 1 as the basis of a positive adjudication in virtually all the cases. Another quantitative element of adjudication criterion is CRP level (a quantifiable parameter associated with inflammation / pericarditis). Number of subjects with NRS ≥ 4 and number of subjects with CRP > 1 mg/dL in RW period (Table 14Error! Reference source not found.) were consistent with the number of subjects with CEC adjudicated Pericarditis Recurrence.

Table 14: Subjects with NRS ≥ 4 and Subjects with CRP > 1 mg/dL in RW Period (ITT Analysis Set)

	RW Period	
	Rilonacept (N=30)	Placebo (N=31)
Subjects with CRP > 1 mg/dL		
Number of subjects with CRP > 1mg/dL, n (%)	3 (10.0)	25 (80.6)
Number of Subjects Censored	27 (90.0)	6 (19.4)
Subjects with NRS ≥ 4		
Number of Subjects with NRS ≥ 4	6 (20.0)	24 (77.4)
Number of Subjects Censored	24 (80.0)	7 (22.6)

Source: applicant's CSR Table 14.2.3.3, verified by statistical reviewer.

Data Quality and Integrity

There was no OSI investigation because no single site impacted the outcome of the trial, and there were no data irregularities leading to the need for an investigation.

In the course of the review, two potential issues emerged: 1) Missing endpoint data; and 2) (b) (4) (b) (4).

1. Missing endpoint data:

An information request was submitted to the Applicant regarding an overall 54% incidence of protocol violations described as missing endpoint assessment. The Applicant's response is summarized below. The clinical reviewer's assessment of this response is as follows:

- The potential to miss an endpoint was equally probable between both arms in the RW period.
- The missing endpoint data represented a splattering of datapoints (24 datapoints per subject) that did not affect the assessment by blinded adjudicators of whether a subject had recurrent pericarditis.
- Consequently, the protocol violations described as missing endpoint data did not significantly affect the quality or integrity of the data.

Applicant's response to the IR regarding 54% incidence of missing endpoint data:
"Important protocol deviations were reported for each data point that was missing e.g., if a PRO

assessment was missed in addition to an ECG there would be a record of two deviations. We would expect each subject to have approximately 24 efficacy datapoints collected from RW baseline up to week 24 of the RW period (which is consistent with the median time in the RW period). Therefore, while approximately 46% of subjects had no important protocol deviations relating to missing assessments in the RW period, of the 54.1% of subjects who did, this represents approximately 5% of the totality of efficacy assessments.

The greatest concern with missing efficacy data would be failure to detect a potential recurrence that should have been adjudicated. However, only 3 of the important protocol deviations relate to a missing CRP value. One of these occurred in a subject who had previously experienced an adjudicated recurrence and hence had already contributed to the primary efficacy endpoint (potential second recurrences are not included in the primary efficacy endpoint). The other two deviations (one for missed blood sample by visiting nurse and one collected with insufficient specimen quantity) occurred in subjects who both reported pain scores of zero throughout the entire RW period.

Only 3 important protocol deviations for missing datapoints were recorded during recurrence visits and included missing vital signs in two cases and one echocardiogram that was technically poor. Although the echocardiogram could not be used for adjudication, the independent committee was able to confirm the recurrence based on the first criterion, which is based solely on a high NRS pain score (NRS ≥ 4) and elevated CRP value ≥1 mg/dL.

On this basis we conclude that the important deviations for missing data did not impact the validity of the primary endpoint.

Finally, it is important to note that a substantial proportion of these deviations occurred in the setting of hospitals being closed to study subjects during the current COVID-19 pandemic; the study team and site personnel have strictly recorded these anomalies in accordance with the FDA's COVID-19 missing data guidance. Subjects for whom study contact was affected by COVID-19 modifications are also listed separately in Appendix 16.1.15 of the KPL-914-C002 CSR."

Summaries of missing data are in the additional analyses subsection at the end of Section 6.

2. Patient Reported Outcome tool:

The Applicant developed the Patient Global Impression of Pericarditis Symptoms to assess global symptom severity specific to recurrent pericarditis. Interviews with ten adults diagnosed with recurrent pericarditis confirmed the relevance of the single-item PGIPS questionnaire to

assess overall symptom severity associated with recurrent pericarditis, as well as the readability and comprehensibility of the questionnaire. Distribution-based analyses, anchor-based analyses, and empirical cumulative distribution functions were conducted/generated to evaluate changes in the PGIPS scores. Due to the small sample size of the clinical trial and the study design causing a restricted range of scores during the RW timepoints used for efficacy, the applicant reported several planned analyses for the evaluation of interpretation of score change were not conducted or not easily interpretable. As an example, for the daily PGIPS scores, distribution-based estimates for between-group differences were between 0.5 and 2 points, respectively, and anchor-based estimates were between 2- and 3- points change.

Additional assessment of PGIPS score is in the Additional Analyses subsection at the end of Section 6.

Efficacy Results – Secondary endpoints

The first key secondary endpoint, proportion of subjects who maintained a clinical response (defined as a weekly average of daily pericarditis pain on the 11-point NRS ≤2.0 and CRP level ≤0.5 mg/dL) at Week 16 of the RW period, was analyzed using a CMH test stratified by the stratification variables at randomization. No stratum was pooled. A composite strategy was used to deal with missing NRS or CRP value and intercurrent events: subjects who discontinued double-blinded treatment, lost to follow up, used bailout rilonacept or rescue medications before Week 16 were considered as non-responders. Subjects who were missing Week 16 NRS or CRP were also considered non-responders. The missing data info are included at the Additional Analysis subsection. The percentages of subjects who maintained clinical response were 81% and 20% in the rilonacept and placebo group, respectively (Table 15). A common odds ratio of 12.7 with 95% CI (2.4, 66.4) and a 2-sided p-value of 0.0002 was obtained from the CMH test, showing a statistically significant difference in number of subjects who maintained clinical response between the two arms. Given the small sample size, an exact p-value was also calculated, the result was similar. Exploratory analyses were done on Week 8 Analysis Set and Week 24 Analysis Set showing that the percentages of clinical response maintained in the rilonacept arm at week 8 and week 24 were 78% and 77% respectively, and 26% and 20% in placebo arm.

Table 15: Maintenance of Clinical Response at RW Weeks 8, 16 and 24

	RW Period	
	Rilonacept	Placebo
RW Week 16, n	21	20
-Number of subjects who maintained response	17	4
-% who maintained response (95% CI)	81.0 (58.1, 94.6)	20.0 (5.7, 43.7)

-Difference in proportions (95% CI)	61.0 (36.7, 85.2)	
Odds Ratio (95% CI)	12.7 (2.4, 66.4)	
2-sided p-value	0.0002	
RW Week 8, n	27	31
-Number of subjects who maintained response	21	8
-% who maintained response (95% CI)	77.8 (57.7, 91.4)	25.8 (11.9, 44.6)
RW Week 24, n	17	15
-Number of subjects who maintained response	13	3
-% who maintained response (95% CI)	76.5 (50.1, 93.2)	20.0 (4.3, 48.1)

Source: applicant's CSR Table 14.2.2.1, verified by statistical reviewer.
Exact 95% CI for percentage who maintained response was calculated with randomization strata pooled. 95% CI for difference in proportions were based on a normal approximation. 95% CI and p-value for odds ratio was analyzed using a Cochran-Mantel-Haenszel test adjusted by oral corticosteroid use and diagnosis of recurrent idiopathic pericarditis at run-in baseline.
CI = confidence interval; ITT = intent to treat; RW = randomized withdrawal.

The second key secondary endpoint is percentage of days with No/Minimal (defined as non-missing NRS ≤2) pericarditis pain in the first 16 weeks in RW Period. For each subject, the percentage was calculated using number of days with No/Minimal pericarditis pain as numerator, and number of days (for example, 16*7 in the Week 16 Analysis Set). Missing values in pain diary or days of using rescue therapy were counted as not meeting the No/Minimal criterion. For bailout patients, each administration was counted as 7 days without qualifying No/Minimal pain (bailout therapy was taken weekly). The mean percentages were analyzed using analysis of covariance with stratification variables at randomization and RI baseline NRS in 2 categories (NRS≤2 vs. NRS>2) as covariates. The least squares mean difference (rilonacept-placebo) (95%CI) was 52 (35, 68) with a p-value of <0.0001, showing a statistically significant difference of mean percentage of days with No/Minimal pericarditis pain in the first 16 weeks in RW period between the two arms (Table 16). Missing rates were balanced between the two arms shown in Table 21 in the Additional Analyses subsection. Exploratory analyses were done on Week 8 Analysis Set and Week 24 Analysis Set showing consistency of efficacy result on different time intervals.

Table 16: Percentage of Days with No/Minimal Pericarditis Pain in the RW Period

	RW Period	
	Rilonacept	Placebo
RW Week 16		
N	21	20
Mean (SD)	92.0 (13.5)	39.1 (34.4)
Median	96.4	24.1

Minimum	41.1	3.6
Maximum	100	100
Least Squares Mean (SE)	91.5 (5.6)	39.7 (5.8)
Least Squares Mean Difference (rilonacept-placebo), 95% CI	51.8 (35.3, 68.4)	
2-sided p-value	< 0.0001	
RW Week 8		
N	27	31
Mean (SD)	89.7 (20.6)	51.1 (31.8)
Median	98.2	44.6
Minimum	3.6	7.1
Maximum	100	100
Least Squares Mean (SE)	90.6 (5.3)	50.9 (4.9)
RW Week 24		
N	17	15
Mean (SD)	91.6 (11.3)	40.5 (34.6)
Median	97.0	31.5
Minimum	6.7	2.4
Maximum	100	100
Least Squares Mean (SE)	92.2 (6.0)	39.8 (6.3)

Source: Generated by statistical reviewer.
The percentage of days with no or minimal pericarditis pain in the first 24, 16, and 8 weeks was calculated for each subject using 24×7, 16×7, 8×7, respectively, as the denominator.
Two-sided p-value were calculated using analysis of covariance with treatment, randomization strata and run-in baseline NRS weekly average category (NRS ≤ 2 versus NRS >2) as covariates. Least square means were calculated based on observation margins accounting for overall distributions of the covariates.
CI = confidence interval; ITT = intent to treat; NRS = numerical rating scale; RW = randomized withdraw; SD = standard deviation; SE = standard error.

The third key secondary endpoint, proportion of subjects with absent or minimal pericarditis symptoms (based on the7-point PGIPS) at Week 16 of the RW period, was a binary endpoint dichotomized from PGIPS scale. Subjects who had received bailout rilonacept or rescue medication before Week 16 or missing assessment at Week 16 were considered non-responders. The CMH test stratified by the stratification variables (no stratum was pooled) showed a statistically significant result with a common odds ratio (95% CI) of 10 (2, 47) with a p-value of 0.0006 (Table 17). Given the small sample size, an exact p-value was also calculated, a similar result was obtained. However, the interpretability of this PRO endpoint is not clear due to the large proportion (44%) of missing data and intercurrent events. More analyses are done in the Additional Analyses subsection.

Table 17 : Proportion of Subjects with No/Minimal Pericarditis Symptoms (PGI-PS): RW Period

	RW Period	
	Rilonacept	Placebo
RW Week 16		
N	21	20
# of subjects with no or minimal pericarditis symptoms	17	5
% with no or minimal pericarditis symptoms (95% CI)	81.0 (58.1, 94.6)	25.0 (8.7, 49.1)
Difference in proportions (95% CI)	56.0 (30.6, 81.3)	
Odds Ratio (95% CI)	10.0 (2.1, 46.8)	
2-sided p-value	0.0006	

Source: applicant's CSR Table 14.2.2.3, verified by statistical reviewer.
Exact 95% CI for percentage who maintained response was calculated with randomization strata pooled. 95% CI for difference in proportions were based on a normal approximation. 95% CI and p-value for odds ratio was analyzed using a Cochran-Mantel-Haenszel test adjusted by oral corticosteroid use and diagnosis of recurrent idiopathic pericarditis at run-in baseline.
CI = confidence interval; ITT = intent to treat; RW = randomized withdrawal.

Dose/Dose Response

The clinical development program did not accommodate a dose-response evaluation for the treatment of recurrent pericarditis.

Durability of Response and Persistence of Effect

In the rilonacept arm of the RW period, only one subject required oral rescue therapy at week 15 and one subject required bailout (i.e., rilonacept) at week 29 (Table 18). In the placebo arm, two subjects required oral rescue therapy at week 5 and twenty-three subjects required bailout at week 8 (median week 5). The same data is shown as a function of time in Table 19. More than 30% of the subjects in the placebo arm required oral rescue therapy or bailout with rilonacept within 4 weeks from randomization in the RW period. More than half the subjects in the placebo arm required treatment within 8 weeks from randomization. These data demonstrate durability of rilonacept with limited persistence (4-8 weeks).

Table 18 : Time to First Use of Rilonacept Bailout During Randomized Withdrawal

Time to 1st use of Bailout Rilonacept (Weeks) in Randomized Withdrawal Period						
	Rilonacept (N=30)			Placebo (N=31)		
	ORT	Bailout	Total	ORT	Bailout	Total
n	1	1	2	2	23	24

Mean (SD)	14.9 (NE)	28.7 (NE)	21.8 (9.8)	4.6 (0.8)	7.7 (7.0)	7.5 (6.9)
Median	14.9	28.7	21.8	4.6	4.9	4.6
Minimum	14.9	28.7	14.9	4.0	2.1	2.1
Maximum	14.9	28.7	28.7	5.1	32.3	32.3

Source: applicant's CSR Table 14.2.3.20.3, verified by statistical reviewer.
Bailout = treatment with rilonacept; NE = not estimable; ORT = Oral Rescue Therapy comprised of analgesics first, then NSAIDs, then colchicine.

Table 19 : Subjects Requiring First Time Rescue or Bailout During Randomized Withdrawal

	Randomized Withdrawal							
Subjects requiring ORT, CS or bailout for the 1st time during the RW period								
	Rilonacept (N=30)				Placebo (N=31)			
	n (%)				n (%)			
	ORT	CS	Bailout	Total	ORT	CS	Bailout	Total
≤ 4 weeks	0	0	0	0	1 (3.2)	0	9 (29.0)	10 (32.3)
≤ 8 weeks	0	0	0	0	2 (6.5)	0	15 (48.2)	16 (51.6)
≤ 12 weeks	0	0	0	0	2 (6.5)	0	19 (61.3)	20 (64.5)
≤ 16 weeks	1 (3.3)	0	0	1 (3.3)	2 (6.5)	0	21 (67.7)	22 (71.0)
≤ 20 weeks	1 (3.3)	0	0	1 (3.3)	2 (6.5)	0	22 (71.0)	23 (74.2)
≤ 24 weeks	1 (3.3)	0	0	1 (3.3)	2 (6.5)	0	22 (71.0)	23 (74.2)
All including > 24 weeks	1 (3.3)	0	1 (3.3)	2 (6.7)	2 (6.5)	0	23 (74.2)	24 (77.4)

Source: applicant's CSR Table 14.2.3.20.3, verified by statistical reviewer.
Bailout = treatment with rilonacept; CS = corticosteroids; ORT = Oral Rescue Therapy comprised of analgesics first, then NSAIDs, then colchicine.

Additional Analyses Conducted on the Individual Trial

Summary of missing data
For the primary endpoint, no event (CEC adjudicated PC Recurrence) dates or censor dates (last PC assessment date before cutoff) were found missing in all 61 ITT population subjects.

For secondary endpoints, information on missing rates are summarized in Table 20. For the first and second key secondary endpoints, missing rates are similar between the two arms. For the third secondary endpoint, 3 subjects are missing Week 16 PGI-PS score in treatment arm, while no Week 16 PGI-PS score is missing. Since missing score assessments are considered as non-responders, the missingness could not potentially alter the efficacy result.

Table 20: Summary of Missing Data for Key Secondary Endpoints

Key Secondary	Components	KPL-914	Placebo

Endpoints		Missing Data N (%)	Total N	Missing Data N (%)	Total N
Proportion of patients with clinical response	Week16 NRS	2(9.5)	21	2(10.0)	20
	CRP	0	21	0	20
Percent of days with no or minimum pericarditis pain	Daily NRS up to Week 16	173(7.4)	2352	212(9.5)	2240
Proportion of subjects with No or minimal pericarditis symptoms	Week16 PGI-PS	3(14.3)	21	0	20

In conclusion, missing data does not have significant impact on the efficacy result. In addition, the ways the missing data were treated (for the first and third key secondary endpoints, missing endpoint assessments were considered as non-responders; for the second key secondary endpoint, missing values in pain diary were counted as not meeting the No/Minimal criterion) were acceptable for the analyses on key secondary endpoints.

PGIPS score assessment

Patient Global Impression of Pericarditis Severity (PGIPS) score is a single-item measure that uses a 7-point rating scale ranging in: Absent, Minimal, Mild, Moderate, Moderately Severe, Severe, and Very Severe. In the Week 16 Analysis Set, the PGIPS score was measured at baseline, Week 8, and Week 16.

The third key secondary endpoint, proportion of subjects with absent or minimal pericarditis symptoms, is a binary endpoint dichotomized from PGI-PS score. Of the 4 non-responders in treatment arm, 3 subjects' Week 16 score were missing. Of the 15 non-responders in placebo arm, 10 subjects received bailout before Week 8, and 5 subjects received bailout between Week 8 and Week 16. 94.7% of the non-responders came from intercurrent event (bailout) or missing data.

The following additional analyses were performed to evaluate the validity of this PRO endpoint without dichotomization. Firstly, PGIPS was converted into numerical scores with Absent (0), Minimal (1), Mild (2), Moderate (3), Moderately Severe (4), Severe (5), and Very Severe (6). Since the proportion of intercurrent events was large, the data was analyzed under both treatment policy strategy and hypothetical strategy. Under treatment policy strategy (without imputation), PGI-PS scores recorded after bailout were used. Under hypothetical strategy (with imputation), to reflect the hypothetical situation that the subjects had not received bailout rilonacept, the scores recorded after bailout were deleted and then imputed with each

subject's worst PGI-PS score in Run-In period and Random Withdraw Period visits. The analyses were based on changes of PGI-PS score in three time intervals: from baseline to Week 8, from Week 8 to Week 16, and from baseline to Week 16.

Table 21 summarizes change of PGIPS scores under different scenarios. Figure 8, Figure 9,

Figure 10, Figure 11,

Figure 12, Figure 13, showed the empirical cumulative density function curves under different scenarios.

Table 21: Summary Statistics for Change in PGI-PS

Data Set	Time Interval	Treatment Arm	Mean	Median	Min.	Max.
Without Imputation	Baseline to wk8	KPL-914	-0.16	0	-1	1
		Placebo	0.74	0	-1	5
	Baseline to wk16	KPL-914	-0.11	0	-1	1
		Placebo	-0.05	0	-1	1
	wk8 to wk16	KPL-914	0	0	-1	2
		Placebo	-0.79	0	-4	0
With Imputation	Baseline to wk8	KPL-914	-0.16	0	-1	1
		Placebo	2.50	2	0	6
	Baseline to wk16	KPL-914	-0.11	0	-1	1
		Placebo	2.90	4	0	6
	wk8 to wk16	KPL-914	0	0	-1	2
		Placebo	0.40	0	-1	3

Figure 8: Baseline to Week 8, Without Imputation

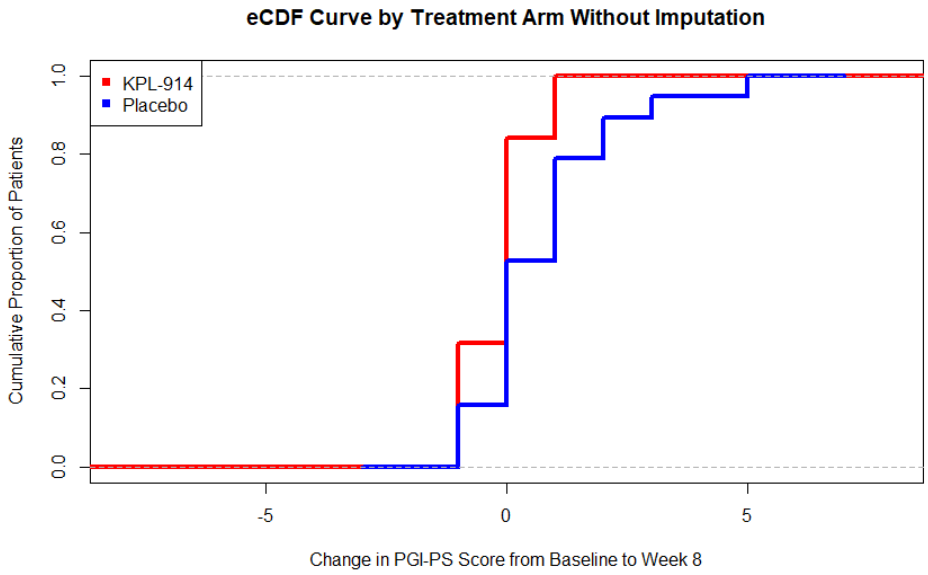


Figure 9: Baseline to Week16, Without Imputation

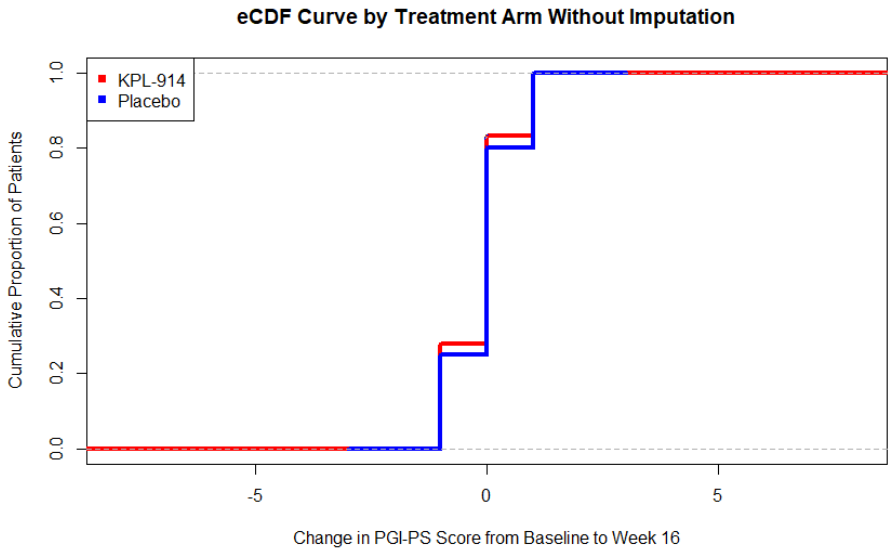


Figure 10: Week 8 to Week 16, Without Imputation

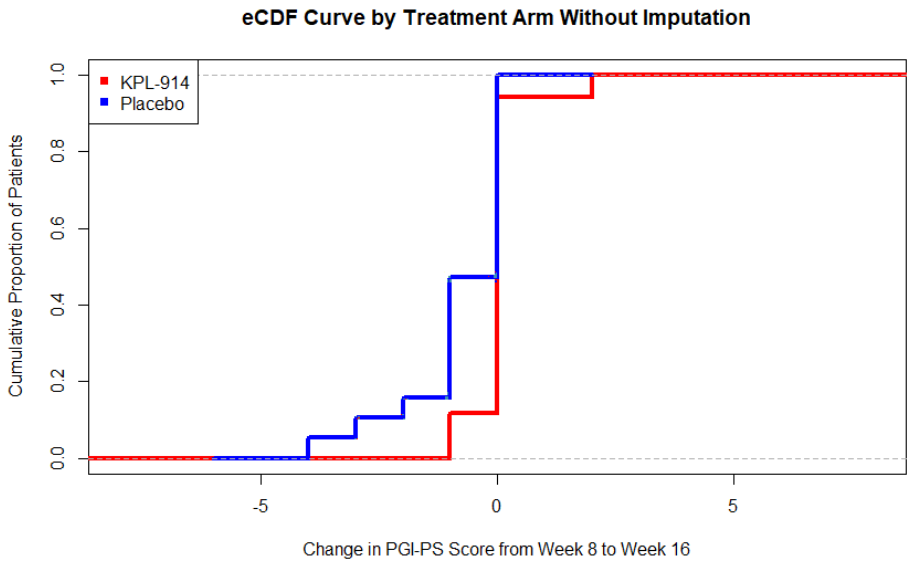


Figure 11: Baseline to Week 8, With Imputation

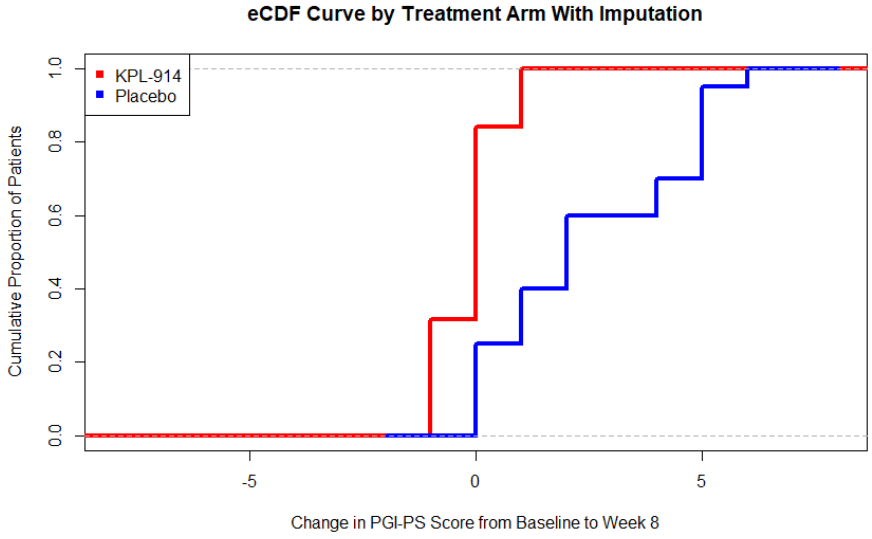


Figure 12: Baseline to Week 16, With Imputation

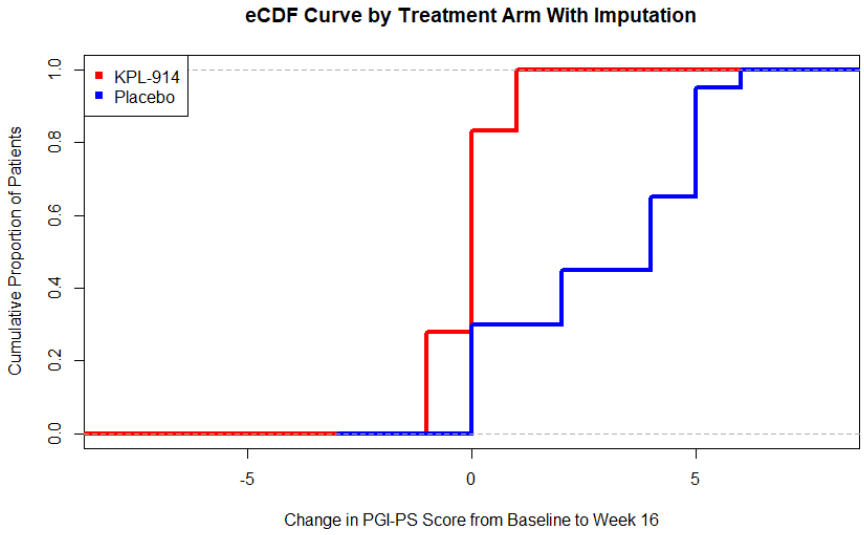
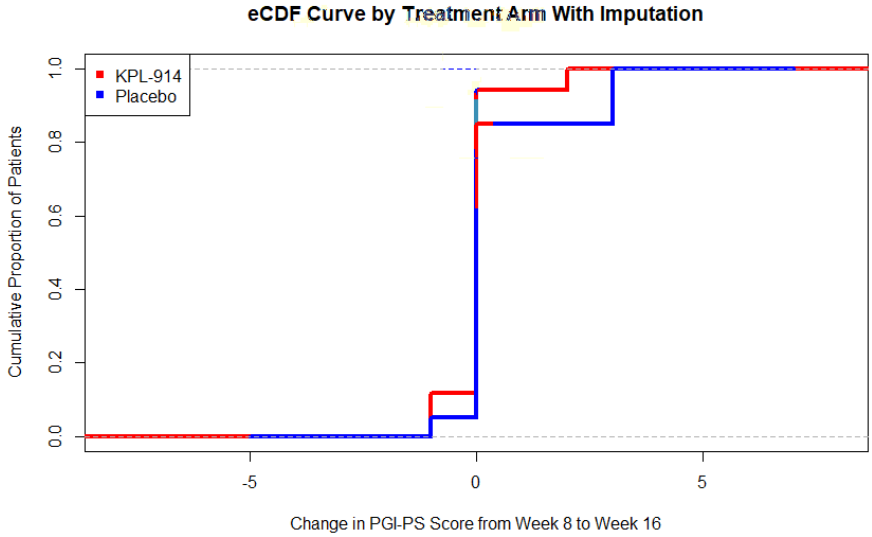


Figure 13: Week 8 to Week 16, With Imputation



In Figure 8, Figure 9, and

Figure 10, eCDF curves did not show noticeable separation between the two arms without imputation. After data imputation, Figure 13 showed a separation of the distributions of change in PGIPS score from baseline to Week 16 between the two arms. However, since 18 of the 19 non-responders in Week 16 Analysis Set were determined from either missing data or bailout, the result could be dominated by the choice of imputation method and is hard to interpret.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Section 7.1 is not applicable in this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The RHAPSODY trial demonstrated that patients with recurrent pericarditis who are treated with standard of care can be successfully weaned off standard of care therapy while treated concomitantly with rilonacept, and that rilonacept monotherapy can successfully reduce the incidence of another recurrent episode. Rilonacept treatment was durable but persistence was limited to approximately 4-8 weeks post termination of treatment.

In the postmarket setting, the use of rilonacept should reflect how it was studied in the clinical trial. As such, it should not be prescribed as first line therapy for pericarditis. Further, the RHAPSODY trial was not designed to provide evidence supporting first-line treatment for an episode of recurrent pericarditis without concomitant standard of care treatment and subsequent weaning of standard of care treatment. The trial did not evaluate a rapid switch from standard-of-care to rilonacept monotherapy. The label should state these facts but leave to clinical judgment the optimal use of rilonacept with respect to when to treat and duration of treatment.

It is not clear how long patients with a history of recurrent pericarditis should be treated. The mean duration of exposure was 6 months, consistent with standard-of-care treatment of recurrent pericarditis. However, cessation of rilonacept resulted in recurrence. It is clinically reasonable to administer rilonacept indefinitely to subjects who would have qualified for the RHAPSODY trial. Long term assessment of safety is ongoing.

Ubiquitous to clinical trials, patient under-representation (i.e., paucity of Black and Latino patients) is apparent in this trial, especially when the majority of participants came from the USA. Consequently, effectiveness in these populations were undetermined.

7.2.2. Other Relevant Benefits

Weekly subcutaneous self-administration or administration with assistance from a health care provider establishes the framework for enhanced medication adherence, driven by ease of administration and pain relief. These aspects considered by the patient are relevant to the overall assessment of rilonacept's benefit.

7.3. Integrated Assessment of Effectiveness

RHAPSODY was a well-controlled and adequately performed clinical trial. The effectiveness of rilonacept demonstrated in RHAPSODY met the statutory evidentiary standard pursuant to §21 CFR 314.126 for the treatment of recurrent pericarditis.

The trial results were deemed clinically meaningful based on pain relief as evaluated by the NRS scale and corroborated by CRP levels.

At baseline, enrolling subjects were required to have experienced a previous event of acute pericarditis and two subsequent recurrences (the 2nd recurrence serving as the qualifying event for enrollment in the trial). As there is no drug approved for recurrent pericarditis, consenting subjects were on off-label treatment (80% on colchicine, 67% on NSAIDS, and approximately 50% on corticosteroids) at baseline. From baseline pain levels and CRP levels, it can be reasonably inferred that the off-label standard of care for pericarditis was not effective in resolving the qualifying recurrence. However, by definition, the antecedent recurrence prior to the qualifying event was ameliorated by off-label standard of care medications.

The pivotal trial data showed that rilonacept treatment for recurrent pericarditis was durable and resolved the chest pain experienced by subjects while on off-label standard of care treatment. However, the data showed limited persistence: cessation of rilonacept precipitated further recurrence. This raised the question of how long patients should be treated. The average exposure was 6 months. For this patient population, a clinical decision to treat patients with rilonacept indefinitely may be reasonable, but long-term effects of rilonacept is not known in this patient population.

8. Review of Safety

Safety Review Approach

There are no concerns regarding submission quality, conduct of the studies with respect to assessment of safety, or the Applicant's characterization of adverse events.

There were two recurrent pericarditis studies: the phase 2 open label study KPL-914-C001 and the phase 3 randomized withdrawal study KPL-914-C002. The safety review focused on the safety population in the phase 3 study.

In addition, to assess the risks of malignancy and cardiac disorders, we reviewed safety data from the gout program including 4 similarly-designed 16-week, randomized, double-blind, placebo-controlled efficacy and safety studies (study IL1T-GA-0810, IL1T-GA-0816, IL1T-GA-0815, and IL1T-GA-0619), totaling 1886 subjects. There were more subjects in the Rilonacept group (1353 subjects, 72%) than the placebo group (533 subjects, 28%). The subjects in the Rilonacept group received doses of either 80 mg (162 subjects) or 160 mg (1191 subjects). The mean age was 52 years and 90% were male. The safety population had significant co-morbidities, including a history of hypertension (52%), hyperlipidemia (13%), hypercholesterolemia (16%), cardiac disorders (12%), diabetes (13%), and obesity (8%).

In this review, unless otherwise specified, safety results are presented for study KPL-914-C002.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The mean duration of treatment was 29 weeks. The exposure to placebo was significantly lower because of the quick bailout in the placebo group during the randomized withdrawal (RW) period (Table 22). Most subjects in the placebo group received Rilonacept after bailout and the Rilonacept administered in the placebo group was similar to the Rilonacept group during the RW period (Table 22). Due to the short exposure to placebo, there was no effective placebo comparison for safety.

Table 22: Extent of Exposure, Safety Population in KPL-914-C002

Arm	Period	N[1]	Mean	SD	Median
Treatment Duration (Weeks)					
	RI	86	11.6	2.2	12.0
Rilonacept	RW total	30	25.1	15.6	25.1

Arm	Period	N[1]	Mean	SD	Median
Rilonacept	RW before BO	30	24.4	15.0	25.1
Rilonacept	RW after BO	1	20.1	NA	20.1
Placebo	RW total	31	23.9	14.6	19.4
Placebo	RW before BO	31	9.9	9.4	6.7
Placebo	RW after BO	23	18.9	13.3	17.0
Rilonacept Dose Admin (mg)					
	RI	86	2003.1	376.6	2080.0
Rilonacept	RW total	30	3904.0	2400.0	3920.0
Rilonacept	RW before BO	30	3802.7	2383.1	3360.0
Rilonacept	RW after BO	1	3040.0	NA	3040.0
Placebo	RW total	23	3166.6	2127.8	2880.0
Placebo	RW before BO	31	0.0	0.0	0.0
Placebo	RW after BO	23	3166.6	2127.8	2880.0

[1]Number of subjects.
Abbreviations: RI, run-in; RW, randomized withdrawal; BO, bailout; SD, standard deviation.

8.2.2. Relevant characteristics of the safety population

The safety population from study KPL-914-C002 consisted of 86 subjects. Of these subjects, 57% were female and 93% were White/Caucasians. The mean age was 45 years; 7 subjects (8%) were aged 12–17 years. Study KPL-914-C001 consisted of 25 subjects with similar demographics as study KPL-914-C002, except there were no subjects below 18 years old.

8.2.3. Adequacy of the safety database

The safety database was adequate. The mean exposure to treatment in the recurrent pericarditis population was over 6 months. Though the controlled recurrent pericarditis study was conducted in under 100 subjects, additional safety concerns such as malignancies were

evaluated in the much larger gout population.

8.3. Safety Results

Summary of Treatment Emergent Adverse Events

Table 23 showed the summary of overall adverse events (AEs). The occurrences of serious adverse events (SAEs), severe AEs, and AEs leading to drug discontinuations were low. All severe AEs and AEs leading to drug discontinuations occurred during the run-in (RI) period.

The most common treatment emergent adverse events (TEAEs) were injection site reactions, infections, arthralgia, and myalgia (Table 24). Arthralgia and myalgia were observed mostly in the RI period and may have been related to the tapering of other pericarditis medications (including corticosteroids). The AE profile of study KPL-914-C002 was consistent with the known safety profile of Rilonacept.

Table 23: Summary of Treatment Emergent Adverse Events, Safety Population in KPL-914-C002

	Run-in		Randomized withdrawal								Study Overall	
	Rilonacept (N = 86)		Rilonacept (N = 30)				Placebo (N = 31)				(N = 86)	
			Before BO (N = 30)		After BO (N = 1)		Before BO (N = 31)		After BO (N = 23)			
Summary	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any AE	69	80.2	24	80.0	1	100	13	41.9	13	56.5	74	86.0
SAEs	1	1.2	1	3.3	0	0	1	3.2	2	8.7	5	5.8
Severe AEs	2	2.3	0	0.0	0	0	0	0.0	0	0.0	2	2.3
AEs lead to drug discontinuations	4	4.7	0	0.0	0	0	0	0.0	0	0.0	4	4.7
AEs lead to drug interruptions	0	0.0	1	3.3	0	0	0	0.0	0	0.0	1	1.2

Abbreviations: BO, bailout; AE, adverse event; SAE, serious adverse event.

Table 24: The Most Common Treatment Emergent Adverse Events (Overall Incidence **≥5%),** Safety Population in KPL-914-C002

	Run-in		Randomized Withdrawal						Study Overall	
	Rilonacept (N = 86)		Rilonacept (N = 30)		Placebo (N = 31)				All (N = 86)	
			Before BO		Before BO		After BO			
MedDRA[1] Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Injection site erythema	18	20.9	5	16.7	0	0.0	1	4.3	21	24.4
Arthralgia	8	9.3	1	3.3	0	0.0	2	8.7	10	11.6
Myalgia	9	10.5	1	3.3	0	0.0	0	0.0	10	11.6
Headache	7	8.1	0	0.0	0	0.0	0	0.0	8	9.3
Injection site pruritus	5	5.8	4	13.3	0	0.0	1	4.3	8	9.3
Nasopharyngitis	6	7.0	2	6.7	0	0.0	0	0.0	8	9.3
Musculoskeletal chest pain	3	3.5	1	3.3	4	12.9	0	0.0	7	8.1
Cough	5	5.8	1	3.3	0	0.0	1	4.3	6	7.0
Diarrhoea	5	5.8	0	0.0	0	0.0	0	0.0	6	7.0
Injection site swelling	5	5.8	1	3.3	0	0.0	0	0.0	6	7.0
Back pain	3	3.5	1	3.3	0	0.0	1	4.3	5	5.8
Fatigue	2	2.3	2	6.7	0	0.0	1	4.3	5	5.8

[1]Version 21.0.
Abbreviations: BO, bailout.

8.3.2. Deaths

There were no deaths in the recurrent pericarditis studies.

8.3.3. Serious Adverse Events

Five subjects (6%) had SAEs. Four SAEs occurred when the subjects were receiving Rilonacept and one was receiving placebo (Table 23). The SAEs were pyrexia, cerebrovascular accident, ileus, cardiac flutter, and squamous cell carcinoma. All SAEs were mild or moderate in severity and no subjects discontinued the treatment due to the SAEs. No SAEs clustered around any AE of special interest (see Section 8.3.5).

8.3.4. Dropouts and/or Discontinuations Due to Adverse Effects

Four subjects (5%) discontinued the study drug due to adverse events; all occurred during the run-in period. The adverse events were erythema, alveolitis allergic, alopecia, and hypersensitivity, none of which were SAEs. The alveolitis allergic was a severe adverse event.

8.3.5. Adverse Events of Special Interest

Injection Site Reactions
Injection site reactions were the most common adverse events in study KPL-914-C002, including MedDRA preferred terms of injection site-erythema, -pruritus, -swelling, -pain, -rash, -bruising, -discoloration, -reaction, -inflammation, -nodule, feeling hot, erythema, pruritus, rash, and rash macular. None of the injection site reactions occurred when the subjects were receiving placebo. Injection site reactions occurred more frequent during the run-in period (Table 25). None of the injection site reactions were SAEs or severe AEs. One AE of erythema that occurred during the run-in period led to the discontinuation of the study drug.

Table 25: Most Common Injection Site Reactions **(≥3%),** Safety Population in KPL-914-C002

	Run-in		Randomized Withdrawal						Study Overall	
	Rilonacept (N = 86)		Rilonacept (N = 30)				Placebo (N = 31)		(N = 86)	
			Before BO (N = 30)		After BO (N = 1)		After BO (N = 23)			
Category/PT	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any ISR	28	32.6	5	16.7	1	100	2	8.7	29	33.7
Injection site erythema	18	20.9	5	16.7	1	100	1	4.3	21	24.4
Injection site pruritus	5	5.8	4	13.3	1	100	1	4.3	8	9.3

	Run-in		Randomized Withdrawal						Study Overall	
	Rilonacept (N = 86)		Rilonacept (N = 30)				Placebo (N = 31)		(N = 86)	
			Before BO (N = 30)		After BO (N = 1)		After BO (N = 23)			
Category/PT	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Injection site swelling	5	5.8	1	3.3	0	0	0	0.0	6	7.0
Injection site pain	4	4.7	0	0.0	0	0	0	0.0	4	4.7
Injection site rash	3	3.5	0	0.0	0	0	0	0.0	3	3.5

Abbreviations: PT, MedDRA preferred term (version 21.0); BO, bailout; ISR, injection site reaction.

Infections and Infestations

Subjects treated with Rilonacept had a high incidence of infections and infestations (MedDRA system of organ class), shown in Table 26. No infection-related AEs were SAEs, severe AEs, or led to discontinuation of the study drug. Nineteen subjects (22%) experience upper respiratory tract infections (URTI) including nasopharyngitis, sinusitis, URTI, viral URTI, pharyngitis, streptococcal pharyngitis, and rhinitis. One subject in study KPL-914-C001 had a serious adverse reaction of subcutaneous abscess, which resolved with standard care.

Table 26: Most Common Infections and Infestations Adverse Events **(≥3%),** Safety Population in KPL-914-C002

	Run-in		Randomized Withdrawal						Study Overall	
	Rilonacept (N = 86)		Rilonacept (N = 30)		Placebo (N = 31)				(N = 86)	
			Before BO (N = 30)		Before BO (N = 31)		After BO (N = 23)			
Category/PT	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any infection and infestation (SOC)	14	16.3	12	40.0	3	9.7	4	17.4	29	33.7
Nasopharyngitis	6	7.0	2	6.7	0	0.0	0	0.0	8	9.3

	Run-in		Randomized Withdrawal						Study Overall	
	Rilonacept (N = 86)		Rilonacept (N = 30)		Placebo (N = 31)				(N = 86)	
			Before BO (N = 30)		Before BO (N = 31)		After BO (N = 23)			
Category/PT	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sinusitis	1	1.2	3	10.0	0	0.0	0	0.0	4	4.7
Upper respiratory tract infection	2	2.3	1	3.3	0	0.0	1	4.3	4	4.7
Urinary tract infection	1	1.2	3	10.0	0	0.0	1	4.3	4	4.7
Influenza	1	1.2	0	0.0	1	3.2	1	4.3	3	3.5
Viral upper respiratory tract infection	2	2.3	1	3.3	0	0.0	0	0.0	3	3.5

Abbreviations: PT, MedDRA preferred term (version 21.0); BO, bailout; SOC, system of organ class.

Hyperlipidemia

The occurrence of hyperlipidemia was consistent with the increasing lipid levels when treated with Rilonacept (see the *Lipids* section below). Five subjects (6%) had six hyperlipidemia-related AEs. All occurred when the subjects were receiving Rilonacept. None were SAEs, severe AEs, or led to discontinuation of the study drug. The preferred terms of these adverse events were lipids increased (3 subjects), blood triglycerides increased (1 subject), hyperlipidemia (1 subject), and blood cholesterol increased (1 subject).

Malignancy

One subject in the Rilonacept group in study KPL-914-C002 had a malignancy event of squamous cell carcinoma during the randomized withdrawal period. The event was a SAE and was moderate in severity. The carcinoma was surgically removed.

In the gout safety database, there was a slight numerical imbalance in malignancy AEs. Six subjects (0.4%) in the Rilonacept group and no subjects in the placebo group had malignancies (Table 27). Kaplan-Meier plot showed a separation between the Rilonacept group and the placebo group (Figure 14). Statistical analysis showed a significant risk difference in malignancy between the Rilonacept and the placebo groups in the pooled safety database from the gout program (Table 28).

During the review of the BLA for the gout indication, the Arthritis Advisory Committee, and the DCN review team during the review of this application, assessed this risk as small but real because of underlying risk of malignancy in the gout population and a plausible mechanism (immunosuppression) in those subjects treated with rilonacept. Safety data was limited to 16 weeks; the lack of long term safety data for a biologic immunosuppressant was not typical. Thus, the risk of malignancy could not be excluded, and a warning was placed in the product label that adequately addresses this risk.

Table 27: Malignancy Events, Safety Population, Gout program (Studies 810, 816, 815, 619)

Table 27: Malignancies (Safety Set 2)†

Patient ID	Malignancy Type (preferred term)	Age/Sex	On Treatment	Doses Received	Study	Country
Rilonacept 80 mg (N=162)						
(b) (6)	Gastric Cancer	70/M	Yes	4	816	S. Africa
Rilonacept 160 mg (N=1191)						
(b) (6)	Prostate Cancer	68/M	Yes	11	619	USA
	Prostate Cancer	71/M	Yes	3	815	USA
	Prostate Cancer	56/M	Yes	9	815	USA
	Breast Cancer	72/F	Yes	10	815	USA
	Oropharyngeal Cancer	52/M	Yes	15	815	S. Africa

Source: Table 28, page 73, Summary of Clinical Safety, Module 2.7.4.
On treatment defined as occurring within 35 days of the last dose of investigational product.
† Placebo group (N=533) had no malignancies reported.

Source: FDA clinical review.

Figure 14: Kaplan-Meier Plot for Malignancies, Safety Population in Gout Program (Studies 810, 816, 815, 619). The Grey Area Indicates the 95% Confidence Interval.

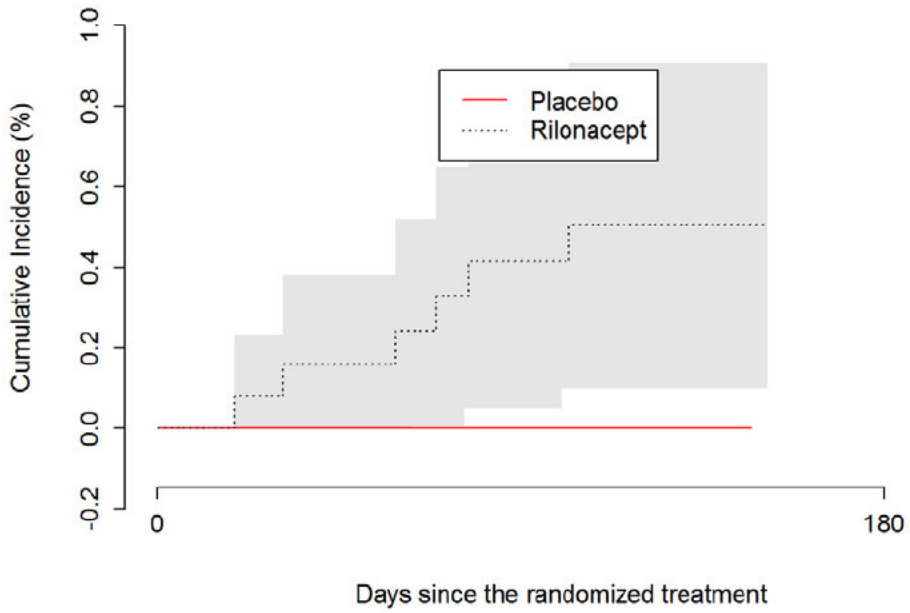


Table 28: Statistical Analysis of Malignancy, Safety Population in Gout Program (Studies 810, 816, 815, 619)

Study	Treatment (No. subjects)	Malignancy	Risk difference (%)	95% CI (%)	P-value	NNT
815	160 mg (985) Placebo (330)	4 0	0.41	[0.01, 0.80]	0.05	246
All studies pool 160 mg	160 mg (1191) Placebo (533)	5 0	0.42	[0.05, 0.79]	0.03	238
All studies	80 mg + 160 mg (1353) Placebo (533)	6 0	0.44	[0.09, 0.80]	0.01	225

Abbreviations: CI, confidence interval; NNT, number need to treat.

Cardiac Disorders

In study KPL-914-C002, 7 subjects (8%) had 8 cardiac disorder-related adverse events (system of organ class: cardiac disorders): 5 (6%) in the run-in period and 2 (6%) in the placebo group before bailout in the randomized withdrawal period. The preferred terms of the adverse events were sinus tachycardia, tachycardia, palpitations, atrial fibrillation, ventricular dyssynchrony,

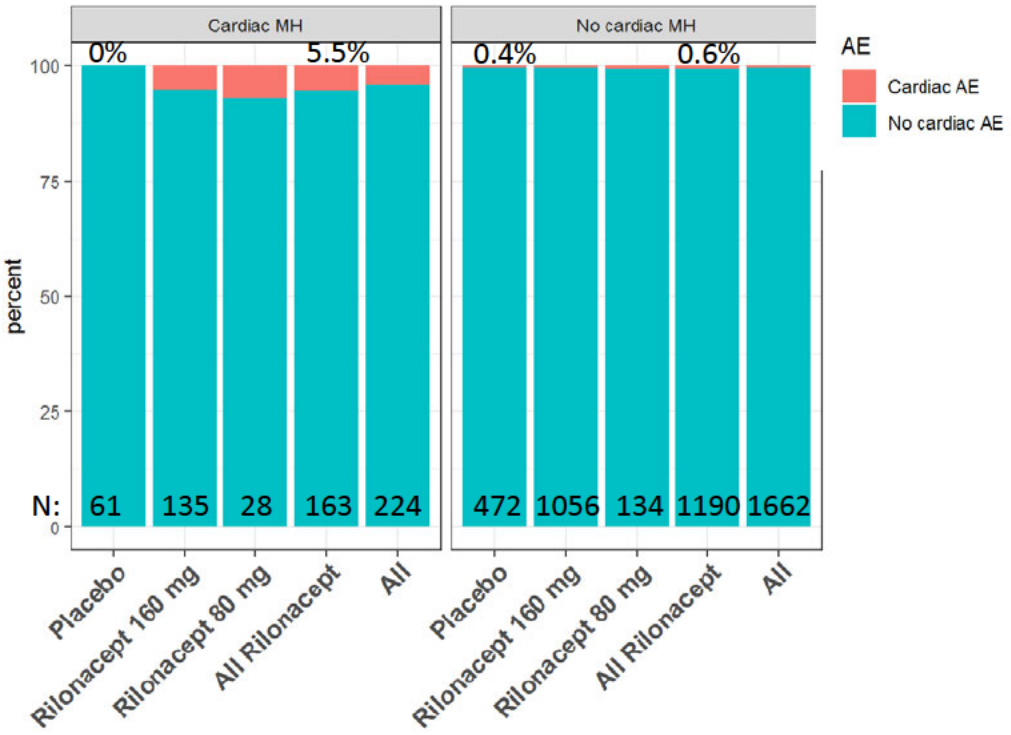
angina pectoris, aortic valve incompetence, and cardiac flutter. One event of tachycardia led to discontinuation. One event of cardiac flutter was a SAE. All events were moderate or mild in severity.

In the gout program, medical history of cardiac disorders was balanced between the Rilonacept group and the placebo group (~12%). There was a slight numerical imbalance between the placebo group and the Rilonacept group in cardiac disorder-related AEs (0.4% vs 1.2%). 8 subjects (0.6%) in the Rilonacept group and 1 subject (0.2%) in the placebo group had cardiac SAEs. Statistical analysis showed a risk difference of 0.8% (95% CI: [0.0%, 1.6%]) in cardiac disorder-related AEs.

The cardiac disorder-related AE profile was different between subjects with or without a cardiac disorder medical history. Among the 224 subjects who had a cardiac disorder medical history, more subjects in the Rilonacept group had cardiac disorder-related AEs compared with placebo, while among the 1662 subjects without a cardiac disorder medical history, similar percent of subjects had cardiac disorder-related AEs in the Rilonacept group and the placebo group (Figure 15).

The small numerical imbalance in cardiac AEs and SAEs in the gout safety database did not rise to the level of a clear safety signal.

Figure 15: Percentage of Subjects had Cardiac Disorder-Related Adverse Events in Each Treatment Group for Subjects With (Left) or Without (Right) a Cardiac Disorder Medical History, Safety Population in Gout Program (Studies 810, 816, 815, 619)



8.3.6. Laboratory Findings

Lipids

Chronic inflammatory conditions are often associated with decreases in serum lipids, particularly cholesterol, and when the inflammation is decreased, cholesterol levels may rise in response.

Mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides all increased at week 12 from baseline during the run-in period. The number of subjects who had lipid levels higher than the normal range also increased from baseline to week 12 (Table 29).

All 61 subjects participated in the RW period had lipid data at RW baseline. However, only 27 subjects had lipid data at RW week 24 and fewer than 10 subjects had lipid data at any other week during the RW period. Only 3 subjects on the placebo arm who did not receive bailout Rilonacept had lipid data at RW week 24. Lipid data after RW baseline were insufficient to determine whether lipid levels return to normal after the Rilonacept treatment.

Table 29: Summary of Lipids in the Run-in Period, Safety Population, Study KPL-914-C002.

				High[2]		Low		Normal	
	N[1]	Mean	CHG from BL	n	%	n	%	n	%
Cholesterol (mg/dL)									
RI Baseline[3]	85	174.3	0	24	28.2	7	8.2	54	63.5
RI Week 12	80	190.4	12.3	32	40.0	1	1.2	47	58.8
HDL Cholesterol (mg/dL)									
RI Baseline	84	50.4	0	22	26.2	24	28.6	38	45.2
RI Week 12	80	56.3	20.3	31	38.8	15	18.8	34	42.5
LDL Cholesterol (mg/dL)									
RI Baseline	84	108.3	0	8	9.5	2	2.4	74	88.1
RI Week 12	80	116.0	12.7	14	17.5	0	0.0	66	82.5
Triglycerides (mg/dL)									
RI Baseline	84	120.4	0	7	8.3	1	1.2	76	90.5
RI Week 12	80	135.2	14.3	13	16.2	0	0.0	67	83.8

[1] Number of subjects.
[2] The High, Low, and Normal columns showed the number of subjects had lipid levels higher than, lower than, or within the normal range of the serum lipids. The normal range was defined by the investigators.
[3] Baseline was defined as the last non-missing data before or on the treatment start date.
Abbreviations: CHG, change; BL, baseline; RI, run-in.

Neutrophil

No subjects had severely or moderately low neutrophil counts (< $1.0x10^3$/µL, Haddy et al., 1999). Seven subjects (8%) had neutrophil counts mildly low (< $1.7x10^3$/µL, lower limit of the normal range, defined by the sponsor) at any visit. One subject was not randomized and had neutrophil count lower than $1.7x10^3$/µL at the end of the RI period. One subject (3%) was randomized to the Rilonacept group and had neutrophil count lower than $1.7x10^3$/µL through the RI and the RW period. Five subjects (16%) were randomized to the placebo group; all of them had neutrophil count lower than $1.7x10^3$/µL at the end of the RW period. No Neutropenia adverse events were reported.

8.3.1. Immunogenicity

The majority of the subjects were anti-drug antibody (ADA) negative at every visit. Overall, 26 subjects (30%) were ADA positive at any visit. There was no imbalance in positive ADA tests at any visit between those subjects who did and did not have an injection site reaction (31% vs 30%).

Six subjects (7%) were neutralizing antibody (NAb) positive at any visit during the study. The NAb positive tests were not associated with any particular time period or treatment group.

8.4. Analysis of Submission-Specific Safety Issues

No new safety issues were identified.

8.5. Safety Analyses by Demographic Subgroups

Subgroup analysis was not performed due to the limited number of subjects in the recurrent pericarditis studies.

8.6. Specific Safety Studies/Clinical Trials

None.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

There is no additional information on human carcinogenicity or tumor development.

8.7.2. Human Reproduction and Pregnancy

There is no information on the effect of Rilonacept on human reproduction and pregnancy.

8.7.3. Pediatrics and Assessment of Effects on Growth

Seven pediatric patients aged 12 to 17 years received Rilonacept for a mean duration of 15 weeks in the recurrent pericarditis studies. No apparent safety difference was observed in this pediatric population.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There have been no Rilonacept overdose reports.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

There have been no new safety concerns identified through postmarket experience. As of March 2018, approximately 365 patients had been exposed to Rilonacept in the postmarket setting since its approval in 2008. The Clinical Review for the gout program identified no safety concerns from the postmarket experience up until 2011. Between February 2011 and February 2020, 31 SAEs were reported through the annual Periodic Adverse Experience Report. The most common SAEs by preferred terms were Pneumonia (4 incidences) and CAPS (4 incidences). The most common SAEs by system of organ class were infections (19 incidences), followed by surgical and medical procedures (7 incidences). One cancer (breast cancer) was reported along with one non-serious squamous cell carcinoma.

8.8.2. Expectations on Safety in the Postmarket Setting

Adverse events commonly seen in the recurrent pericarditis studies such as injection site reactions, upper respiratory infections, and increased lipid levels are expected in the postmarket setting. With increasing number of patients exposed to Rilonacept, more malignancies could potentially appear.

8.8.3. Additional Safety Issues From Other Disciplines

None.

8.9. Integrated Assessment of Safety

Rilonacept was generally well tolerated. No new safety findings were identified.

- No subjects died during the recurrent pericarditis studies.
- The occurrences of serious adverse events (6%), severe adverse events (2%), and treatment discontinuations (5%) were low. No SAEs clustered around any AE of special interest.
- The most common adverse reactions were injection site reactions (34%) and upper respiratory tract infections (22%); none were serious nor severe adverse events.
- Combined with the gout safety data, an increase in the risk of malignancy cannot be excluded despite the low number of malignant AEs and short duration of Rilonacept exposure in the gout clinical trials. The warning in the product labeling has sufficiently addressed this risk.

- Lipid levels increased with the treatment of Rilonacept. The incidence of hyperlipidemia was low (6%); none were SAEs or severe AEs.
- The majority of subjects were ADA negative throughout the study. The safety profile in ADA-positive subjects was similar to that of ADA-negative subjects.

9. Advisory Committee Meeting and Other External Consultations

There was no Advisory Committee.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The evidence can best be presented in the label by indicating rilonacept for the treatment of recurrent pericarditis. Treatment with rilonacept should continue for 6 months, but clinical judgement should be used on duration of therapy given data showing durability but limited persistence.

- There is no evidence to support initiation of rilonacept monotherapy for acute pericarditis or for a rapid switch to rilonacept from standard of care treatment for recurrent pericarditis. With approximately 50% of the ITT population on steroids, the RHAPSODY trial could not accommodate a rapid switch.
- There is a paucity of evidence demonstrating effectiveness in Black and Latino patients.

10.2. Nonprescription Drug Labeling

None.

11. Risk Evaluation and Mitigation Strategies (REMS)

There is no REMS requirement.

12. Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments.

13. Appendices

13.1. References

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Lombardi, M, 2017, Pericarditis and Recurrent Pericarditis, Journal of the American College of Cardiology: Cardiovascular Imaging, http://dx.doi.org/10.1016/j.jcmg.2016.10.019

Haddy, T. et al., 1999, Benign ethnic neutropenia: What is a normal absolute neutrophil count? Journal of Laboratory and Clinical Medicine, 133 (1): 15-22

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): KPL-914-C001 and KPL-914-C002 (Rhapsody)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 184 total: 46 investigators + 138 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 237		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. List of Investigators in RHAPSODY

Site No.	Investigator Name / Location	Sub-Investigator(s) Name
100[a]	Dr. David Colquhoun, MBBS Core Research Group Pty Ltd. 1/18 Kilroe Street Milton, Queensland, 4064 Australia	Dr. Lynette Williams, MBBS
101[b]	Dr. David Bruce Cross, MBBS HeartCare Partners Clinical Research Unit Wesley Testing, Level 2 The Wesley Hospital 30 Chasely Street Auchenflower, Queensland, 4066 Australia	Dr. Terri Hall, MBBS Dr. Robert Fathi, MBBS, PhD Dr. Anthony Rafter, MBBS Dr. Samual Hayman, MBBS
102[b]	Dr. Pey Wen Lou, MBBCh Genesis Care – Cardiology Research HeartCare Victoria - Doncaster 1008 Doncaster Road Doncaster East, Victoria, 3109 Australia	Dr. Jayashree Chandrasekhar, MBBS Dr. Wai-Ee Thai, MBBS Dr. Rajika Karunadasa, MBBS
103[a]	Dr. Stephen Nicholls, MBBS, PhD Monash Medical Centre 246 Clayton Road Clayton, Victoria, 3168 Australia	Dr. Adam Brown, MBBS, PhD Dr. Kuhendra Balakrishnan, MBBS Dr. Sophie Gettens, MBBS Dr. Siobhan Lockwood, MBBS Dr. It Meng Tsay, MBBS Dr. Nancy Khav, MBBS
104[a]	Dr. Philip Roberts-Thomson, MBBS Royal Hobart Hospital 48 Liverpool Street Hobart, Tasmania, 7000 Australia	Dr. Andrew Black, MBBS Dr. Nathan Dwyer, MBBS, PhD Dr. Harsh Thakkar, MBBS Dr. David Russell, MBBS
105[a]	Dr. Michael Benjamin Stokes, MBBS The Queen Elizabeth Hospital	Dr. John Beltrame, MBBS, PhD Dr. Jessica Marathe, MBBS, PhD
	28 Woodville Road Woodville South, South Australia, 5011 Australia	
106[a]	Dr. Girish Dwivedi, MBBS, DM, PhD Fiona Stanley Hospital 11 Robin Warren Drive Murdoch, Western Australia, 6150 Australia	Dr. Cara Winnall, MBBS

Site No.	Investigator Name / Location	Sub-Investigator(s) Name
200[b]	Dr. Antonio Luca Brucato, MD ASST Fatebenefratelli Sacco – Ospedale Fatebenefratelli e Oftalmico Corso Di Porta Nuova 23 Milan, Lombardy, 20121 Italy	Dr. Andrea Arensi, MD Dr. Simona Bollani, MD Dr. Elisa Calabro, MD Dr. Valeria Giosia, MD Dr. Luca Matteucci, MD Dr. Daniela Montori, MD Dr. Massio Pancrazi, MD Dr. Francesco Cianci, MD Dr. Mariangela Nivuori, MD Dr. Alive Mule, MD Dr. Lucia Trotta, MD
201[b]	Dr. Antonella Insalaco, MD IRCCS Ospedale Pediatrico Bambino Gesù Piazza Sant Onofrio 4 Rome, Lazio, 00165 Italy	Dr. Susanna Livadiotti, MD Dr. Giuseppe Pontrelli, MD Dr. Alessandra Simonetti, MD
202[c]	Dr. Marco Gattorno, MD Instituto G Gaslini Ospedale Pediatrico IRCSS Largo G. Gaslini 5 Genova, Liguria, 16147 Italy	Dr. Roberta Caorsi, MD Dr. Stefano Volpi, MD
203[b]	Dr. Massimo Imazio, MD Azienda Ospedaliera Città della Salute e della Scienza di Torino Corso Bramante, 88/90 Dipartimento Cardiovascolare S.C. Cardiologia Universitaria Ospedale Le Molinette Turin, Piedmont, 10126 Italy	Dr. Alessandro Andreis. MD Dr. Alessandra Volpe, MD
300[b]	Dr. Shaul Atar, MD Galilee Medical Center Cardiology Department 1 Ben Tzvi Boulevard Nahariya, 2210001 Israel	Dr. Or Tsafrir, MD Dr. Gassan Muady, MD
301[b]	Dr. Michael Arad, MD Sheba Medical Center at Tel-Hashomer Heart Institute Derech Sheba 2	Dr. Dor Lotan, MD Dr. Michael Shechter, MD Dr. Yishay Wasserstrum, MD Dr. Micha Feinberg, MD
	Ramat-Gan, 52621 Israel	

Site No.	Investigator Name / Location	Sub-Investigator(s) Name
302[a]	Dr. Nahum Adam Freedberg, MD Ha'Emek Medical Center Cardiology Department 21 Rabin Road Afula, 18101 Israel	Dr. Youri Rabkin, MD Dr. Mohamed Jabaren, MD Dr. Mahamid Muhamad, MD Dr. Yana Shkolnikova, MD Dr. Ehud Rozner, MD Dr. Ofir Koren, MD
303[b]	Dr. Elad Schiff, MD Bnai Zion Medical Center Internal Medicine B 47 Golomb Street Haifa, 31048 Israel	Dr. Leonard Saiegh, MD Dr. Nizar Jiries, MD Dr. Shira Ginsberg, MD
304[b]	Dr. Mady Moriel, MD Shaare Zedek Medical Center Department of Cardiology 12 Shmuel Bait Street Jerusalem, 9103102 Israel	Dr. Marc William Klutstein, MD
305[c]	Dr. Majdi Halabi, MD Ziv Medical Center Department of Cardiology Heart Institute Derech Ha'Rambam Safed, 13100 Israel	Dr. Aehab Khateeb, MD Dr. Saleem Dabbah, MD Dr. Inna Rosenfeld, MD Dr. Saeed Khateeb, MD
306[c]	Dr. David Leibowitz, MD Hadassah Medical Center, Mount Scopus Coronary Care Unit Hadassah Har Hazofirm Jerusalem, 91240 Israel	Dr. Ronny Alcalai, MD
307[c]	Dr. Robert Zukermann, MD Rambam Medical Center Department of Cardiology Haaliya Hashniya Street Haifa, 31096 Israel	Dr. Faheem Shehadeh, MD Dr. Sirouch Petcherski, MD Dr. Nadav Willner, MD
308[a]	Dr. Valentin Witzling, MD Edith Wolfson Medical Center Heart Institute 62 Halohamim Street Holon, 58100 Israel	Dr. Sharabi Itzhak, MD Dr. Yoseph Rozenman, MD
309[a]	Dr. Shmuel Fuchs, MD Shamir Medical Center (Assaf Harofeh Medical Center) Be'er Ya'akov Tzarin, 70300 Israel	Dr. Gil Uri Marcus, MD Dr. Mark Katz, MD Dr. Inna Yofik, MD Dr. Gil Moravsky, MD Dr. Itzhak Vitkon Barkay, MD

Site No.	Investigator Name / Location	Sub-Investigator(s) Name
310[c]	Dr. Alon Eisen, MD Rabin Medical Center Department of Cardiology 39 Jabotinski Street Petach Tikva, 49100 Israel	Dr. Aviv Mager, MD Dr. Maya Wiessman, MD
401[a]	Dr. Bipul Baibhav, MD Rochester General Hospital 1425 Portland Avenue Rochester, NY 14621 USA	Dr. Devesh Rai, MD Tia Albro, ACNP, MSN, RN Megan Littleton, RN
402[b]	Dr. Antonio Abbate, MD Virginia Commonwealth University West Hospital, 5th floor, West Wing Rm. 5025 1200 E. Broad Street Richmond, VA 23298 USA	Dr. Dinesh Kadariya, MD Dr. Salvatore Carbone, PhD, MS Dr. George F. Wohlford IV, PharmD. Dr. Benjamin Q. Van Tassell, PharmD. Virginia Mihalick, MS, ACSM EP-C Hayley E. Billingsley, RD
403[c]	Dr. Asif Akhtar, MD BI Research Center Biopharma Informatic, LLC. 19255 Park Row Drive, Suite 205 Houston, TX 77084 USA	Dr. Syed Farhat Abbass Zaidi, MD Faraz Arif, CRC Deepthi Annakula, CRC
404[b]	Dr. Paul Grena, DO Cardiology Consultants of Philadelphia 301 Oxford Valley Road Suite 901 Yardley, PA 19067 USA	Dr. Steven Paul Goldberg, MD Dr. Christopher M. Schulze, DO Dr. Kevin P. Furey, DO Dr. Samuel W. Stever, DO Dr. Clifford S. Strauss, DO
405[a]	Dr. David Harris, MD University of Cincinnati 231 Albert Sabin Way Cincinnati, OH 45267 USA	Dr. Mohamed Effat, MD Dr. Imran Arif, MD Dr. Dylan Steen, MD Dr. Alexandru Costea, MD
406[b]	Dr. S. Allen Luis, MBBS Mayo Clinic - PPDS 200 First Street SW Rochester, MN 55905 USA	Dr. Jae K. Oh, MD Dr. Benjamin W. Eidem, MD
407[b]	Dr. Paul G. Sutej, MD 908 Johnson Ferry Road NE Suite 220 Atlanta, GA 30342 USA	Dr. Paula A. Tanasa, MD Dr. Gary E. Myerson, MD

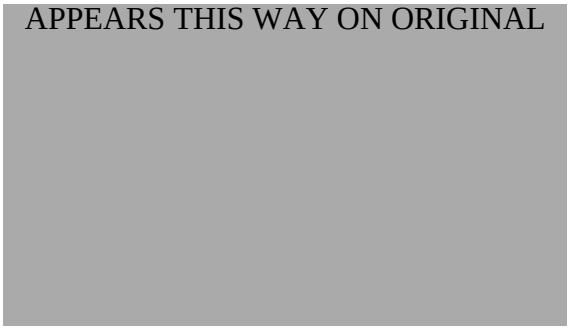
Site No.	Investigator Name / Location	Sub-Investigator(s) Name
408[b]	Dr. Samuel G. Wittekind, MD Cincinnati Children's Hospital Medical Center Heart Institute 3333 Burnet Avenue, MLC 2003 Cincinnati, OH 45229 USA	Dr. Thomas D. Ryan, MD, PhD Dr. Sean M Lang, MD Alyssa Rohde Joshua Freytag
412[a]	Dr. Sean P. Collins, MD Vanderbilt University Medical Center Department of Emergency Medicine 1211 Medical Center Drive Nashville, TN 37232 USA	Dr. Daniel Munoz, MD, MPA
413[b]	Dr. David Lin, MD Minneapolis Heart Institute Foundation 920 East 28th Street Suite 300 Minneapolis, MN 55407 USA	Dr. Matthew Chu, MD Dr. Scott Sharkey, MD Dr. Said Alsidawi, MD Dr. Joao Cavalcante, MD Dr. Desmond Jay, MD
414[b]	Dr. Martin M. LeWinter, MD University of Vermont Medical Center 111 Colchester Avenue Department of Cardiology Burlington, VT 05401 USA	Dr. Peter C. VanBuren, MD Dr. Johannes Steiner, MD
415[c]	Dr. Amin Karim, MD 10021 Main Street Suite B1 Houston, TX 77025 USA	Rashidat Titilope Boyeejo, FNP Cecilia Valerio, CRC
416[b]	Dr. Paul C. Cremer, MD Cleveland Clinic Heart & Vascular Institute Department of Cardiovascular Medicine 9500 Euclid Avenue Cleveland, OH 44195 USA	Dr. Allan L. Klein, MD
418[a]	Dr. Faisal Latif, MD Oklahoma City VA Medical Center 921 NE. 13th Street Oklahoma City, OK 73104 USA	Dr. Phuong Ngo, MD Dr. Udho Thadani, MD
419[b]	Dr. Kirk U. Knowlton, MD Intermountain Healthcare 5121 S. Cottonwood Street Murray, UT 84107 USA	Dr. Jeffrey L. Anderson, MD Viet T. Le, MPAS, PA-C

Site No.	Investigator Name / Location	Sub-Investigator(s) Name
420[b]	Dr. Eliyazar Gaddam, MD The Loretto Hospital 645 South Central Avenue Chicago, IL 60644 USA	Dr. Lois M. Clarke, MD Dr. Nikhila Juvadi, MD
422[a]	Dr. Apostolos Kontzias, MD Stony Brook University 101 Nicolls Road, HSC T-16 Room 040 Stony Brook, NY 11794 USA	Dr. Ayse Bag Ozbek, MD
423[b]	Dr. Robert J. Siegel, MD Cedars-Sinai Medical Center Smidt Heart Institute 127 S. San Vicente Boulevard AHSP, Suite A3417 Los Angeles, CA 90048 USA	Dr. Nir Flint, MD Dr. Balaji K. Tamarappoo, MD, PhD Dr. Yehezkel Shmueli, MD
427[b]	Dr. John Louis Petersen, II, MD Swedish Medical Center 500 17th Avenue Cherry Hill Professional Building, Suite 303 Seattle, WA 98122 USA	Dr. Christopher J McGann, MD Debra Jean Laurent, MN, ARNP, ACNP-BC Dr. Oana Madalina Petrescu, MD Jennifer A. Nagel, BS Alexa Stead Charlene R Boisjolie, MA, RN
431[c]	Dr. Robert Kornberg, MD Icahn School of Medicine at Mount Sinai 425 West 59th Street, Suite 9C New York, NY 10019 USA	Dr. Jeffrey Bander, MD Dr. Bette Kim, MD
432[a]	Dr. Eli V. Gelfand, MD Beth Israel Deaconess Medical Center Cardiovascular Division W/PA-214 185 Pilgrim Road Boston, MA 02215 USA	Dr. Jordan B. Strom, MD, MSc Dr. Susan Mcilvaine, MD M. Jenifer Kaufman, RN, MS, NP Patricia Tyler, MSN RN, FNP-C
435[a]	Dr. Michael A. Portman, MD Seattle Children's Hospital 190 Ninth Avenue Seattle, WA 98101 USA	Dr. Sathish Mallenahalli Chikkabyrappa, MD
436[c]	Dr. Wael Abo-Auda, MD Cardiovoyage 5325 W. University Drive McKinney, TX 75071 USA	Dr. Vinod Prasad, MD Dr. Luis Torres, MD

Site No.	Investigator Name / Location	Sub-Investigator(s) Name
439[c]	Dr. Karan Bhalla, MD Orion Medical Center 5413 Crenshaw Road, Suite 400 Pasadena, TX 77505 USA	Jane Varpon, NP

[a]Activated but did not screen any subjects
[b]Enrolled subjects
[c]Screened subjects but did not enroll

13.4. Adjudication Listing



Subject Number[b]	NRS Pain Value	CRP Value (mg/dL)	Pericardial Rub	ECG Changes	Effusion Local Read	WBC	Fever	CEC Adjudication Decision	Recurrence Criterion Number Met[c]
(b) (6)	5	0.6	Negative	Negative	New (reported physiologic by central read)	N/A	Negative	Positive (Day 46: (b) (6)	1
(b) (6)	6	2.7	Positive	Negative	Worsened (reported physiologic by central read)	N/A	Negative		
(b) (6)	7	12.0	Negative	Positive	New	N/A	Negative	Positive	1
(b) (6)	6	1.3	Unknown	Negative	Negative	N/A	Negative	Positive	1
(b) (6)	5	1.8	Negative	Positive	Negative	N/A	Negative	Positive	1
(b) (6)	5	0.7	Positive	Negative	Negative	N/A	Negative	Positive	2
(b) (6)	7	7.0	Unknown	Negative	New	N/A	Negative	Positive	1

Subject Number[b]	NRS Pain Value	CRP Value (mg/dL)	Pericardial Rub	ECG Changes	Effusion Local Read	WBC	Fever	CEC Adjudication Decision	Recurrence Criterion Number Met[c]
(b) (6)	8	3.0	Negative	Negative	New	N/A	Negative	Positive	1
	10	4.8	Negative	Negative	Negative	N/A	Negative	Positive	1
	4	2.6	Negative	Negative	Negative	N/A	Negative	Positive	1
	4	1.2	Negative	Positive	New	N/A	Negative	Positive	1
	8	1.7	Negative	Negative	Negative	N/A	Unknown	Positive	1
	8	2.0	Negative	Negative	Negative	N/A	Negative	Positive	1
	4	1.9	Negative	Positive	Negative	N/A	Unknown	Positive	1
	4	0.2	Negative	Negative	Negative	N/A	Negative	Negative	N/A
	4	1.2	Negative	Negative	New	N/A	Negative	Positive	1
	8	9.0	Negative	Negative	Worsened	N/A	Negative	Positive	1
	5	4.0	Negative	Negative	New	N/A	Negative	Positive	1
	6	5.0	Negative	Positive	New	N/A	Negative	Positive	1
	5	2.4	Negative	Negative	Negative	N/A	Negative	Positive	1
	4	1.0	Negative	Negative	Negative	N/A	Negative	Positive	1
	8	29.0	Positive	Positive	New	N/A	Negative	Positive	1
	8	3.6	Negative	Negative	Negative	N/A	Negative	Positive	1
	9	2.5	Negative	Negative	New	N/A	Negative	Positive	1
	7	1.8	Negative	Negative	Negative	N/A	Negative	Positive	1
	4	3.0	Negative	Negative	Negative	N/A	Negative	Positive	1
	4	0.6	Negative	Negative	Negative	N/A	Negative	Positive (Day 31:	1

Subject Number[b]	NRS Pain Value	CRP Value (mg/dL)	Pericardial Rub	ECG Changes	Effusion Local Read	WBC	Fever	CEC Adjudication Decision	Recurrence Criterion Number Met[c]
(b) (6)	4	1.0	Negative	Negative	Negative	N/A	Negative	(b) (6)	

[a]Source: Listing 16.2.6.1.2

13.5. RHAPSODY Schedule of Events

APPEARS THIS WAY ON ORIGINAL

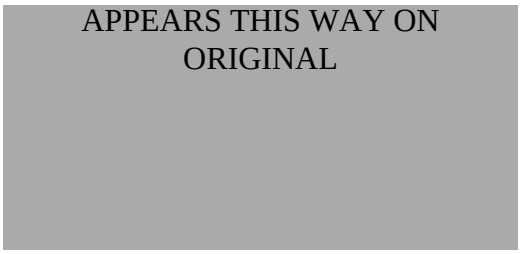
Trial Period		RUN-IN (12 weeks)[b]								
	Screening[a]	Enrollment								Randomization[c]
Visit Name	Screening Visit	RI Baseline	RI Day 2	RI Day 4	RI Week 1	RI Week 2	RI Week 4	RI Week 6	RI Week 10	RI Week 12/ RW Baseline
Visit Window[d] (days)	(-28)	NA	NA	+/- 1	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 3
Visit Type	Clinic	Clinic	Clinic	TC/RN	TC/RN	TC/RN	TC/RN	Clinic	TC	Clinic
Informed Consent Form	X									
Inclusion and Exclusion criteria	X	X								
Demographics	X									
Medical/Surgical History	X									
Pericarditits Diagnosis & History	X	X								
Concomitant medications	X	X		X	X	X	X	X	X	X
Pericarditis Concomitant medications	X	X		X	X	X	X	X	X	X
Pericarditis Concomitant medication tapering					X	X	X	X	X	
Full Physical Examination[e]	X									
Abbreviated Physical Examination[f]		X								X
Body weight and height		X								X
12-Lead ECG		X								X
Echo[g]		X								X
MRI (substudy only)		X								
Pericardial pain (11-point NRS)	X[h]	DAILY[i]								X[i]
EQ-5D		X								X
SF-36		X								X
ISI		X								X
PGI-PS		X						X		X
PGA-PA		X						X		X
Hematology, Chemistry Labs (Central)		X						X		X

Trial Period		RUN-IN (12 weeks)[b]								
	Screening[a]	Enrollment								Randomization[c]
Visit Name	Screening Visit	RI Baseline	RI Day 2	RI Day 4	RI Week 1	RI Week 2	RI Week 4	RI Week 6	RI Week 10	RI Week 12/ RW Baseline
Visit Window[d] (days)	(-28)	NA	NA	+/- 1	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 3
Visit Type	Clinic	Clinic	Clinic	TC/RN	TC/RN	TC/RN	TC/RN	Clinic	TC	Clinic
Lipid Panel (Central)[j]		X								X
CRP (Local)	X[h]									X
CRP (Central)	(X)	X		X	X	X	X	X		X
Hematology, Chemistry, IGRA[k], hepatitis serology, HIV (Local)	X									
Chest X-Ray	X									
Urine Pregnancy (Local or Central)[l]	X	X								
Urinalysis (Central)		X								
PK (Central)[m]			X[n]		X	X	X			X
ADA (Central)[m]		X				X		X		X
Biomarkers (Central)		X			X		X			
Pharmacogenomics Informed Consent[o]		X								
Pharmacogenomics Sampling (Central)[o]							X			
IWRS Subject Status Update	X	X								X
IWRS Weight Input (pediatric only)		X								X
IWRS Drug Dispensing		X		X				X		X
In Clinic Study Drug Administration[p]		X[q]						X		X
Outpatient Study Drug Administration[p]					WEEKLY					
Study Drug Compliance Review		X			X	X	X	X	X	X
Clinical Response Evaluation										X[r]
Adverse Event Reporting[s]	X	X		X	X	X	X	X	X	X

Note: The Schedule of Assessments (eg. footnote numbering) was reformatted based on protocol Amendment 2.

ADA = anti-drug antibodies; CRP = C-reactive protein; ECG = electrocardiogram; ECHO = echocardiogram; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; IWRS = interactive web response system; LTE = long-term extension; PGA-PA = Physician Global Assessment-Pericarditis Activity; PGI-PS = Patient Global Impression-Pericarditis Symptoms; PK = pharmacokinetics; RI = run-in; RN = registered nurse, RW = randomized withdrawal; SC = subcutaneous; TC = telephone contact.

a The screening and enrollment visit could be combined.
b All procedures were to be completed prior to study drug administration.
c The randomization visit served as both the RI Week 12 visit and the RW baseline visit.
d Scheduling of visits within visit windows required cautious planning to ensure there is no interruption to subject evaluation and study drug treatment.
e Full physical examination included at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. The decision to perform examination of genitourinary system should have been guided by clinical judgment.
f Abbreviated physical examination included at minimum evaluation of vital signs, lung and heart sounds, including evaluation for pericardial rub.
g ECHO was required to be obtained according to the central core lab parameters and then read locally and submitted to the central core lab for separate review and analysis.
h Both a documented CRP ≥ 1.0 mg/dL AND a pericarditis pain level of ≥ 4 was required 7 days prior to and including the run-in baseline visit. These were not required to occur on the same day.
i Subjects missing ≥ 4 daily pain measurements during the 7 days prior to and including the RW baseline visit were unable to proceed to randomization due to lack of data required for treatment response evaluation.
j Lipid panels were non-fasting and were to be drawn at a minimum of every 6 months during the randomization withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
k IGRA and hepatitis serology could be done centrally if necessary.
l For women of child bearing potential, urine pregnancy testing could be repeated as needed throughout the course of the study and serum pregnancy could be drawn as needed; urine pregnancy was required to be performed at enrollment and 6 weeks after the last dose of study drug.
m PK and ADA samples were collected prior to study drug administration. PK at enrollment/baseline was taken from ADA.
n Applicable to 24-hour post dose PK substudy participants only.
o Pharmacogenomics informed consent and subsequent sampling could be performed at any time in the study however, it was preferable to have this completed at the beginning of the study.
p Study drug administration was once weekly with a minimum of 5 days required between doses.
q The first dose of study drug was a loading dose. Adult subjects received 2 SC doses 160 mg (total 320 mg); pediatric subjects (subjects ≥12 and <18 years of age) received 2 SC doses of 2 x 2.2 mg/kg.
r Randomization and subsequent study drug dispensing were to occur after confirmation of clinical response.
s Adverse event reporting began following the subject providing informed consent.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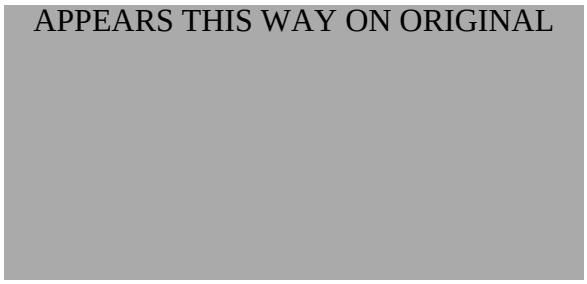
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/s/

FORTUNATO F SENATORE
03/16/2021 07:57:39 AM

YANYAN JI
03/16/2021 09:16:38 AM

DALI ZHOU
03/16/2021 09:43:35 AM

JIALU ZHANG
03/16/2021 09:53:40 AM

CHRISTINE E GARNETT
03/16/2021 10:20:47 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125249Orig1s049

PRODUCT QUALITY REVIEW(S)

Product Quality (Biotechnology)
Filing Assessment for BLA/NDA supplements

Application Type (BLA or NDA): BLA
Submission Number and Type: 125249, SN 0145, S-49, Efficacy supplement
Stamp Date: 09/21/2020
Filing Date: 11/20/2020
Goal date: 03/21/2021
Established/Proper Name: Arcalyst (rilonacept)
Applicant: Regeneron
Indication: (b) (4)

Initial overview of the BLA/NDA Supplement for filing:
This is an efficacy supplement. The ADA assay used was changed from what was previously used and reviewed in the BLA.
Microbiology review and Facility review were assigned to DBM (Refer to Panorama). No consult is needed.
During filing assessment, a potential filing issue was identified in the form 356h that Kiniksa (b) (4) was listed as an analytical testing site of DP on page 9. An IR was sent to the Sponsor on 10/6/2020 to address this issue. On 10/8/2020, the Sponsor responded that Kiniksa is not a site of analytical testing of DP and was incorrectly included in the list of establishments, with submission of the updated 356h form. Thus, this issue was resolved.

i) Brief description of the change(s) proposed:
In this submission, there was no Quality section, and product and dosage were the same as those in the original BLA.
For immunogenicity assay, ADA assay and Nab assay information with their validation data were submitted.

ii) The following was submitted in support of the change (check all that apply):

☒	A detailed description of the proposed change.
☒	Identification of the product(s) involved.
☐	A description of the manufacturing site(s) or area(s) affected.
☐	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.
☒	The data derived from any studies conducted.
☒	Relevant validation protocols and data.
☐	A reference list of relevant standard operating procedures (SOPs)
☐	A reference to DMF(s)
☒	A statement for GMP inspection of the facility

Is the Immunogenicity assay validation section of the supplement fileable?
☒ Yes; ☐ No

If fillable, identify and list any potential review issues, not including the filing comments to be forwarded to the Applicant for the 74-day letter.
None

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SANG BONG LEE
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CHANA FUCHS
11/13/2020 06:50:58 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125249Orig1s049

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

sBLA	125249 SDN 227
Submission Dates	9/21/2020
Brand Name	ARCALYST®
Generic Name	Rilonacept
OCP Reviewer	Kunal Jhunjhunwala, MS, Ph.D. Jiajun Liu, PharmD, MSc
Team Leader	Manoj Khurana, PhD (Clinical Pharmacology Team Lead) Justin Earp, PhD (Pharmacometrics Team Lead)
OCP Division	Division of Cardiometabolic & Endocrine Pharmacology (DCEP)
OND Division	Division of Cardiology & Nephrology (DCN)
Sponsor	Kiniksa Pharmaceuticals, GmbH (Kiniksa)
Indication	(b) (4)

Recommendations
The Office of Clinical Pharmacology/ Division of Cardiometabolic & Endocrine Pharmacology (OCP/DCEP) has reviewed sBLA 125249's Clinical Pharmacology data submitted on 21st September 2020. OCP/DCEP recommends that the submitted data are acceptable to fulfill the supplemental BLA for Recurrent Pericarditis (RP) for BLA 125249.

Labeling Recommendations (Preliminary):
The sponsor proposed following addition to Section 12.3 of the label:

(b) (4)

This proposed change in the label is acceptable.

Background
The sponsor is seeking approval for previously approved Rilonacept (KPL-914) (b) (4) (b) (4).

The application included clinical pharmacology data from the following 2 clinical studies:
KPL-914 C001 – A phase 2 Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis
KPL-914 C002 – A phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study with Open Label Extension, to Assess the Efficacy and Safety of Rilonacept Treatment in Subjects with Recurrent Pericarditis

The sponsor (Kiniksa) has previously received breakthrough therapy designation (BTD) for rilonacept for the treatment of RP and has been granted orphan drug designation (ODD) for rilonacept for "the treatment of pericarditis".

Review of the Current Submission

1) What are the objectives of clinical pharmacology evaluations under the current sBLA submission?

The clinical pharmacology objectives were:

1. To characterize the serum concentration-time profiles and PK properties of rilonacept after multiple SC administrations in subjects with RP.
2. To compare the serum concentration-time profiles and PK observed in the RP subject population with the PK observed in normal healthy volunteers and the CAPS, RA, and gout subject populations from previous studies.
3. To investigate the potential effect of population demographics on PK using population PK and covariate analyses.
4. To assess the potential for development of ADA to rilonacept and potential impact of ADA on the PK of total rilonacept in RP subjects

This review focused more on the adequacy of data for objectives 1, 3, and 4 given the limitations of cross-trial comparisons and the acknowledgement by the applicant over the use of different bioanalytical methods between RP and the previous studies in subjects with CAPS, RA, and gout.

2) What are the general pharmacokinetics characteristics of Rilonacept?

ARCALYST (rilonacept) is an interleukin-1 blocker approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). Based on approved label, the average trough levels of rilonacept were approximately 24 mcg/mL at steady-state following weekly SC of 160 mg for up to 48 weeks in patients with CAPS. The steady-state appeared to be reached by 6 weeks.

3) What are the study designs of the clinical studies supporting this submission?

KPL-914 C001 – This was a phase 2, open-label, single-active-arm 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 consisted of 5 distinct parts enrolling different subsets of RP, and all subjects were treated with once-weekly (QW) SC-administered injections of rilonacept. Subjects received a 320 mg subcutaneous (SC) loading dose, followed by 160 mg SC QW for 5 weeks (total of 6 rilonacept SC doses). After the first 6 weeks of treatment, responding subjects, as judged by investigators, could receive an additional 18 weeks of rilonacept treatment. Rilonacept PK, ADA and biomarker samples was withdrawn from all subjects and archived for future testing in the study.

KPL-914 C002 – This was a phase 3 double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of rilonacept treatment in adult and pediatric subjects with RP. The study was comprised of 3 dosing periods, an open-label run-in (RI) period, a double-blinded randomized withdrawal (RW) period, and an open-label, long-term extension (LTE) period, adult subjects in the 12-week RI period received a 320 mg SC loading dose of rilonacept, followed by 160 mg SC QW, for a total of 12 SC doses.

Pediatric subjects enrolled in the RI period (≥12 and <18 years old) received an initial 4.4 mg/kg SC loading dose of rilonacept (up to a maximum of 320 mg), followed by 2.2 mg/kg (up to a maximum of 160 mg) SC QW, for a total of 12 doses. Subjects that met certain criteria were randomized in the RW

period in a 1:1 double-blinded manner to receive doses of placebo or rilonacept (160 mg for adult subjects, or 2.2 mg/kg for pediatric subjects) SC QW, from 0 to 51 weeks (event-driven duration).

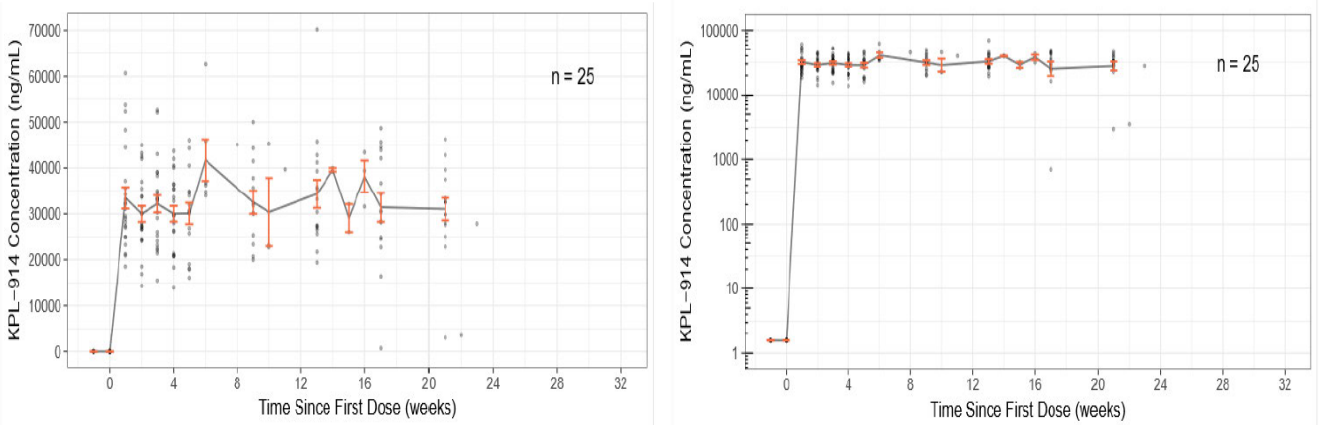
In the LTE period, certain subjects are allowed to receive rilonacept (160 mg for adults, or 2.2 mg/kg for pediatric subjects) SC QW, based on their clinical status and at the discretion of the Investigator up to an additional 24 weeks. The LTE is ongoing at the time of this submission. Pharmacokinetics and ADA information were obtained from all subjects.

4) What are the pharmacokinetic characteristics of rilonacept in RP patients from studies KPL-914 C001 & KPL-914 C002?

Study KPL-914 C001:

The mean ± standard error of the mean (SEM) rilonacept concentration-time profile and individual rilonacept serum concentration values are shown in Figure 1 below. The data corresponds to a 320 mg subcutaneous (SC) loading dose, followed by 160 mg SC QW for 5 weeks (total of 6 rilonacept SC doses) from 25 subjects in the study. Blood samples were collected at prior to the first dose and prior to each subsequent dose during the base treatment period to measure rilonacept trough concentrations (C_{trough}).

Figure 1. Linear (left) and linear-log mean +/- SEM (right) Rilonacept serum concentration-time profiles – KPL-914-001 Study



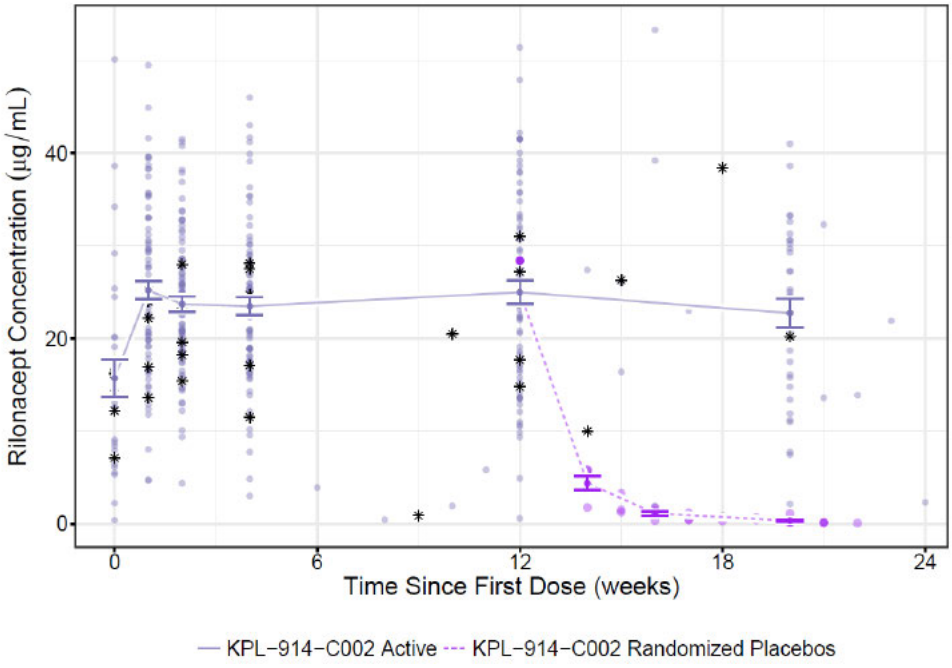
Source: Sponsor's analysis

The mean concentration time profile demonstrated moderate to high variability (30.1 – 69.2 %CV) between subjects across the duration of the study. Following the first dose (320 mg loading dose), no additional accumulation of rilonacept appeared to be observed, with the median concentration of ~ 30,000 ng/mL over the first 6 weeks. Steady state concentration was followed from week 6 to week 21, with the following median concentrations: 34,250 ng/mL, 33,150 ng/mL, and 31,000 ng/mL for weeks 6 – 9, 13 – 15, and 21, respectively.

Study KPL-914 C002:

The mean (± SD) rilonacept trough concentration-time profiles and observed individual subject values over the 12-week RI period, 4 week RW period and 8 week LTE periods are shown in Figure 2 below. An SC loading dose of 320 mg and 12 × QW SC injections of 160 mg of rilonacept resulted in comparable C_{trough} concentrations from week 2 to week 12 of the RI Period.

Figure 2: Mean (± SEM) and individual adult and pediatric subject rilonacept serum trough concentration-time profiles in the run-in, randomized withdrawal and long-term periods of the KPL914-002 Study



Source: Sponsor's analysis

Steady state appeared to reach between week 3 and week 4 of the RI Period. Significant reductions in rilonacept serum concentrations were observed at 2 weeks post end of the RI Period in subjects that were randomized in the RW Period to receive QW SC injections of placebo. Individual rilonacept serum concentrations of pediatric subjects (limited sample N=7) with RP were within the range of the adult subjects

5) How did the ADAs affect the Rilonacept serum exposure?

Study KPL-914 C001: In total, 14 out of 25 subjects (56%) were classified as being ADA positive. Subjects were termed ADA positive if at least one ADA positive sample post the first study drug administration and at titer higher than observed prior to dosing. For subjects who had an ADA positive status a lower mean concentration (4.7% decrease) was observed during the treatment period (Day 0 – Week 6). This weak ADA effect was more apparent in the extension period (Week 6 – 24), with a 1.9% decrease in mean rilonacept serum concentration observed in ADA positive subjects.

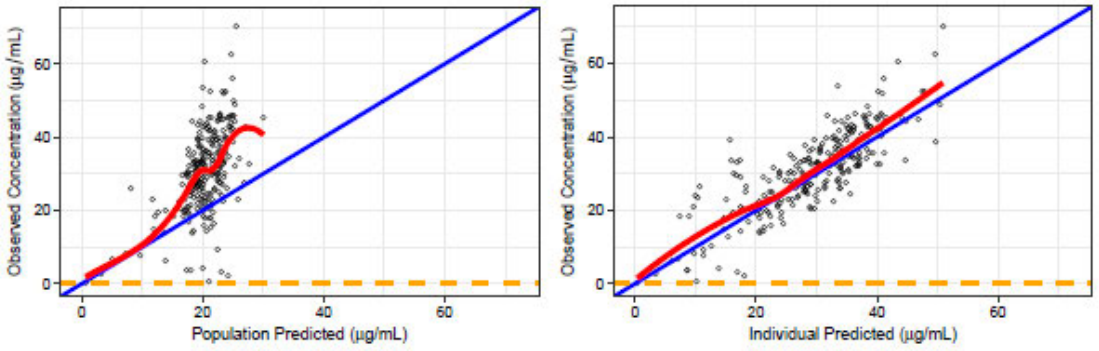
Study KPL-914 C002: In total, 26 of 86 subjects (30.2%) were classified as being ADA positive. An ADA-positive subject was defined as having at least 1 confirmed ADA-positive sample over the evaluation period. In pediatric subjects, low titer positive ADA responses were detected in 2 subjects after the RI Period. Mean rilonacept serum concentrations at week 12 of the RI period were slightly lower in ADA-positive (20.6 µg/L) compared to ADA-negative subjects (27.1 µg/mL) but were within the range of the ADA negative individual subject values. The overall C_{max} and $AUC_{0-\tau}$ values at week 12 of the RI Period were similar for both ADA-positive and ADA-negative subjects indicating no impact of ADA on PK.

6) What were the key findings from the population PK analysis regarding the PK characteristics and sources of variability in PK for rilonacept?

Summary of Population PK Analyses (See Appendix for additional Details):
Population pharmacokinetics of rilonacept were best described by a one-compartmental model with first-order absorption rate constant (subcutaneous route of administration) and first-order elimination. Briefly, the applicant fitted a previously finalized model to the RP data, and underpredictions were observed in the population observed vs. predicted goodness-of-fit plots for C001 and C002 study data (Figure 3).

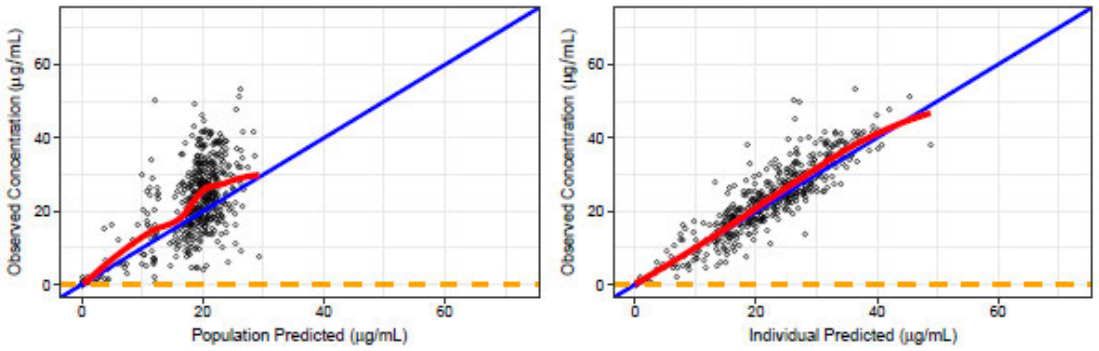
Figure 3. Goodness of Fit Plots Using the Prior PK Models

Figure 11: Goodness of Fit Plots using the Prior PK Model (KPL-914-C001)



The blue lines represent the line of unity, the red lines show the trend in the data (Loess smooth), and the orange dashed lines represent the lower limit of quantification (0.078 µg/mL).

Figure 12: Goodness of Fit Plots using the Prior PK Model (KPL-914-C002)



The blue lines represent the line of unity, the red lines show the trend in the data (Loess smooth), and the orange dashed lines represent the lower limit of quantification (0.078 µg/mL)

Source: Graphical Analysis, Population Pharmacokinetic Analysis, and Non-Compartmental Analysis for Rilonacept (KPL-914) in Subjects with Recurrent Pericarditis, Figures 11, 12; page 54

As such, the applicant developed a base model and evaluated covariates via the covariates modeling step and subsequently re-estimated all PK parameters with the one-compartment model. The applicant conducted analyses in the Model Answers Standard Operating Environment version 20160530, using NONMEM version VII level 3.0 (ICON, Hanover, MD), compiled using the Intel Fortran Composer XE

2013 SP1.4.211 for Linux, and PsN version 4.6.0. Data management, simulations, computation of summary statistics, and graphical analyses were performed using R version 3.2.5 and higher.
The final population PK model fits were acceptable (see Figure 4 and 5 below and Section 1.4 of this review for additional details) for descriptive labeling of rilonacept PK.

Figure 4. Goodness of Fit Plots for the Final PK Model (KPL-914-C001)

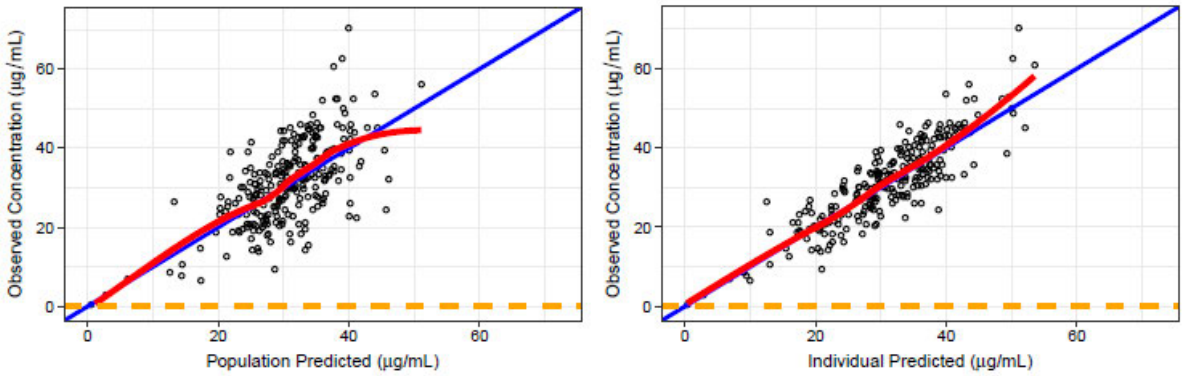


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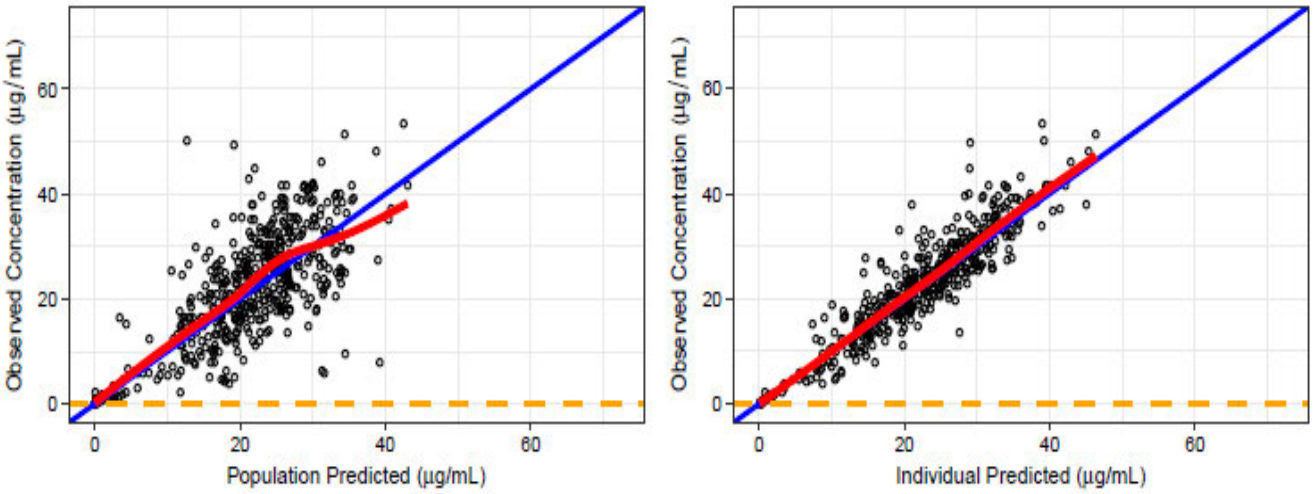
Figure 5. Goodness of Fit Plots for the Final PK Model (KPL-914-C002)



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The summary of population PK analysis derived estimates for PK parameters and covariate effects from the final model is presented in Table 1 below.

Table 1. Parameter Estimates of the Final PK Model

Parameter Name	Estimated Value	%RSE	95% CI
Apparent Clearance (CL/F, L/day)	0.839	2.8	0.790, 0.881
Covariate of Weight on CL/F	0.883	10.0	0.702, 1.064
Apparent Central Volume of Distribution (V/F, L)	8.24	4.2	7.52, 8.85
Covariate of Weight on V/F	0.837	17.2	0.560, 1.130
Rate of Absorption (K_a, day^{-1})	0.478	9.2	0.399, 0.570
Relative Bioavailability for Study KPL-914-C002 (F)	1 FIX	–	
Fractional Increase in F for Study KPL-914-C001	0.411	20.3	0.252, 0.583
Between Subject Variability for CL/F (%)	25.4	15.7	21.8, 29.5
Between Subject Variability for V/F (%)	37.4	22.4	29.5, 45.9
Between Subject Variability for K_a (%)	49.7	31.0	34.3, 64.6
Correlation between CL/F-V/F (CV%)	0.68	20.4	0.656, 0.691
Residual Unexplained Variability (Log μg/mL)‡	0.0021	6.4	0.0020, 0.0023

CL/F was modeled as follows: $CL/F\ (L/day) = 0.839 \cdot (Weight\ (kg)/80)^{0.883}$
V/F was modeled as follows: $V/F\ (L) = 8.24 \cdot (Weight\ (kg)/80)^{0.837}$
%RSE and 95%CI were obtained from SIR using the covariance matrix from NONMEM as an initial proposal distribution.
‡ Additive RUV model in log scale.
Note: CV = coefficient of variation, RSE = relative standard error, CI = confidence interval.

Source: Graphical Analysis, Population Pharmacokinetic Analysis, and Non-Compartmental Analysis for Rilonacept (KPL-914) in Subjects with Recurrent Pericarditis, Table 8, Page 56

The covariate effects of age, sex, race, and CRP were found to have no impact on the PK of rilonacept. Although a minor correlation between ADA titer and rilonacept concentration was observed, ADA titer was not statistically significant (to be included in the final model). Body weight was the only significant covariate included in the model on CL/F and V/F and was described by a non-linear power function. Overall, the effect of weight on rilonacept exposure is expected to have <20% change in C_{max} and $AUC_{0\text{-}tau}$ at steady state. The final population PK model supported derivations of mean trough concentration with CV% following a loading dose, steady-state mean trough concentration (CV%) following maintenance dosages, and elimination half-life in labeling 12.3 Pharmacokinetics.

RP was observed in trial C002 (n=25, 29%) and a majority of recurrence events occurred in subjects after randomization to placebo (23/25, 92%).

7) Were the bioanalytical methods utilized in both clinical studies appropriate?

The Table 1 below summarizes the bioanalytical method validation parameters utilized to determine serum Rilonacept concentrations in Clinical studies KPL-914 C001 and KPL-914 C002

Parameter	**Results**
Capture reagent	Mouse anti-human IL-1 Trap monoclonal antibody (REGN514)
Detection reagent	Biotinylated mouse anti-human IL-1 Trap monoclonal antibody (Biotin-REGN739)
Assay Range CS concentration (LLOQ – ULOQ)	5 – 0.078 ug/ mL
Accuracy and Precision (%CV)	102 – 106% (2-6%)
Sensitivity and range	102 – 106% (2-6%)
Inter-assay linearity (%CV)	99 – 101% (0-3%)
Dilution Recovery	92 – 103% (0-5%)
Short-term analyte stability	91 – 104%

Subjects were enrolled in the study KPL-914-001 starting 24th January 2018 to 17th May 2019. To ensure sample stability during longer term storage, additional long-term analyte stability study is ongoing. However, the consistency in the results from analysis of quality control (HQC, MQC and LQC) sample data during the study period from 06/2018 through 06/2019 provides assurance of the assay performance over the study duration. Similarly, 100% samples passed the incurred sample reanalysis (ISR) conducted during the study period and end of study. Therefore, the bioanalytical methods used to measure serum rilonacept concentration from human PK studies are adequate and acceptable to support the PK data generated from the two clinical studies.

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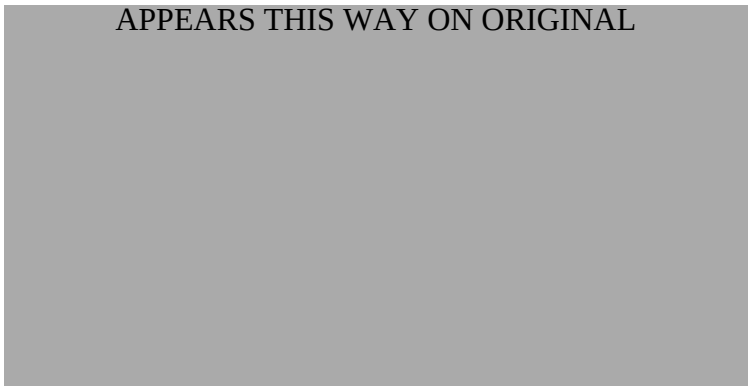

APPENDIX

PHARMACOMETRIC REVIEW

1.1 Summary of Population PK Model

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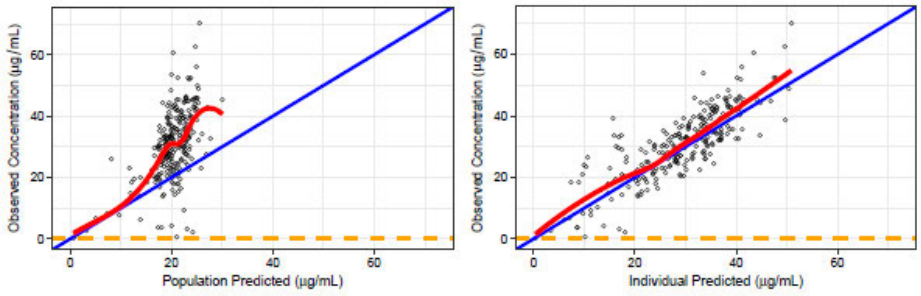

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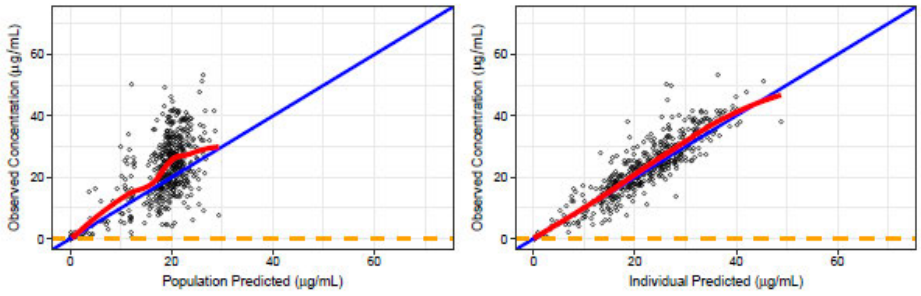
Figure 12: Goodness of Fit Plots using the Prior PK Model (KPL-914-C002)



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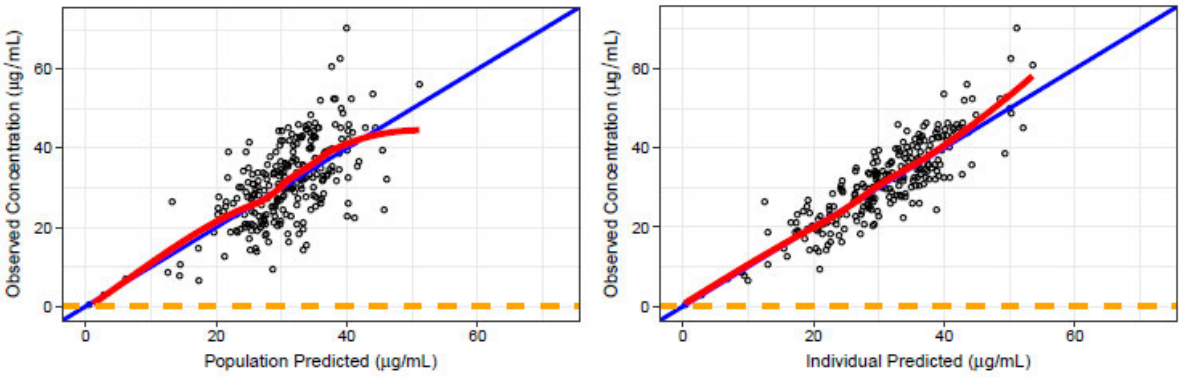

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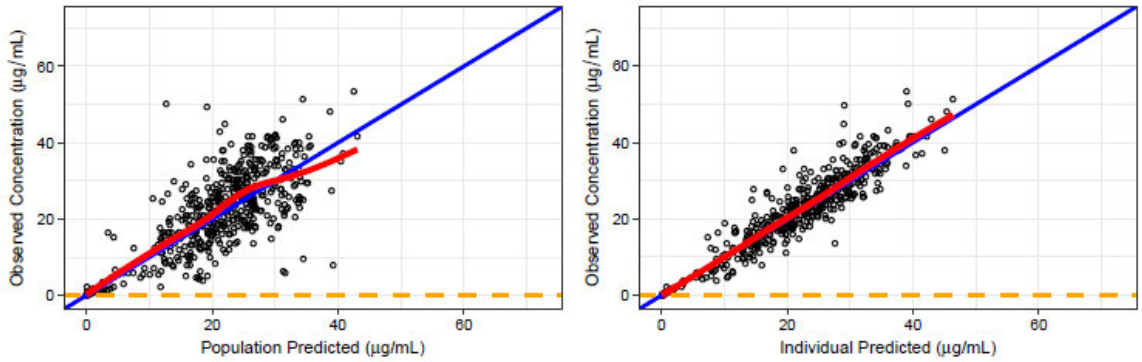

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‡ Additive RUV model in log scale.
Note: CV = coefficient of variation, RSE = relative standard error, CI = confidence interval.

Source: Graphical Analysis, Population Pharmacokinetic Analysis, and Non-Compartmental Analysis for Rilonacept (KPL-914) in Subjects with Recurrent Pericarditis, Table 8, Page 56

The covariate effects of age, sex, race, and CRP were found to have no impact on the PK of rilonacept. Although a minor correlation between ADA titer and rilonacept concentration was observed, ADA titer was not statistically significant (to be included in the final model). Body weight was the only significant covariate included in the model on CL/F and V/F and was described by a non-linear power function. Overall, the effect of weight on rilonacept exposure is expected to have <20% change in Cmax and AUC0-tau at steady state. The final population PK model supported derivations of mean trough concentration with CV% following a loading dose, steady-state mean trough concentration (CV%) following maintenance dosages, and elimination half-life in labeling 12.3 Pharmacokinetics.

RP was observed in trial C002 (n=25, 29%) and a majority of recurrence events occurred in subjects after randomization to placebo (23/25, 92%).

1.2 Objectives

The applicant's objectives were:

- Perform graphical analysis of serum rilonacept concentration-time profiles;
- Develop population PK model and quantification of random IIV and residual variability;
- Capture covariate effects that describe variability in PK data;
- NCA analysis for RP patient in C002 study (to derive exposure metrics)

1.3 Patient Demographics and Study Data

In this application, PK data from two studies (phase 2 KPL-914-C001 and phase 3 KPL-914-C002) were utilized. Of note, the phase 2 study was an open-label, single-arm study that included relatively sparse PK data; the phase 3 study was double-blind, placebo-controlled and randomized with a relatively more robust PK sampling design.

Overall, there were a total of 7 pediatric subjects from C002 between 12 to 17 years of age. Brief summaries and demographics of phase 2/3 PK data as follows:

Table 2. Summary of Available Data Used for the PK Model Development

Study	Study Description	Dose	N	Sampling Schedule
KPL-914-C001	An open-label, single-active-arm pilot study to explore clinical and biochemical endpoints of peri-carditis symptomatology	Age ≥18 years 320 mg SC LD, then 160 mg SC MD×5 doses Age 6 – <18 years 4.4 mg/kg SC LD, then 2.2 mg/kg SC MD×5 doses	26	PK (Run-in): screening (Day -3 to Day 0) PK (Treatment): Day 0, then Weeks 2, 3, 3-4 (optional), 4, 5, 6, EOT PK (Extension): Monthly, final visit (Week 25) ADA (Run-in): screening (Day -3 to Day 0) ADA (Treatment): Day 0, then Weeks 2, 3, 4, EOT ADA (Extension): Month 2, final visit
KPL-914-C002	Double-blind, placebo-controlled, randomized withdrawal, study with open-label extension, to assess the efficacy and safety of rilonacept in recurrent pericarditis	Age ≥18 years 320 mg SC LD, then 160 mg SC MD Age ≥12 – <18 years 4.4 mg/kg SC LD, then 2.2 mg/kg SC MD	86	PK: Day 2, and then Weeks 1, 2, 4, 8, 24, EORW ADA: Baseline, Weeks 2, 6, 8, 24, EORW

N = number of subjects, SC = subcutaneous, LD = loading dose, MD = maintenance dose, EOT = end of trial, EORW = end of randomized withdrawal. Note: One subject in study KPL-914-C001 was enrolled twice.

Table 3. Summary of Excluded Data from the Final NONMEM Dataset

	KPL-914-C001	KPL-914-C002	Total
Original observations	298	621	919
Missing date/time	0	84 (13.5%)	84 (9.1%)
Pre-dose BLQ exclusions	36 (12.1%)	1 (0.2%)	37 (4%)
Post-dose BLQ exclusions	0	19 (3.1%)	19 (2.1%)
Duplicated exclusions	0	4 (0.6%)	4 (0.4%)
Outliers	6 (2%)	1 (0.2%)	7 (0.8%)
Analysis observations	256	512	768

Table 4. Continuous & Categorical Covariates in the Final Model Dataset

	Age (years)	Weight (kg)	Sex	Race	Anti-Drug Antibodies Status (if any Positive)	ADA Titer Carried Forward
N	112	112	Male: 47	White: 103	ADA Positive: 41	0: 103
Mean	44.3	84.3	(42%)	(92%)	(36.6%)	(92%)
SD	14.9	23.9	Female: 65	Black: 8	ADA Negative: 71	50: 3
CV%	33.7	28.4	(58%)	(7.1%)	(63.4%)	(2.7%)
Median	46.5	80.4		Other: 1		150: 5
Min	13	46.6		(0.9%)		(4.5%)
Max	78	169				450: 1
						(0.9%)

Note: One subject in study KPL-914-C001 was enrolled twice.

Figure 4. Demographic Histograms

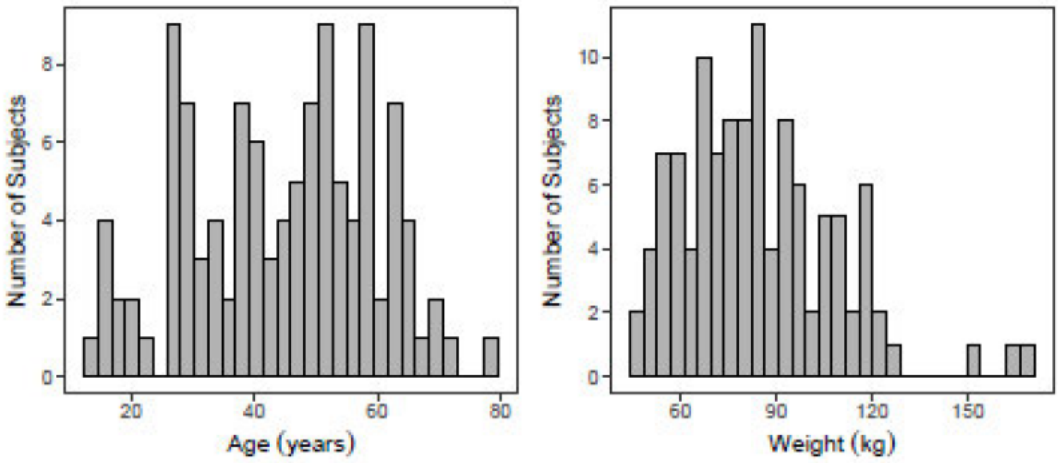
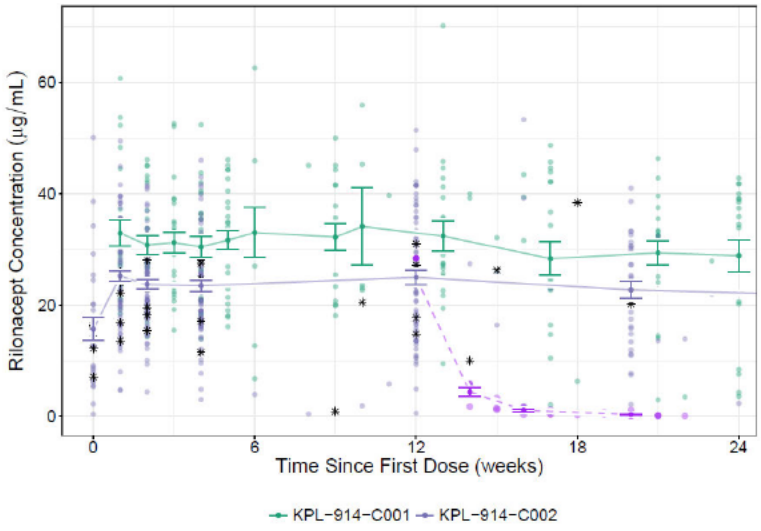


Figure 5. Mean Concentration Time Profiles of Rilonacept by Study



Source: Graphical Analysis, Population Pharmacokinetic Analysis, and Non-Compartmental Analysis for Rilonacept (KPL-914) in Subjects with Recurrent Pericarditis, Tables 1, 2, 3; Figures 5 and unnumbered Figure; pages 7, 31, 34, 35, 36

Reviewer's comments:

The reviewer has independently examined and confirmed data in the pooled dataset for C001 and C002. Age summary: median, 46.50; min, 13; max, 78; Q1, 31.75; Q3, 56.25.

The reviewer has examined raw concentrations (excluding BLQ) by study and adult vs. pediatric subjects and noted that the median observed concentration is approximately 40-50% higher in C002 when compared to those in C001 (Fig. R1). As a reference, the concentration data from C002 is consistent with what was observed in the CAPS study subjects (under another indication approval). While the applicant acknowledged this elevated exposure observed in C001 despite the same type of study subjects, the exact reasons were unknown per applicant. The points outlined below may potentially partially explain such exposure differences following an IR request:

- *C001 was a phase 2 study and did not have robust data for evaluating rilonacept PK (data was less reliable; data not collected as intended trough concentrations)*
- *These data may have introduced variability to evaluation of rilonacept PK*
- *No assay methodology difference between studies*
- *No changes in product formulation between studies*
- *Even within C002, concentration data showed moderate variability between subjects (30.1-69.2% per IR response)*

Figure 6. Graphical examination demonstrated an approx. 50% median exposure elevation in C001 subjects.

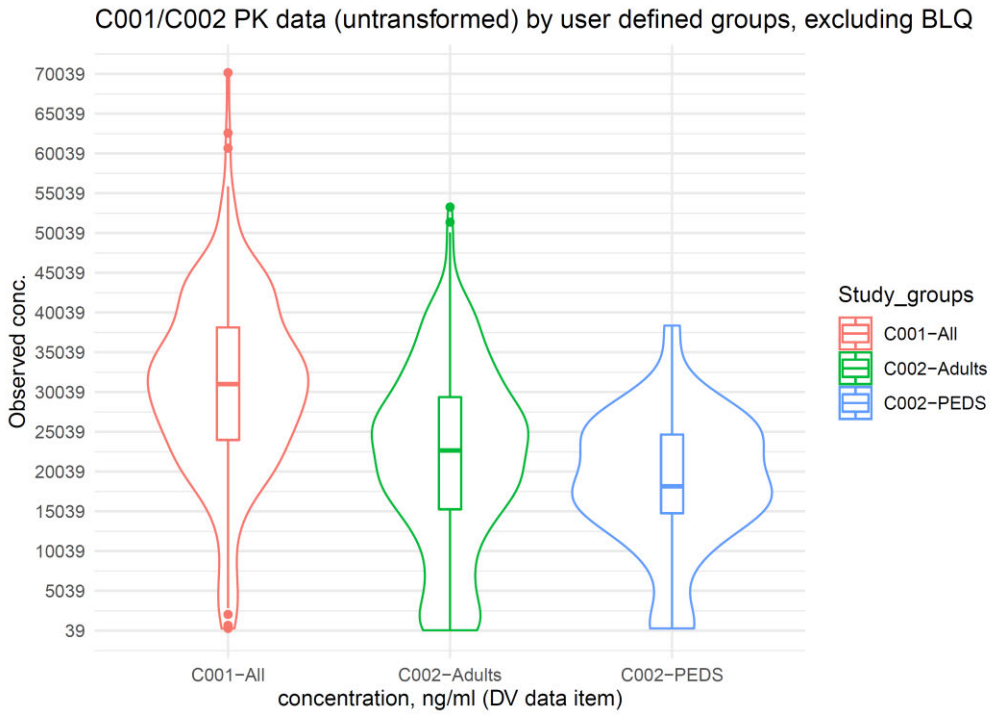


Figure 7. Graphical examination of relative time and frequency of PK samples for 4 weeks

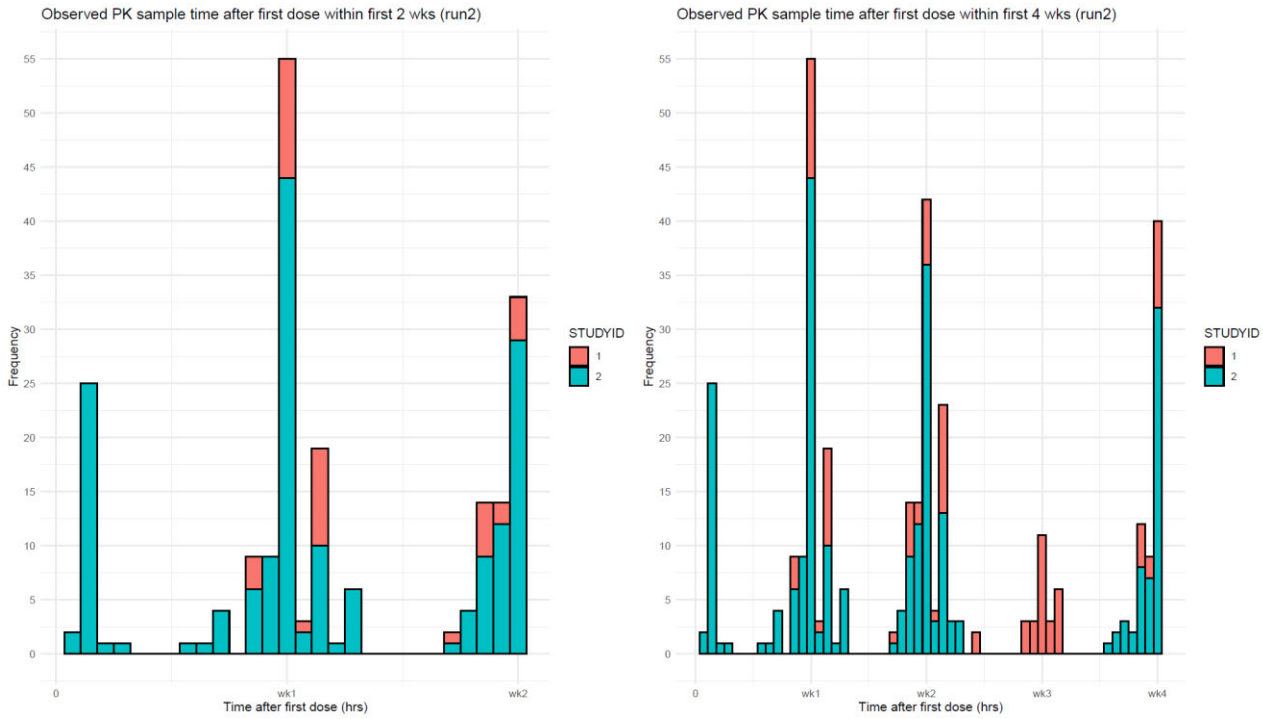
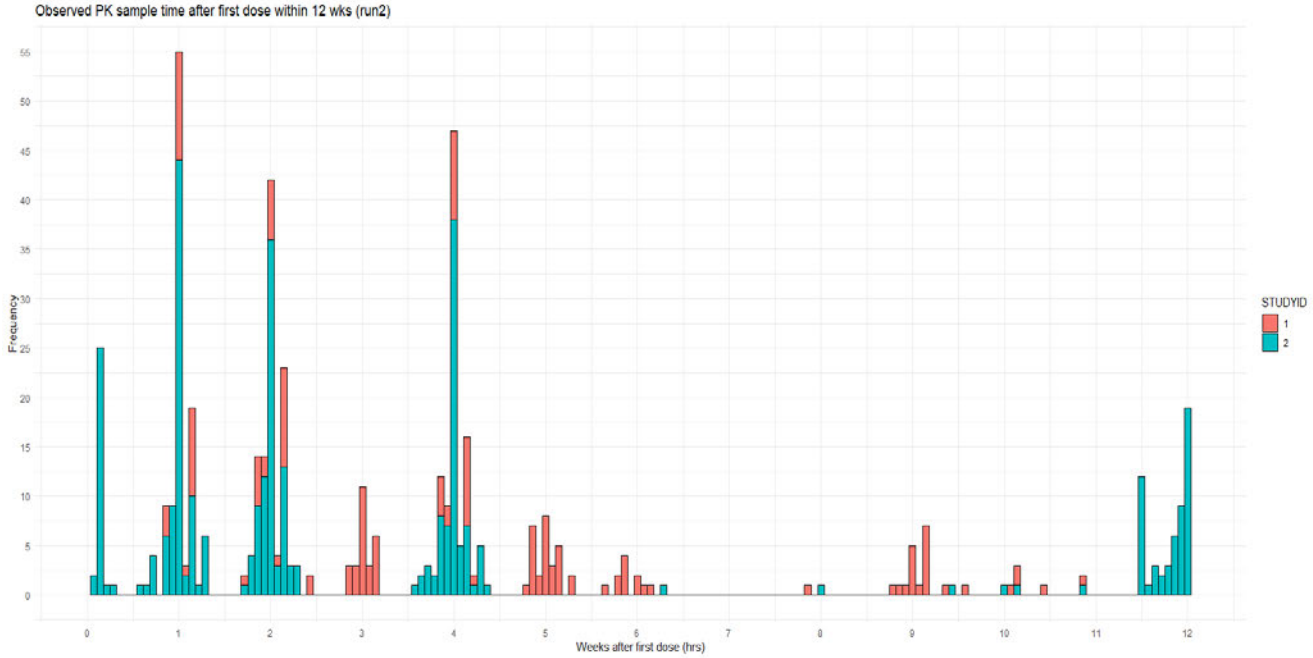


Figure 8. Graphical examination of relative time and frequency of PK samples for 12 weeks



1.4 Final Model

Population pharmacokinetics of rilonacept were best described by a one-compartmental model with first-order absorption rate constant (subcutaneous route of administration) and first-order elimination (Table 1, Figures 2,3, and 9-11).

Figure 9 (partial). CWRES Plots for Final PK Model

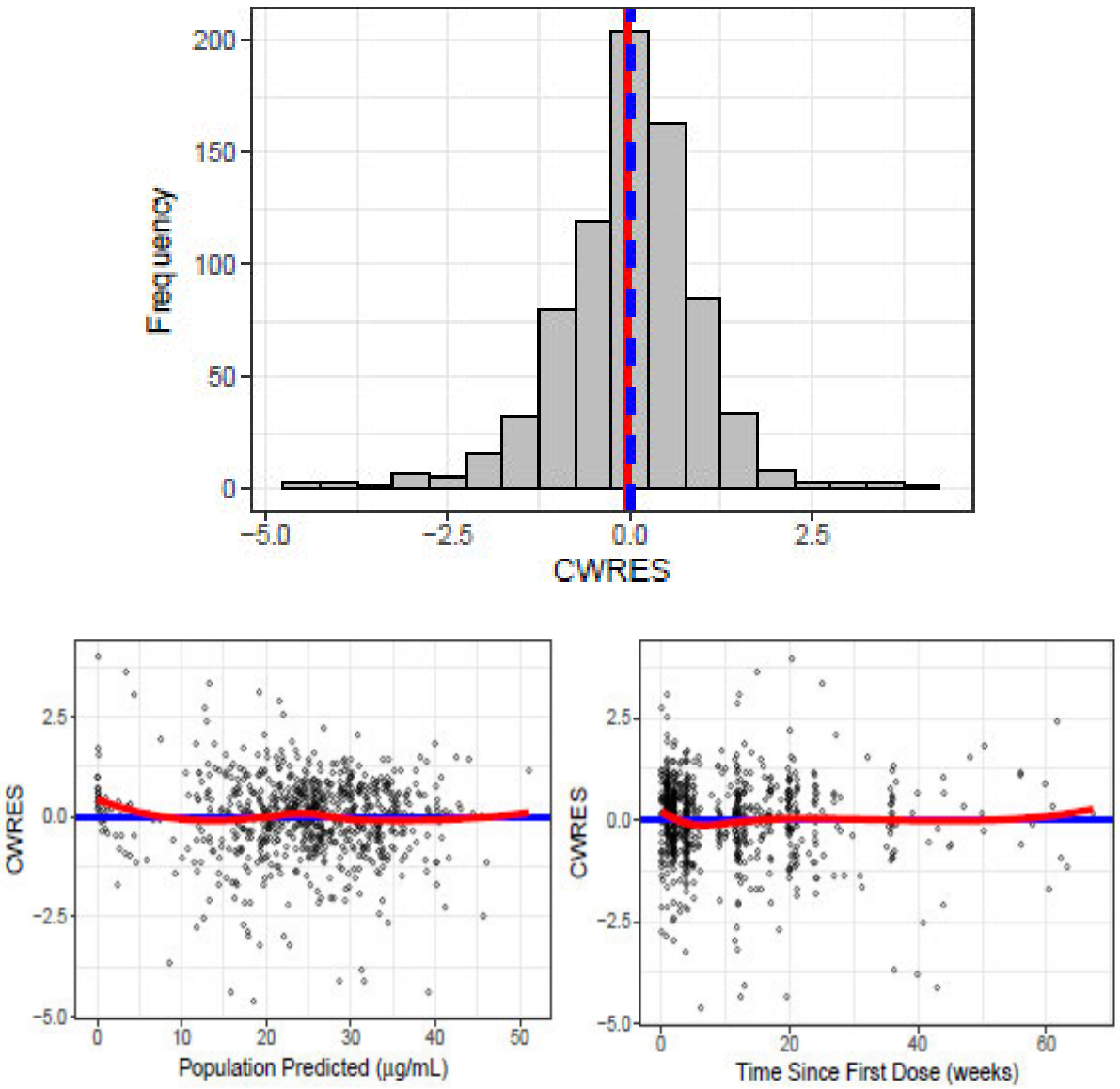


Figure 10. pvcVPC for the Final PK Model (KPL-914-C001)

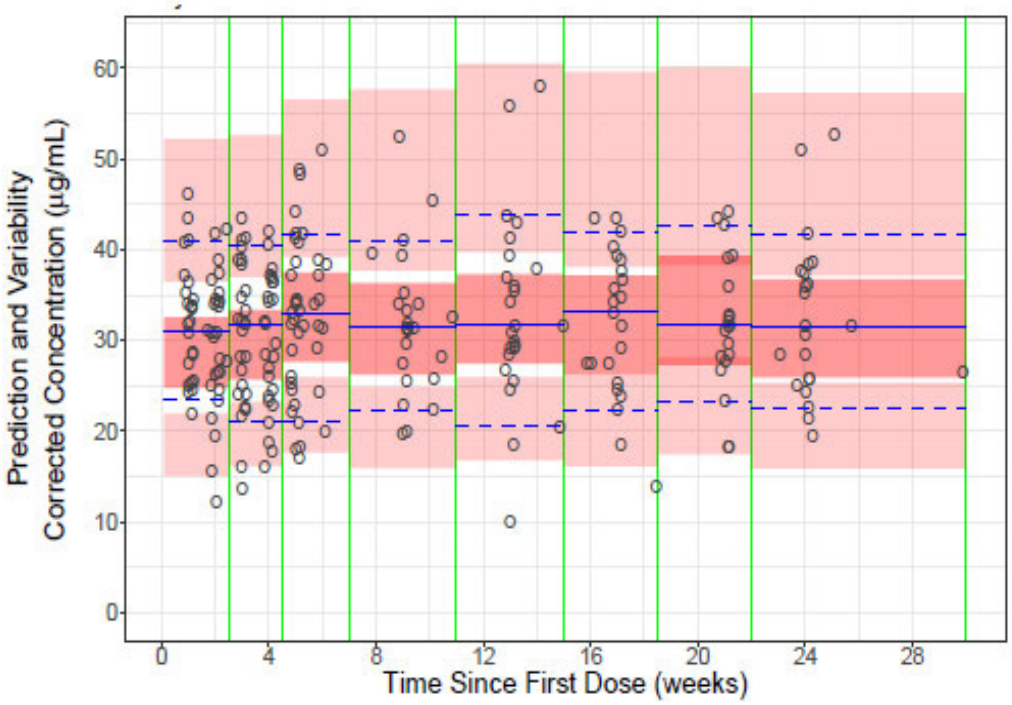
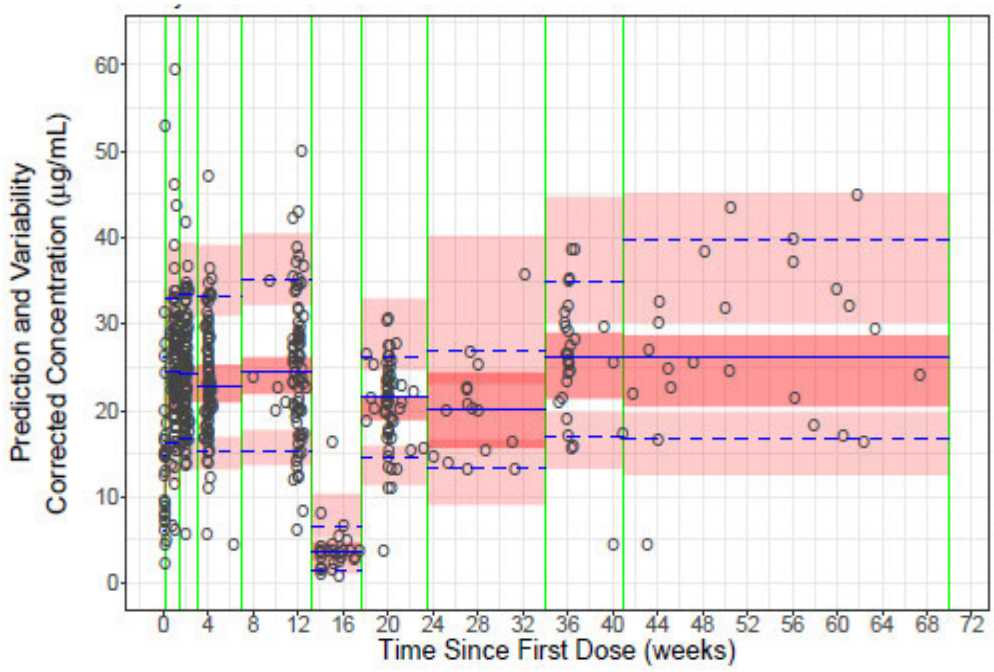


Figure 11. pvcVPC for the Final PK Model (KPL-914-C002)



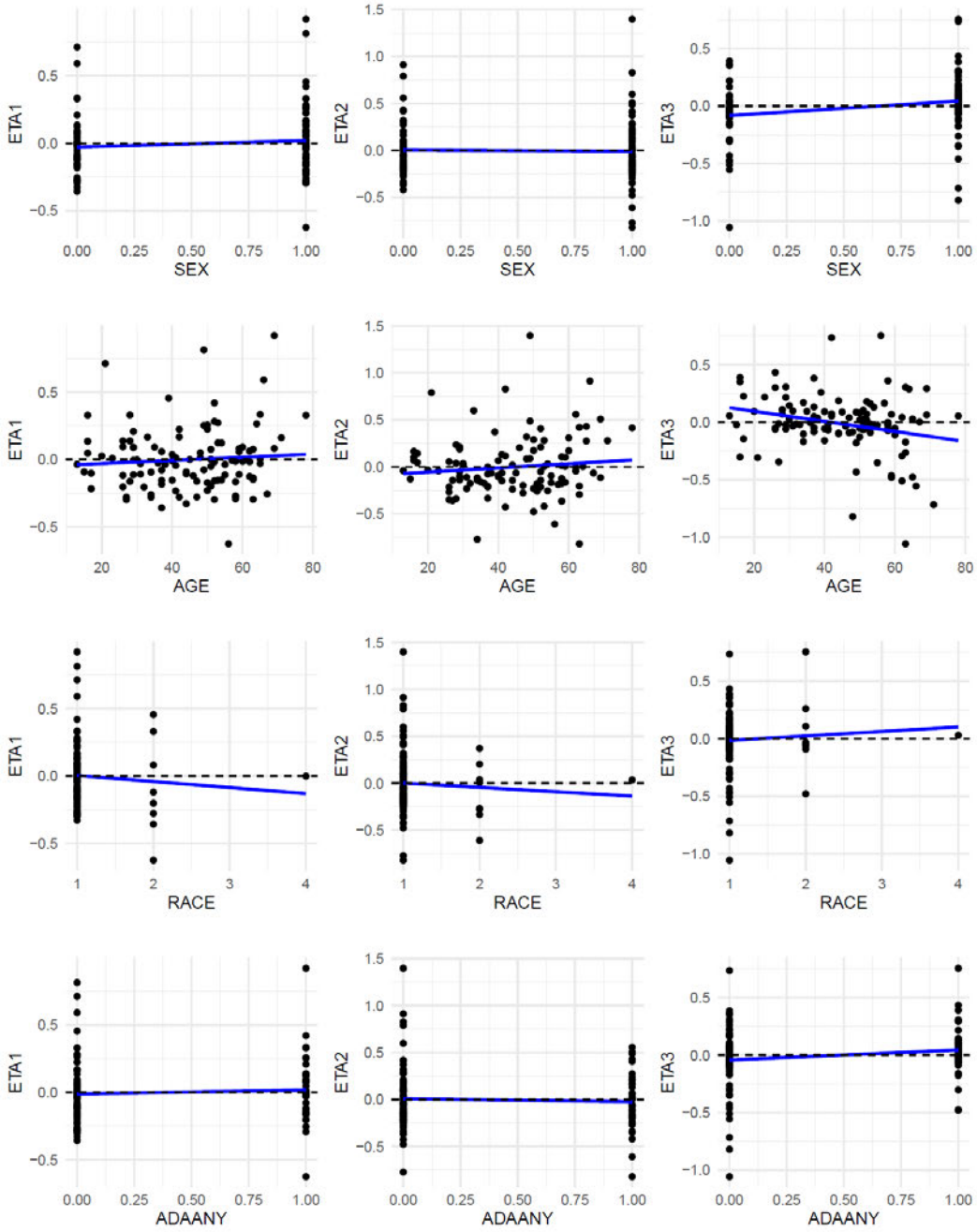
Source: Applicant's Population PK Report "Graphical Analysis, Population Pharmacokinetic Analysis, and Non-Compartmental Analysis for Rilonacept (KPL-914) in Subjects with Recurrent Pericarditis", pages 57-59, 61

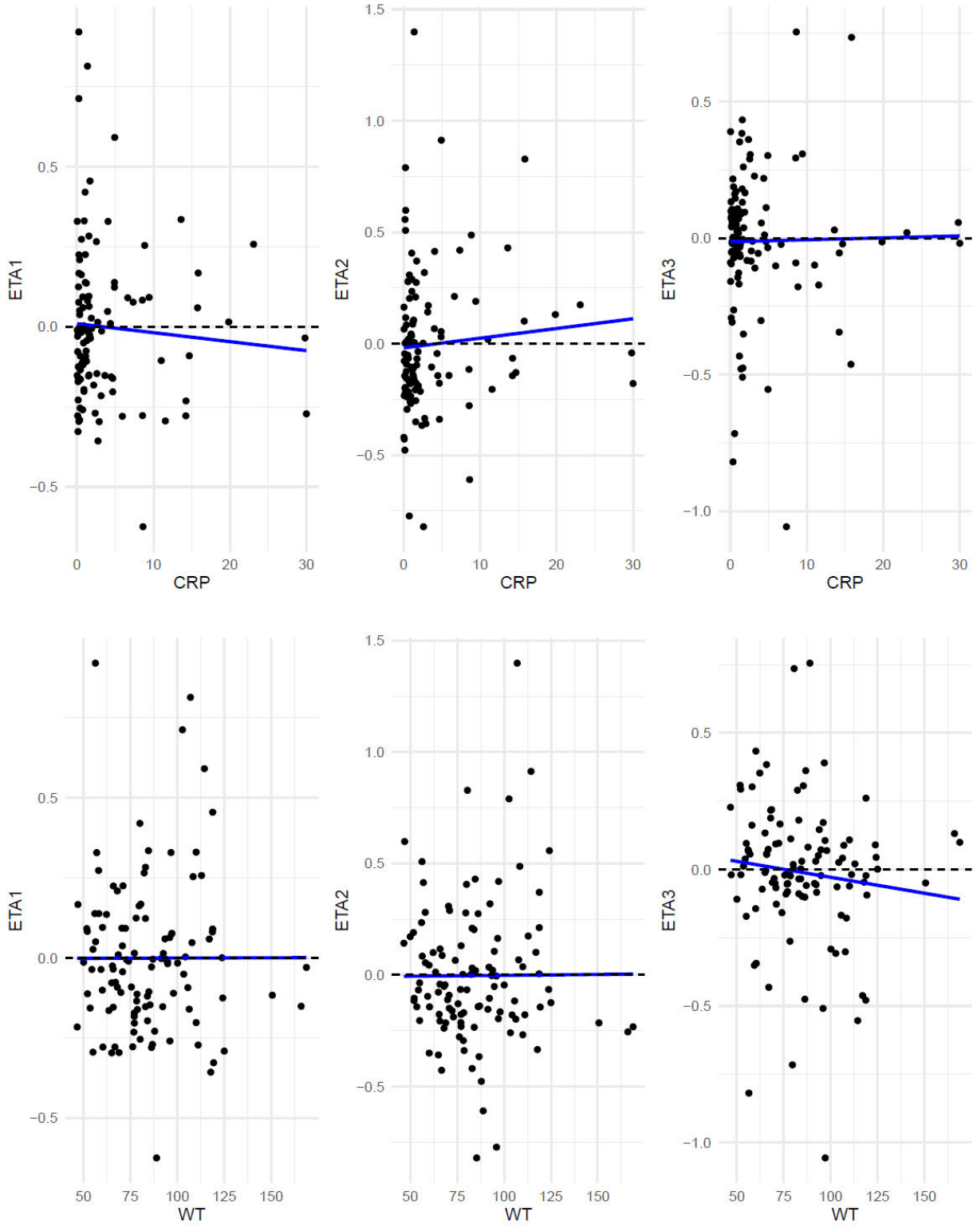
Reviewer's Comments:

The final population PK model is acceptable for describing rilonacept concentration-time data adequately across 2 studies for descriptive labeling purposes. The diagnostic plots for evaluating the final model were acceptable. Summary points follow:

- *All parameters, except for BSV Ka (31%), had RSE% < 25%*
    - *Given potential variability associated with subcutaneous route of administration, relatively higher RSE% and BSV may be acceptable*
- *BSVs for CL and F were <50%, including the upper bound of 95% CI*
- *Adequate shrinkage (<20%) for population CL and V*
- *Shrinkage is moderately high for Ka; however, Ka parameter estimate is consistent with previously studies (for CPAS patients)*
- *The goodness of fit plots for the final model, stratified by study number, demonstrated minimal bias (acceptable) and acceptable correlation for both population and individual predictions.*
- *CWRES plots for population predicted and time showed minimal bias (acceptable) and adequate homoscedasticity; CWRES frequency plot (bar graph) showed relatively adequate normal distribution around zero and no skewness was observed*
- *pcVPC plots (by study) showed that the PK model adequately describes the rilonacept concentration data*

Figure 12. ETA Plots vs Covariates (Reviewer's Analysis)





Overall, the applicant's model is acceptable for describing exposure metrics in the product label.

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JUSTIN C EARP
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MANOJ KHURANA
02/22/2021 04:21:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125249Orig1s049

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 18, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	BLA 125249/S-049
Product Name and Strength:	Arcalyst (rilonacept) for Injection, 220 mg/vial
Applicant/Sponsor Name:	Kiniksa Pharmaceuticals GMBH
OSE RCM #:	2020-1973-1 and 2020-1974-1
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 16, 2021 for Arcalyst. We reviewed the revised container label and carton labeling for Arcalyst (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Straka, M. Label and Labeling Review for Arcalyst (BLA 125249/S-049). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 5. RCM No.: 2020-1973 and 2020-1974.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 16, 2021

Carton labeling

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/s/

MAXIMILIAN STRAKA
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HINA S MEHTA
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DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

BLA: 125249/s-049
Drug: Arcalyst (rilonacept)
Applicant: Kiniksa Pharmaceuticals (UK), Ltd.
Indication:

- Proposed: (b) (4)
- Approved: for the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years and older.

Date of submission: September 21, 2020
PDUFA date: March 21, 2021
Target Action date: March 19, 2021

II. REVIEW TEAM

Division of Cardiology and Nephrology:
Norman Stockbridge, MD, PhD, Director
Mary Ross Southworth, PharmD, Deputy Director for Safety
Michael Monteleone, MS, RAC, Associate Director for Labeling
Fortunato Senatore, MD, PhD, FACC, Clinical Team Leader
Christine Garnet, PharmD
Yanyan Ji, PhD, Safety Reviewer

Office of Biostatistics, Division of Biometrics I
Jialu Zhang, PhD, Team Leader
Dali Zhou, PhD, Statistician

Office of Biotechnology Products:
Sang Bong Lee, PhD, Reviewer
Chana Fuchs, PhD, Team Leader
Kristine Leahy, Regulatory Business Process Manager
James Barlow, PhD, Labeling reviewer

Office of Clinical Pharmacology:
Kunal Jhunjhunwala, MS, PhD, Clinical Pharmacology Reviewer

Jiajun Liu, PharmD, MSc, Pharmacometrics, Reviewer
Manoj Khurana, PhD, Clinical Pharmacology Team Leader
Justin Earp, PhD, Pharmacometrics Team Leader

***Division of Medication Error Prevention and Analysis**
Maximilian Straka, PharmD, FISMP, Reviewer
Hina Mehta, PharmD, Team Leader

****Office of Prescription Drug Promotion:***
Zarna Patel, PharmD, Regulatory Review Officer

****Division of Medical Policy Programs*:**
Kelly Jackson, PharmD, Patient Labeling Reviewer

****Division of Clinical Outcome Assessment:***
Susan Pretko, PharmD, MPH, Reviewer
Onyeka Illoh, OD, MPH, Acting Team Leader, DCOA
Elektra Papadopoulos, Acting Deputy Director, DCOA

III. BACKGROUND

ARCALYST was approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) on February 27, 2008.

- IND 136,896 for the treatment of recurrent idiopathic pericarditis (RIP) was submitted on September 2017 which consisted of 2 studies, a.) KPL-914-C001, An Open-Label Pilot Study, and b.) KPL-914-C002, a Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study with an Open Label Extension. FDA agreed with a single phase 3 trial to support a supplemental application in the EOP2 meeting comments dated July 17, 2018.
- A meeting request to discuss a proposed expedited sBLA submission strategy including feedback on the overall study analysis changes of the Phase 3 study (KPL-914-C002), the Integrated Safety Summary (ISS) strategy and the extent of the safety database needed was submitted in January 3, 2020 and cancelled after receipt of the FDA's preliminary comments.
- On July 2020, Regeneron Pharmaceuticals transferred the ARCALYST BLA to Kiniksa Pharmaceuticals, GmbH (Kiniksa).
- On December 11, 2020, the Applicant informed the Agency that Kiniksa Pharmaceuticals, GmbH, U.S. License No. 2236, had undergone a minor name change to Kiniksa Pharmaceuticals (UK), Ltd and will continue to manufacture Arcalyst (rilonacept) in the same manner as before, using the same equipment, facilities, manufacturing procedures, controls, and methods, and responsible personnel.
- A topline results meeting was held on July 31, 2020.
- Breakthrough Therapy designation was granted November 19, 2019.
- Orphan Drug Designation was granted in July 2020.
- The Application was granted a priority review at the filing meeting.

IV. APPLICATION REVIEW

1. User Fee:

This efficacy supplement was grated Orphan Designation and it is exempt from User Fee.

2. Pediatric Review Committee (PeRC):

On July 14, 2020, Kiniksa was granted Orphan Drug Designation for rilonacept for the treatment of pericarditis and therefore exempt from PREA requirements.

3. Advisory Committee:

There was no Advisory Committee meeting for this efficacy supplement because it did not raise any significant safety of efficacy issues.

4. Trade name:

N/A

5. Facilities Inspections:

N/A

6. Regulatory Timeline

Received: September 21, 2020
Filing date: November 20, 2020
PDUFA Goal Date: March 21, 2021

7. Reviews

a) Divisional and Cross-Discipline Team Leader Review (3/16/21):

Drs. Stockbridge and Senatore recommended Approval for this sBLA. In their combined review the concluded that RHAPSODY was a well-controlled and adequately performed phase 3 clinical trial. The data from the trial met the evidentiary standard pursuant to §21 CFR 314.126 to support an indication (b) (4) .

Treatment with rilonacept should continue for 6 months for recurrent pericarditis, but clinical judgement should be used for optimal timing and duration of treatment.

b) Clinical, Statistical, and Safety Review (3/16/21):

Dr.'s Senatore, Ji, Zhou provided a combined review discussing safety and efficacy. They recommended approval stating that the benefits outweigh the risks. Please see review for more details.

c) Clinical Pharmacology Review (02/22/21):

The Office of Clinical Pharmacology/ Division of Cardiometabolic & Endocrine Pharmacology (OCP/DCEP) has reviewed sBLA 125249's Clinical Pharmacology data submitted on September 21, 2021. OCP/DCEP recommends that the submitted data are acceptable to fulfill the supplemental BLA for Recurrent Pericarditis (RP) for BLA 125249.

d) Office of Biotechnology Products Review (02/16/21):

Office of Biotechnology Products provided an Immunogenicity Assay review for this efficacy supplement. In their review they concluded that the assay used for immunogenicity is acceptable for analysis of recurrent pericarditis patient samples.

8. Consults

Please see the following reviews and their corresponding dates:

- DMEPA (02/21/21):
  Dr. Straka reviewed the proposed Container Labels, Carton Labeling, Prescribing Information (PI) and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors. In his review he concluded that the proposed Container Labels, Carton Labeling, IFU and PI can be improved from a medication error perspective. We provide recommendations in section 4.1 for the Division and in section 4.2 for the Applicant.

- OPDP (03/02/21):
  Dr. Patel reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for Arcalyst (rilonacept) for injection, for subcutaneous use.

  Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN on February 18, 2021 and are provided below. A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

  Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 1, 2021, and we do not have any comments.

- Patient Labeling Team (PLT) (03/04/21):
  Dr. Jackson concluded in her review that the PPI and IFU are acceptable with our recommended changes.

- Clinical Outcome Assessment (02/16/21):
  (b) (4)

(b) (4) .

9. Labeling

Labeling discussions occurred with the applicant. The final agreed-upon labeling will be attached to the approval letter.

V. CONCLUSION

The review team recommended approval. An approval letter for this supplemental BLA was signed by Dr. Stockbridge on March 18, 2021.

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/s/

MARYAM K CHANGI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 4, 2021
To:	Maryam Changi, PharmD Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ARCALYST (rilonacept)
Dosage Form and Route:	for injection, for subcutaneous use
Application Type/Number:	BLA 125249
Supplement Number:	S-049
Applicant:	Kiniksa Pharmaceuticals

1 INTRODUCTION

On September 21, 2020, Kiniksa Pharmaceuticals submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their Biologics License Application (BLA) for ARCALYST (rilonacept) for injection, for subcutaneous use. The purpose of the supplement is to add an indication for recurrent pericarditis to the Prescribing Information.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on October 29, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ARCALYST (rilonacept) for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft ARCALYST (rilonacept) PPI and IFU received on September 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 19, 2021.
- Draft ARCALYST (rilonacept) Prescribing Information (PI) received on September 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on February 19, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 2, 2021

To: Maryam Changi, Regulatory Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: Zarna Patel, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ARCALYST (rilonacept) for injection, for subcutaneous use

BLA: 125249/Supplement 49

In response to DCN consult request dated October 29, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for Arcalyst (rilonacept) for injection, for subcutaneous use. This supplement (S049) provides for a new indication for recurrent pericarditis.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN on February 18, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 1, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Zarna Patel at zarna.patel@fda.hhs.gov.

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ZARNA PATEL
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Clinical Outcome Assessment Review Memorandum

From	Susan Pretko, PharmD, MPH Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) Onyeka Illoh, OD, MPH Acting Team Leader, DCOA Elektra Papadopoulos Acting Deputy Director, DCOA
To	Division of Cardiology and Nephrology
COA tracking number	C2020555
BLA#	BLA 125249/S-049 (ref IND 136869)
Drug Applicant	Kiniska
Meeting type	BLA Mid-Cycle, Labeling, and Wrap-up Meetings
Indication:	(b) (4) Please check all that apply: ☒ **Rare Disease/Orphan Designation** ☒ Pediatric
Instrument(s) reviewed:	Patient Global Impression of Pericarditis Severity (PGIPS) ☒ Patient-reported outcome (PRO)

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by the Division of Cardiology and Nephrology (DCN) on January 9, 2021 (DARRTS Reference ID: 4728937) for BLA 125249/S-049 regarding rilonacept for the treatment of recurrent pericarditis (RP).

(b) (4)

RHAPSODY was a double-blind, placebo-controlled, multinational, phase 3 study to assesses the efficacy and safety of rilonacept treatment on RP.[1] Eligible subjects were aged ≥ 12 years with a diagnosis of RP and had at least 1 day with pericarditis pain ≥ 4 on the 11-point pain numeric rating scale (NRS) in the 7 days prior to the first administration of study drug. The primary endpoint in RHAPSODY is time to pericarditis recurrence, defined as the time from randomization to the date of the first pericarditis recurrence for each subject. Pericarditis recurrence is defined as the recurrence of typical pericarditis pain (at least one pain numeric rating scale (NRS) recording ≥ 4) associated with supportive objective evidence of pericarditis, shown below.

[1] Applicant's submission SN 0145(227) received September 21, 2020 containing the RHAPSODY study protocol version 3 and the RHAPSODY SAP version 2.

Supportive Evidence (Pericarditis manifestations):

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

The PGIPS was used to support the secondary endpoint defined as the proportion of subjects with absent or minimal pericarditis symptoms (i.e., rating of "Absent" or "Minimal" at week 16 of the randomized withdrawal (RW) period). Secondary endpoints in RHAPSODY were multiplicity controlled.

< Reviewer's Comment(s): The PGIPS is a single-item patient-reported outcome (PRO) questionnaire that assesses overall current severity of RP symptoms. The PGIPS is in Appendix 1.

The study design for RHAPSODY included 3 treatment periods:

1. *A single-blind run-in (RI) period during which treatment with blinded rilonacept was administered and subjects were weaned off background standard of care (SOC) therapy for their pericarditis disease. Subjects were blinded regarding the time of transition from the single-blind to the double-blind period (i.e., they were not aware of the duration of the RI period).*
    a. *Subjects who stopped background pericarditis medications and achieved Clinical Response on rilonacept proceeded into the double-blind placebo-controlled RW period of the study.*

    b. *Subjects who were unable to achieve Clinical Response[2] on rilonacept monotherapy at RI Week 12/RW baseline were discontinued from study drug, transitioned to SOC pericarditis therapy at the Investigator's discretion, and followed through the end of the RW period.*

2. *A double-blind RW period during which subjects that achieved Clinical Response on rilonacept monotherapy at RI Week 12/RW baseline were randomized to double blinded administration of the study drug or matching placebo. Upon pericarditis recurrence in the RW period, subjects received bailout rilonacept irrespective of randomized treatment assignment, and Oral Rescue Therapy (i.e., analgesics, NSAIDS, and colchicine) at the discretion of the Investigator.*

3. *At the end of the RW period, all subjects that did not discontinue study drug had the option to continue treatment with open-label rilonacept in the long-term open label extension treatment period. >*

[2] Clinical Response was defined by a weekly average of daily pericarditis pain of ≤ 2.0 on an 11-point NRS and low levels of C-Reactive Protein. Refer to the RHAPSODY study protocol for more detail.

(b) (4)

DCOA attended the Mid-Cycle meeting on January 5, 2021 and the labeling meeting on January 21, 2021. Please see below for DCOA's review conclusions.

Review Conclusions:

(b) (4)

< *Reviewer's Comment(s)*:
Subjects in the RHAPSODY study completed the pain NRS on a daily basis and completed the PGIPS at baseline, week 6, and week 12 or the run-in period. (b) (4)

>

Appendix 1. Patient Global Impression of Pericarditis Severity (PGIPS)

Select the response that best describes the severity of pericarditis symptoms right now: QSTEST/QSORRES *where* QSTESTCD=PGI	Absent: no symptoms ☐ Minimal: can be easily ignored without effort ☐ Mild: can be ignored with effort ☐ Moderate: cannot be ignored but does not influence my daily activities ☐ Moderately severe: cannot be ignored and occasionally limits my daily activities ☐ Severe: cannot be ignored and often limits my concentration on daily activities ☐ Very severe: cannot be ignored and markedly limits my daily activities ☐
Date of assessment (timestamp)	QSDTC
Sitemode enabled	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN M PRETKO
02/16/2021 09:00:37 AM

ONYEKACHUKWU A ILLOH
02/16/2021 09:47:53 AM

ELEKTRA J PAPADOPOULOS
02/16/2021 02:02:04 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 5, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	BLA 125249/S-049
Product Name, Dosage Form, and Strength:	Arcalyst (rilonacept) for Injection, 220 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kiniksa Pharmaceuticals GMBH
FDA Received Date:	September 21, 2020 and January 8, 2021
OSE RCM #:	2020-1973 and 2020-1974
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Kiniksa Pharmaceuticals GmbH submitted a supplemental BLA 125249/S-049 on September 21, 2020 for Arcalyst (rilonacept) proposing a new indication (b) (4) (b) (4). We reviewed the proposed Container Labels, Carton Labeling, Prescribing Information (PI) and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Arcalyst (rilonacept) approved on February 27, 2008 is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. It is a lyophilized powder available at 100 mg/vial. On July 23, 2020 Regeneron Pharmaceuticals transferred BLA 125249 to Kiniksa Pharmaceuticals, GmbH.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Kiniksa Pharmaceuticals GmbH submitted a prior approval supplement for Arcalyst (rilonacept) proposing a new indication (b) (4) They also submitted updated container labels and carton labeling to reflect the change in Applicant.

Kiniksa proposes to change the needle gauge of the needle used to reconstitute and withdraw the recommended dose volume of Arcalyst and to update the Instructions for Use (IFU) accordingly. The change proposed would be to use 1 18-gauge needle for reconstitution, 1 18-gauge needle

for withdrawing, and 1 26-gauge needle for administration. As part of the submission Kiniksa conducted a formative analysis of the change in needle gauge. As the analysis was formative in nature thus, it does not require review by the Agency. Per Kiniksa, "the rationale for changing the needle sizes is to improve the overall patient experience for preparing and self-administering Arcalyst". In addition, "the risk to a patient of mistakenly using the 18-gauge needle to inject is practically very low given the difference in size which makes it obvious it is not intended for sc injections. If this occurs then there may be a slightly increased risk of injection site pain and injection site bleeding due to the larger diameter puncture wound". We note the needles would be obtained separately from the pharmacy.

Our review of the IFU noted clear instructions on the needle size and at which step the different needles are to be used. We note several statements that can be improved for clarity in the PI and IFU and we provide recommendations below for the Division. Our review of the proposed carton label and container labeling identified several areas of concern from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Container Labels, Carton Labeling, IFU and PI can be improved from a medication error perspective. We provide recommendations in section 4.1 for the Division and in section 4.2 for Kiniksa Pharmaceuticals..

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration Section

   a. As currently presented the [redacted] (b) (4)

B. Instructions for Use

1. We recommend revising first sub-bullet under the additional supplies needed section for clarity. We recommend revising to "1 18-guage needle to mix ARCALYST".

4.2 RECOMMENDATIONS FOR KINIKSA PHARMACEUTICALS GMBH

We recommend the following be implemented prior to approval of this BLA Supplement:

A. General Comments (Container labels & Carton Labeling)

1. The labels currently state: [redacted] (b) (4) ". To ensure consistency with the Prescribing Information, revise the statement to read "See enclosed Prescribing Information for reconstitution instructions and complete information on dosage and administration"

2. As currently presented, there is [redacted] (b) (4). Revise the storage information to read: Store at “2°C to 8°C (36°F to 46°F) until use.” for consistency with the Prescribing Information.

3. We note that package type term has been changed from “single use vial” to “single-dose vial” throughout the PI in accordance with USP chapter <659> Packaging and Storage Requirements. We recommend changing the package type term on the Carton and Container labels to “single-dose vial” to align with the PI. In addition, we recommend including the statement “Discard unused portion” next to the package type term.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Arcalyst received on January 8, 2021 from Kiniksa Pharmaceuticals GMBH.

Table 2. Relevant Product Information for Arcalyst	
Initial Approval Date	February 27, 2008
Proper Name	rilonacept
Indication	ARCALYST (rilonacept) is an interleukin-1 blocker indicated for: • 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. • maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing at least 10 kg. • (b) (4)
Route of Administration	subcutaneous
Dosage Form	for Injection
Strength	220 mg/vial
Dose and Frequency	• **CAPS, FCAS, MWS, and RP** Adults 18 years and older: o Loading dose: 320 mg, delivered as two 160 mg (2 mL) injections o Maintenance dose: 160 mg (2 mL) injection once weekly. Pediatrics 12 years to 17 years: o Loading dose: 4.4 mg/kg, up to a maximum of 320 mg, delivered as 1 or 2 injections (up to 2 mL/injection). o Maintenance dose: 2.2 mg/kg, up to a maximum of 160 mg (2 mL) injection, once weekly. • **DIRA** Adults and Pediatric Patients weighing at least 10 kg: o 4.4 mg/kg up to a maximum of 320 mg, delivered as 1 or 2 injections (2 mL/injection) once weekly.
How Supplied	ARCALYST (rilonacept) for injection is supplied as a sterile, white to off-white, preservative-free, lyophilized powder in single-dose vials.

	Each 220 mg vial of ARCALYST is supplied in a carton containing four vials (NDC 73604-914-04).
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in 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.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 21, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, BLA 125249, Arcalyst and rilonacept. Our search identified one previous review[a] and we considered our previous recommendations to see if they are applicable for this current review.

[a] Vee, S. Label and Labeling Review for Arcalyst (BLA 125249/S-047). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Oct 22. RCM No.: 2020-1477.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Arcalyst labels and labeling submitted by Kiniksa Pharmaceuticals GMBH.

- Container label received on September 21, 2020.
- Carton labeling received on September 21, 2020.
- Prescribing Information (Image not shown) received on January 8, 2021, available from \\CDSESUB1\evsprod\bla125249\0174\m1\us\annotated-draft-labeling.pdf.

G.2 Label and Labeling Images

Container Label

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
02/05/2021 03:55:38 PM

HINA S MEHTA
02/05/2021 08:32:52 PM