EMA/63022/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

Rilonacept FGK Representative Service GmbH

International non-proprietary name: Rilonacept

Procedure No. EMEA/H/C/006537/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation	Definition
AcP	IL-1 receptor accessory protein
ADA	Anti-Drug Antibody
AE	Adverse event
AOSD	Adult-onset Still's disease
AUC	Area under the curve
BLA	Biologics License Application
CAPS	Cryopyrin-Associated Periodic Syndrome
CEC	Clinical Endpoint Committee
CFU	Colony forming unit
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CIA	Collagen-induced arthritis
C_{max}	Maximum concentration
CRP	C-reactive protein
ECG	Electrocardiogram
EU	Endotoxin unit
DP	Drug product
DS	Drug substance
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicine Agency
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
EU	European Union
FCAS	Familial cold autoinflammatory syndrome
FDS	Formulated drug substance
FMF	Familial Mediterranean fever
GI	Gastrointestinal
GLP	Good Laboratory Practice
HDL	High-density lipoprotein
HEPA	High efficiency particulate air (filter)
HIC	Hydrophobic interaction chromatography
IB	Investigator's Brochure
ICH	International Council for Harmonisation
iCIEF	Imaging capillary isoelectric focusing
IEF	Isoelectric focusing
IgG1	Immunoglobulin G1
IL-1	Interleukin-1
IL-1ra	IL-1 receptor antagonist
IL-1RAcP	IL-1 receptor accessory protein
IL-1R1	IL-1 Type 1 receptor
IPC	In process controls
ISI	Insomnia Severity Index
ISR	Injection-site reaction
IV	Intravenous
K_d	Equilibrium binding constant
LDL	Low-density lipoprotein
LMW	Low molecular weight

Abbreviation	Definition
LTE	Long-term extension
MAA	Marketing Authorisation Application
MCB	Master cell bank
MRI	Magnetic resonance imaging
MSU	Monosodium urate
MWS	Muckle-Wells syndrome
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
ORT	Oral rescue therapy
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEG	Polyethylene Glycol
PGA-PA	Physician Global Assessment of Pericarditis Activity
PGI-PS	Patient Global Impression of Pericarditis Severity
PK	Pharmacokinetic
PT	Preferred term
QP	Qualified person
RA	Rheumatoid arthritis
RI	Run in
RP	Recurrent pericarditis
RPM	Revolutions per minute
RW	Randomised withdrawal
SAA	Serum amyloid A
SAE	Serious adverse event
sBLA	supplemental Biologic License Application
SF-36	36-item Short Form Health Survey
SC	Subcutaneous
SDS-PAGE	Sodium dodecyl-sulphate polyacrylamide gel electrophoresis
SDS-PAGE-NR	Sodium dodecyl-sulphate polyacrylamide gel electrophoresis – (Non-reduced Coomassie Blue)
SDS-PAGE-R	Sodium dodecyl-sulphate polyacrylamide gel electrophoresis – (Reduced Coomassie Blue)
SEC	Size Exclusion Chromatography
SE-HPLC	Size-exclusion high-performance liquid chromatography
SJIA	Systemic juvenile idiopathic arthritis
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TNF	Tumour necrosis factor
UF/DF	Ultrafiltration / Diafiltration
US	United States
WCB	Working cell bank
WFI	Water for injection

1. CHMP Recommendation

Based on the review of the data on quality, safety and efficacy, the hybrid application according to Article 10(3) of Directive 2001/83/EC for Rilonacept powder for solution for s.c. injection weekly in the treatment of:

"Rilonacept is indicated in adults and paediatric patients from 12 years for the treatment of idiopathic recurrent pericarditis and reduction in risk of recurrence."

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Clinical-Benefit/Risk:

1. Considering the high incidence of pericarditis recurrence of 74% in the placebo group, the population included in the RHAPSODY study was limited to patients at high risk for recurrent pericarditis despite a combination of therapies. The Applicant is asked to discuss whether this should be reflected in the indication.
2. Data supporting an indication in patients aged 12 – 17 years are limited. In the pivotal Phase 3 study, only 7 patients aged 12 years to 17 years were treated with rilonacept subcutaneously for a median duration of 15 weeks. No results were presented on efficacy and safety for paediatric patients 12 – 17 years separately, only 3 out of 7 patients included in the RI period embarked the RW period. It should be justified that data are sufficient to conclude on a positive benefit risk balance in the paediatric population. Consistency of efficacy between adults and paediatric patients should be discussed. The applicant is also asked to discuss the possibility to extrapolate from adults to children based on PK bridging.

Quality

3. The pharmaceutical form of the final drug product stated on the MA application form is the same as for the reference product Rilonacept Regeneron - "powder and solvent for solution for injection". However full information on the manufacture and quality of the solvent is missing from the submitted Module 3 which is not acceptable. The dossier should be updated to contain full information of all aspects of the intended applied dosage form. Module 3 and respective parts of Module 2 containing adequate information of the solvent intended to be used with lyophilised powder should be submitted as part of MA documentation.

1.1. Questions to be posed to additional experts

Not applicable.

1.2. Proposal for inspection

1.2.1. GMP inspection(s)

A request for GMP inspection is not required.

1.2.2. GCP inspection(s)

The applicant claims that all clinical studies in the recurrent pericarditis (RP) programme were conducted in accordance with the ICH and GCP guidelines, national regulatory requirements, and the current Declaration of Helsinki.

A routine GCP inspection for Rilonacept was adopted by the CHMP on 14 Nov 2024 (results pending, proposed deadline for availability of inspection report: 06/06/2025).

1.3. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no EMA authorised orphan medicinal product for a condition related to the proposed indication.

1.4. Derogation(s) from market exclusivity

Not applicable

2. Executive summary

2.1. Problem statement

Disease or condition

The therapeutic indication proposed by the Applicant in section 4.1 of the SmPC is as follows: *"Rilonacept is indicated in adults and paediatric patients from 12 years for the treatment of idiopathic recurrent pericarditis and reduction in risk of recurrence."*

Aspects of development

ARCALYST® (rilonacept) was approved by the FDA in the US on 27 Feb 2008 for the treatment of cryopyrin-associated periodic syndrome (CAPS), including familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome (MWS) in adults and children aged 12 years and older and later on 16 Dec 2020 also for the deficiency interleukin-1 receptor antagonist (DIRA) syndrome and on 18 Mar 2021 for treatment and risk reduction of recurrent pericarditis in adults and children 12 years and older.

Rilonacept (Rilonacept Regeneron, previously ARCALYST) received marketing authorisation under exceptional circumstances (EU/1/09/582/001) in the EU on 23 Oct 2009 for the treatment of Cryopyrin-associated periodic syndrome (CAPS), including familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome (MWS) in adults and children aged 12 years and older.

Based on a request from Regeneron Pharmaceuticals Inc., the marketing authorisation was withdrawn as of 25 Oct 2012 in EU. The withdrawal was a business/commercial decision and was not related to any concerns with the safety or efficacy of ARCALYST.

Recurrent pericarditis has been recognised as an orphan disease in both the United States (US) and the EU. On the 06 January 2021, orphan drug designation was granted by the European Commission (EU/3/20/2390) for rilonacept for the treatment of idiopathic pericarditis.

The original ownership of the Biologics License Application for ARCALYST (rilonacept) was held by Regeneron Pharmaceuticals, Inc and was subsequently transferred to the Kiniksa Pharmaceuticals (UK), Limited on 19 Jan 2021.

The applicant claims that drug substance manufacture is a continuation of manufacture of rilonacept by an established process initially used to produce the reference product Arcalyst.

Epidemiology and risk factors

In the Western world, the incidence of acute pericarditis in the general population is estimated as approximately 27.7 cases per 100,000 subjects per year, whereas the standardized incidence rate of hospital admissions for pericarditis is 3.32 cases per 100,000 person-years. Pericarditis, similarly to myocarditis, is more common among younger males.

Biologic features, aetiology and pathogenesis

Pericarditis is an inflammation of the pericardium and may be due to one of a number of causes including viral, bacterial, fungal or parasitic infection, cancer and/or cancer treatments such as chemotherapy and radiotherapy, autoinflammatory diseases, kidney failure (uraemia) and as a complication from a heart attack or heart surgery.

80% of the pericarditis cases in developed countries are either post viral or "idiopathic" in that it cannot be attributed to a specific condition (Imazio 2010; Zayas 1995).

Clinical presentation, diagnosis and stage/prognosis

Diagnosis of pericarditis is based on the presence of chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic changes, pericardial effusion, and/or elevated markers of inflammation (white blood cell count, C-reactive protein [CRP], or erythrocyte sedimentation rate).

Recurrent pericarditis (RP) is characterised by the recurrence of pericarditis signs and symptoms after a symptom-free period of at least 4 to 6 weeks. Recurrent pericarditis affects 15% to 30% of patients who have had an initial acute pericarditis episode (Adler 2015).

Patients with pericarditis can develop serious, life-threatening complications, such as pericardial effusion, cardiac tamponade and constrictive pericarditis. (Imazio 2005; Imazio 2007).

Management

There are no EMA-approved therapies for pericarditis. In some EU countries, colchicine is nationally approved for the treatment of pericarditis. Conventional therapy with various non-specific inhibitors of inflammation, e.g. aspirin, NSAIDs, and colchicine, show only limited effects, especially in colchicine-resistant patients. In patients with severe disease, inadequate response to conventional therapy, and/or continued recurrence, corticosteroids are usually added on. In patients with continued recurrence, other exploratory immunomodulators are also used (Adler 2015). In the most severe cases, in patients with chronic recurrent pericarditis in whom medical management has failed, pericardiectomy, a major surgical procedure, is frequently performed, with additional risk of mortality and morbidity (Khandaker 2012).

There are significant limitations with all existing therapeutic options. Conventional anti-inflammatory therapies, as well as corticosteroids, are frequently associated with significant adverse outcomes, especially in the case of long-term corticosteroid use, which has been shown to be associated with weight gain, cushingoid appearance, osteoporosis, osteonecrosis, infections, diabetes, and cataracts, in

addition to the risk of adrenal insufficiency upon withdrawal (Adler 2015; Soler 2004). If not controlled, RP patients typically end up receiving chronic corticosteroid treatment, accompanied by the associated severe side effects and/or need risky surgical treatment.

Recent clinical data (Klein 2021a) support the targeted IL-1 pathway inhibition ahead of corticosteroids to effectively manage recurrent pericarditis without the known adverse effects associated with corticosteroids. These recent data support a paradigm shift according to a steroid-sparing strategy to effectively manage recurrent pericarditis and improve patients' quality of life. The only EU-approved (national approvals only) treatment, colchicine, is not effective in a considerable proportion of patients with recurrent pericarditis (RP), and its use is often associated with gastrointestinal (GI) side effects, e.g. diarrhoea (Andreis 2021).

Due to the limitations of available therapies and the frequent persistence or recurrence of pericarditis despite therapeutic efforts, there is a high unmet need for new targeted treatments for recurrent pericarditis that have an acceptable safety profile which also allow for the sparing of corticosteroid use and pericardiectomy procedures. Selectively targeting the inflammatory pathway involving the cytokine interleukin-1 (IL-1) is considered one of the most promising approaches to meet this unmet clinical need (Andreis 2021).

2.2. About the product

Rilonacept is a novel therapeutic molecule designed as a soluble decoy receptor ("cytokine trap") for the blockade of inflammation caused by the cytokines interleukin-1α and interleukin-1β which are the primary pro-inflammatory cytokines implicated as a causative factor in recurrent pericarditis (RP).

2.3. The development programme/compliance with CHMP guidance/scientific advice

Development programme

Rilonacept was investigated in 24 completed clinical studies for various therapeutic indications. However, only two clinical studies (one Phase 2 study C001 and the RHAPSODY Phase 3 study C002) were performed for the recurrent pericarditis (RP) target indication.

In the two completed clinical studies for the recurrent pericarditis (RP) target indication, a total of 111 patients have received at least 1 dose of rilonacept: 25 patients in the Phase 2 study and 86 patients in the RHAPSODY Phase 3 study.

Scientific Advice

The Applicant received Scientific Advice on the development of Rilonacept for the treatment of idiopathic pericarditis from the CHMP on 13/10/2022 (EMA/SA/0000103922). The Scientific Advice pertained to the following Quality, non-clinical and clinical aspects:

• Adequacy of the description of the cell substrate and cell line characterisation, including impurity profile, for commercial manufacturing of the finished product
• Sufficiency of the nonclinical safety program performed for a previous indication to support an MAA in the current indication
• Adequacy of the overall clinical development program for the determination of the benefit-risk in the intended indication, including sufficiency of the expected safety database.

At the time of the scientific advice the two clinical studies were already finalized. Time-to-first pericarditis recurrence was accepted as a primary efficacy endpoint, if supported by data on concomitant medication,

maintenance of efficacy and relevance for patients. It was noted that the number of paediatric patients included in the phase 3 study is limited and the robustness of these data will be a matter of assessment. It was mentioned that relevance of the efficacy results for the population in the EU will have to be discussed at the time of a MAA.

Regarding safety it was noted that even when considering other indications and post-marketing experience the numbers do not entirely meet the requirements of ICH E1. However, in rare diseases, feasibility often limits safety information available at the time of a MAA. Whether collecting additional information on safety is needed post-marketing would be a matter of assessment. Safety concerns associated with the mechanism of action (e.g., underlying infections, tuberculosis, unknown impact in patients with underlying cancer disease, patients with neoplasms as a reason for pericarditis) should be sufficiently addressed in the dossier.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

For the active substance manufacturing authorisations granted by US-FDA up to December 2024 and reflected by representative screenshots thereof are provided for several listed DS manufacturers.

For the US sites included in rilonacept finished product manufacturing activities, screenshots are provided on 'Certificates per FDA inspection classification database', indicating the latest GMP inspection and outcome. In general, acceptable certificates of conformance with GMP are available. For the EU batch certification site, a valid GMP certificate is available in the EudraGMP data base.

No product-related pre-approval GMP inspection is currently considered necessary according to the manufacturing authorisations provided.

GLP

All pivotal nonclinical safety studies (safety pharmacology and toxicology studies) were conducted in conformance with the principles of Good Laboratory Practice (GLP).

GCP

All clinical studies in the recurrent pericarditis (RP) programme were conducted in accordance with the ICH and GCP guidelines, national regulatory requirements, and the current Declaration of Helsinki.

A routine GCP inspection for Rilonacept was adopted by the CHMP on 14 Nov 2024 (results pending, proposed deadline for availability of inspection report: 06/06/2025).

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(3) of Directive 2001/83/EC (hybrid application).

The chosen reference product is ARCALYST (rilonacept) which was approved in EU for the treatment of Cryopyrin-Associated Periodic Syndrome (CAPS), familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) in adults and children aged 12 and older on 23 October 2009 (EU/1/09/582/001) and withdrawn in the EU on 25 October 2012 for commercial reasons.

2.5.2. Orphan designation

Orphan designation EU/3/20/2390 was granted on 06 January 2021 by the European Commission for rilonacept for the treatment of idiopathic pericarditis.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

2.5.3. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no EMA authorised orphan medicinal product for a condition related to the proposed indication.

2.5.4. Derogation(s) from orphan market exclusivity

Not applicable

2.5.5. Information on paediatric requirements

According to the "European Medicines Agency procedural advice for users of the centralised procedure for similar biological medicinal products applications", there are no paediatric requirements for an EU hybrid MAA in accordance with EU Directive 2001/83, Article 10(3).

It was confirmed by the EMA on the pre-submission meeting with the Applicant on 7 June 2024 that an agreed paediatric investigation plan (PIP) is not needed to validate an MAA under an Article 10(3) hybrid submission.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The active substance rilonacept, also referred to as interleukin (IL)-1 Trap, is a dimeric fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human IgG1. Rilonacept incorporates in a single molecule the extracellular domains of both receptor components required for IL-1 signalling: the IL-1 Type I receptor (IL-1RI) and the IL-1 receptor accessory protein (AcP). Rilonacept is a dimeric glycoprotein with a calculated total MW of ~251 kDa, of which 80% is protein (201 kDa) and 20% is carbohydrate (50 kDa). The dimeric rilonacept binds a single molecule of IL-1β with high affinity.

Rilonacept is a potent in vivo inhibitor of IL-1, since binding of IL-1 by rilonacept blocks the bioactivity of the cytokine interleukin-1. It has the advantage that because of its structure, the Fc portion of rilonacept provides the basis for dimerization and a long circulating half-life.

The finished product is presented as lyophilised powder in 20 mL glass vials, each containing 220 mg rilonacept as active substance. Reconstitution with 2.3 mL of sterile water for injection yields 2.7 mL solution with a drug substance concentration of 80 mg/mL. 2 mL can be withdrawn to receive a dose of 160 mg rilonacept.

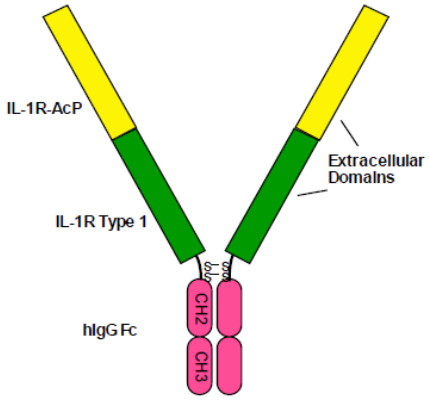
Other ingredients are: histidine, histidine HCl monohydrate, polyethylene glycol 3350, glycine, L-arginine HCl and sucrose.

The product is available in clear type I glass vial with rubber stopper and lacquered flip-off aluminium seal as described in section 6.5 of the SmPC.

3.1.2. Active Substance

3.1.2.1. General Information

Figure 1: Active substance structure



3.2.S.2.1 Manufacturer(s)

3.1.2.2. Manufacture, process controls and characterisation

Manufacturing process and process controls

The active substance, presented as formulated bulk drug substance, is manufactured by Regeneron Pharmaceuticals, Inc.

The manufacturing process is described in a clear, transparent way including the performance/handling at each process step together with respective controls established (process parameters and in-process tests). All controls are additionally tabulated with their action limits / set points / target ranges for each process step.

Briefly, CHO-cells from a cell bank vial are sequentially expanded via a number of steps to reach a volume sufficient to inoculate the production bioreactor

The product-related quality attributes are tested and controlled by the release specification as no batch with insufficient purity will pass the criteria.
A number of inconsistencies are observed within the narrative or between information provided tabulated versus the accompanying narrative thus clarification is requested.

Clarification is further necessary with respect to the formulation step. Apparently, two versions of formulation exist, historical and current, but cannot be derived from the data presented. Since this is a relevant aspect for comparability of the current rilonacept with that manufactured for the former product Arcalyst, the Company needs to adequately address this discrepancy also providing information on the various buffers used after virus filtration in preparation for and for the formulation step. The composition of the final formulated drug substance should be stated.

Control of Materials

The control strategy applied to qualification of raw materials is described with sufficient detail. Chemical raw materials are either controlled by compendial specifications or by respective in-house specifications that are provided. Formulation excipients are of the required compendial grade. Sufficient information on control of non-chemical raw materials including chromatography resins and membranes / filter material is presented as well.

Control of Critical steps and Intermediates

The rationale for classifying controls as critical or non-critical is discussed. As already mentioned above, the Company considers safety-related parameters as critical. This includes all steps and parameters that are related to potential presence /removal of adventitious agents or microbes. While all relevant virus-related controls are considered critical, it appears that a risk-based approach was applied in control of bioburden. This is not consistently reflected in narrative and tabulated summaries. Hold times are established for various intermediates and are discussed with more detail in the process validation section.

Process validation

Manufacture of Rilonacept at the commercial manufacturing site of Regeneron in Rensselaer was successfully validated in 2005 for the MAA of Arcalyst. Validation included evaluation of the manufacturing process, formulation of DS (i.e. UF/DF solution), intermediate and media hold times, filter challenge, resin reuse, membrane lifetime, transport and shipping.
According to the Applicant of the current MAA, the validation data of 2005 are still applicable and thus no new process validation data were submitted. Quality follow-up measure (FUM 2) from Arcalyst CHMP Assessment report in 2009. has been resolved in the current MA documentation. A review and recalculation of IPC action limits was undertaken after commercial scale batches since product approval. These recalculated limits have been the valid IPCs for the process since then.

When comparing the list of IPCs applied in 2005 and those recalculated and implemented to the process as reflected by the current manufacturing process description, it can be resumed that very little change was implemented. Based on this observation, it is acceptable not to repeat process validation. However, as none of the batches manufactured for the current MAA with the new indication is reflected in the data provided so far, it is expected that at least continued process verification data are provided on the batches manufactured up to today. The Company is therefore asked to provide data to support successful "continued process verification" with batches manufactured since 2010. A review and recalculation of IPC action limits is expected. In order to substantially support that Rilonacept is 100% identical to Arcalyst, these data are essential.

No obvious difference exists between the data on formulation of DS at the time of process validation and since commercial production. However, the Company indicates differences between the historical formulation process and that currently performed. If this is the case, the formulation of the drug substance may need to be re-validated. Therefore, the Company is asked to substantially describe the differences between the historical formulation process and the current formulation process and clarify any potential impact of difference in formulation on DS quality and comparability of DS according to the historical and the current formulation process.

Elucidation of Structure and other Characteristics

Characterisation as such is considered comprehensive. It comprises physical, chemical and biological characterisation of Rilonacept. This includes verification of amino acid sequence and N- and C-terminal variability, verification of correct disulphide bonding, charge variant and size variant analysis, as well

as methionine oxidation and asparagine deamidation analysis. Investigation of methionine oxidation and asparagine deamidation using peptide mapping in combination with liquid chromatography and mass spectrometry (LC/MS) resolves Quality FUM 5. Glycan structures were analysed by various orthogonal methods at high level of detail. Based on comparable, consistent tryptic peptide maps, only one of the four characterisation batches was in-depth analysed. Analysis includes mass spectrometric detection of glycopeptides with all N-glycan structures detected for each site, an orthogonal oligosaccharide profile analysis of the overall N-glycan moiety, and a separate analysis of N-glycan structures for each glycosylation site. The oligosaccharide profile was alternatively analysed by MALDI-TOF MS with assignment of sugar structure to the masses observed. Finally, oligosaccharides were also analysed by capillary electrophoresis with fluorescence detection. By this method, a number of peaks remained unidentified. Since, structural identification should have progressed since 2005 the Company is expected to provide updated results.

Two biological assays are performed. The Company is asked for some complementary information on the assays.

Impurities

The residuals of process- and product-related impurities were characterised by various approaches. Levels of the main process-related impurities were presented for P1 to P4 batches demonstrating that levels are below the established acceptance criteria. For the huge number of process additives a worst case calculation of removal by the final UF/DF step was established. The estimated levels are well below levels of potential concerns.

Impurities leaching from the chromatography column, added buffer are cleared to consistent, acceptable levels.

Those leachables and extractables known to be potentially present from use of tubings, bags, filters and resins, and classified as high risk category were evaluated with biological reactivity tests and found to be low risk.

Product-related impurities comprise HMW species and LMW species.

No obvious change is observed in accelerated and stress stability studies with respect to one parameter. Thus, oxidation is not routinely controlled.
Overall, investigation of impurities is considered satisfactory.

3.1.2.3. Specification (s)

The active substance specification shown in the table below includes tests for appearance, pH, bioburden, endotoxins (Ph. Eur.), total protein content (UV measurement), potency (target protein binding and secondly, cell-based response assay).

In general, the specification is considered adequate to control FDS quality. However, the level of protein degradation via e.g oxidation is currently only indirectly controlled by iCIEF, whilst peptide mapping is mentioned as an analytical method for the reference standard, it is not included in the DS specification. The Applicant should introduce peptide mapping as an additional method to control protein degradation. (**OC**)

The Applicant has justified many acceptance criteria based on the mean ± 3SD of a defined set of data, which is in general considered acceptable. However, the Applicant should tighten the specifications based on historic data taking into account the additional manufacturing history, including all batches, unless otherwise justified. (**OC**) In regards to bioburden analysis, the Applicant should also justify, why the

monocyte activation test method is not performed instead of the LAL method, to adequately control non-bacterial pyrogens. (**OC**)

The analytical methods used have been adequately described and most non-compendial methods have been validated towards accuracy, precision, specificity, linearity, range and robustness. The general validation approach is considered acceptable. However, the following points should be made regarding individual methods. In the validation for method specificity should be evaluated and an exemplary chromatogram of the method should be added. (**OC**) Validation of the isoaspartate assay finds that precision is low, for many proteins and peptides denaturation or cleavage may be required. The Applicant should clarify if this has been evaluated and if not, should evaluate this. (**OC**))

Batch analysis data of the active substance are provided, of which 31 are according to the currently applied for DS specification. In general, the results are acceptable, there were temporary problems with one impurity, and the Applicant is asked to explain the reason for the OOS results and which corrective actions were taken. (**OC**)

In Arcalyst MAA specifications in the Drug Substance part of the dossier were applied to DS release and in the current Rilonacept MAA specifications are applied to FDS release and stability. In case of Arcalyst, the DS was an intermediate that was formulated to FDS. The information of FDS was given within the Drug Product section of the dossier, not in the Drug Substance part as in the current Rilonacept application. This however is not regarded as critical and can be considered acceptable.

Some differences in FDS release specifications between current Rilonacept and previous Arcalyst applications were observed during the evaluation. These changes made are considered acceptable. Bioburden acceptance criteria have been tightened notably from.

Reference Standards and Materials

It is acknowledged that at the time of development of rilonacept for the MAA of Arcalyst, no reference was available, thus an extinction coefficient had to be empirically calculated and experimentally confirmed. However, from the time of licensing onwards, reference standards for rilonacept were available. It is therefore unclear to which standard the first in-house reference standard established for the current MAA (PDRS-IL1T-2) refers to. The reference standard system discussed in the current application is thus disconnected from reference standards in previous Arcalyst MA. Clarification is requested.
Moreover, it is noted that apparently no two-tiered system exists for the reference standards, i.e. a primary reference standard and a working standard. The reference standards are in-house standards, no primary reference standard is available. This situation questions how the Company will prevent drift in quality attributes for each new reference standard established. The acceptance criteria for biological activity (relative potency by bioassay (65 – 140%) and relative potency by binding assay (75 – 130%), used in release of the drug substance, need to be sufficiently tightened for "single" reference standard qualification. It is highly recommended to use a two-tiered system for the reference standards.
The current reference standard (RS) (PDSRS-IL1T-6) was manufactured from the filtered UF/DF pool of clinical batch no. 8001800028 (manufactured 14.02.2018) and is representative of the FDS and DP, differing only in the protein concentration and formulation buffer excipients (55 mg/mL vs. 40 mg/mL). Qualification results for all reference standards generated since establishment of PDRS-IL1T-2 are provided. A protocol for establishment of future reference standards is also available. This is endorsed.

Container Closure System

Rilonacept FDS is dispensed into sterile containers, all resins and colorants used comply with the latest revision of EMA/410/01. The purchased component(s) used in this product also comply with the latest revision of EMA/410/01. The manufacturer has the information on file that the components to

manufacture this step have passed United States Pharmacopoeia (USP) class VI testing and comply with USP <661> requirements.

The assembled bottles and caps are sterilized by gamma irradiation and dosimetric released per ISO 11137.

The bottle and the closure packed as a single unit. The same container closure system is used for stability studies. The provided information is acceptable and also identical to container closure system described for FDS in Arcalyst MA.

Stability

Stability data from commercial scale batches of active substance from the manufacturer under long term conditions (-20 ºC) and for up to 6 months under accelerated conditions (5 ºC) according to the ICH guidelines were provided. Since 2019, 48, 24, 18 and 9 months of stability data are available. At long-term storage, most parameters are stable, with the exception of small changes in purity . Storage at 25 °C over 7 days showed no OOS results and only some changes in purity as determined. Short-term-excursions will thus probably not affect FDS quality negatively. Photostability testing was performed on one batch using Option 2 light sources as described in ICH Guidance for Industry, Q1B: Photostability Testing of New Drug Substances and Products.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. While the stability results generally support the proposed retest period in the proposed container, the Applicant should clearly identify, which stability studies were performed according to the currently applied for specification and the current methods. Additionally, the Applicant should update the ongoing stability studies. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA. (**OC**)

The Applicant states that the containers used for stability studies are representative of the 1 L bottles from the manufacturing process and is asked to demonstrate how these containers are representative. (**OC**)

The analytical methods used were the same as for release and from the currently applied-for specification, acceptable stability-indicating parameters were studied.

Due to the historical manufacturing process, data from primary and secondary FDS stability studies are presented. Presented stability data are generally considered acceptable, although some values are considered OOS for the current specification. As this regards results from previous methods with different specifications, this is still acceptable. There were no meaningful trends overall despite the small statistically significant trends observed. Some discrepancies are observed in one product-related impurity using a preliminary method in older studies and stability stopped reporting that impurity in some timepoints before the validation of the method. The method was then validated to test this impurity. However, there were some issues with commercially-sourced reagents used in the validated method, which prompted the development and validation of a modified method. An update of acceptance criteria of the formulated drug substance and drug product specifications followed. Impurity test results meet current acceptance criteria in more recent stability studies using the modified method.

However, it is unclear, when new specifications were applied, as there is conflicting information in section 3.2.S.4.4 (batch analyses) and S.7.3. (Stability data). The Applicant should clearly identify, which stability studies were performed according to the currently applied for specification and the current methods. Additionally, the Applicant should update the ongoing stability studies. (**OC**)

The Applicant commits to add at least one commercial batch of Rilonacept FDS annually to the ongoing stability program (provided manufacture occurred during the calendar year) and analyse it according to the specification. This is endorsed.

3.1.3. Finished Medicinal Product

3 . 1 . 3 . 1 . Description of the product and Pharmaceutical Development

The finished product is presented as a lyophilized powder in 20 mL glass vials each containing 220 mg rilonacept. Reconstitution with 2.3 mL of sterile water for injection yields 2.7 mL solution with a drug substance concentration of 80 mg/mL. 2 mL can be withdrawn to receive a dose of 160 mg rilonacept. There is an overfill of 0.7 mL.

The composition of the finished product is presented.

Rilonacept is the drug substance contained in the rilonacept finished product. All excipients included in the rilonacept FP are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Seq 0001 eAF with pharmaceutical form "powder and solvent for solution for injection" is noted to be not consistent with Module 1 and Module 3 documents and thus, it needs to be clarified for which pharmaceutical form the Applicant applies. Either the pharmaceutical form in the eAF should be revised (See seq 0000, "powder for solution for injection") or, documents should be updated to contain full information of all aspects of the applied dosage form. In the latter case, Module 3 and respective parts of Module 2 containing adequate information of the solvent intended to be used with lyophilised powder should be submitted as part of MAA documents. This is raised as a **Major Objection (MO)**.

Comprehensive investigations had been performed to justify the choice of the components of the formulation mixture and their quantities. The results presented support final composition to be optimal for drug product stability. The robustness of the manufacturing process was examined by varying a subset of process parameters and their effect on drug product stability. Formulation and manufacturing process development took into account the applicable critical quality attributes (CQAs) for a sterile lyophilised powder in vials.

Comprehensive studies were carried out to optimise lyophilisation process with regard to water content, IL-1 Trap stability, pH, reconstitution time and quality of the dried cake. The results justify the conditions chosen for the commercial process. Finally, the quality of the dried powder was assessed by conducting characterisation studies with the reconstituted drug product after lyophilisation with the optimal process. No significant differences were observed when compared with pre-lyophilised and liquid formulations. This result supports the lyophilisation conditions chosen. Vial location in the commercial lyophiliser was demonstrated to have no effect on drug product quality and the acceptance criteria established for water content in the specification of the drug product were evaluated with refer to IL-1 Trap stability.

Suitability of the container closures system chosen for lyophilised drug product was confirmed with respect to moisture exposure, gas permeation and closure integrity. Considering the state of the drug product (lyophilised cake) the lack of interaction studies and leachable monitoring is considered acceptable. The primary packaging is clear type I glass vial with rubber stopper and lacquered flip-off aluminium seal. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The finished product is reconstituted with sterile WFI before administration. In-use and compatibility with the primary packaging materials are discussed in the stability section.

Manufacture of the product and process controls

The batch size for the finished product will result in a stated number of vials. Multiple different FDS batches can be pooled for one finished product batch.

The manufacturing process of rilonacept finished product is a standard aseptic filling process consisting of thawing of FDS batches, pooling and dilution of multiple formulated drug substance batches, sterile filtration, vial filling and partial stoppering, lyophilisation and oversealing, visual inspection, secondary packaging and labeling. In general, the manufacturing process is described in sufficient detail in the application file including information on control parameters such as mixing times, hold times and temperatures. Tests for in-process controls are indicated. There seem no differences to the finished product manufacturing process approved in 2007. Sterilisation of the container components (vials and stoppers) is requested to be described. (**OC**)

As in 2007, the proposed IPCs and their limits are generally acceptable based on the validation of the drug product manufacturing process.

For FP manufacturing process validation, data are presented for three consecutive FP batches that have been manufactured in 2006 using the commercial process. These data have already been evaluated in the precedent MAA in 2007. In addition, PV data are provided from three consecutive rilonacept batches manufactured in 2009 and using the full-scale commercial process. Results provided for process parameter and in-process tests were found complying with the acceptance criteria. In addition, data are presented for two batches reflecting lyophiliser shelf homogeneity. These data complied with the acceptance criteria.

In general, sufficient information has been provided on the qualification of the sterelising filters used for aseptic processing including study results for filter retention capacity, solution compatibility and filter extractables. Filter integrity limits are defined for the FP manufacturing process.

The proposed hold time is considered justified based on the provided study results.

The presented media fill results including results from media fills under stress conditions, are considered adequate for demonstrating the aseptic filling process for rilonacept with the specific type of vial and for the proposed filling duration is in a validated status.

There are no intermediates in the rilonacept DP manufacturing processes.

Overall, the proposed control strategy seems adequate and can be agreed.

Regarding shipping of formulated drug substance in bottles, narration of the validation procedures performed and test results provided support the conclusions of the Applicant, i.e. that the quality and physicochemical properties of the Rilonacept DP were demonstrated being not impacted by the shipping conditions evaluated.

All excipients used for manufacturing rilonacept DP are of compendial grade of the Ph.Eur. quality and controlled in line with the current version of the respective Ph.Eur. monographs. The sterilisation of excipients is a critical process and the sterility of the excipients including nitrogen gas is a critical quality attribute to ensure the sterility of the finished drug product. The nitrogen gas should be included in excipients table as footnote. As nitrogen is used in the final step of DP manufacture as backfilling gas, the sterility of nitrogen according to EU GMP, Annex 1 quality standards should be confirmed and the sterilisation method used for excipient nitrogen gas should be included in dossier ***(OC).***

3.1.3.2. Product specification (s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form (appearance, content, identity, potency, purity and impurities and general tests). The general tests include pH, reconstitution time, subvisible particles, sterility, CCIT, endotoxin and product related variants.

Overall, the release testing program complies with the FP specification concluded on the MAA in 2007. The proposed FP specification is considered sufficient to control drug product quality. As regards determination of potency and product-related variants/impurities, the proposed acceptance criteria should be reconsidered, and the provided justification of specification should be revised by inclusion of more recent rilonacept FP batches into the calculations.

Product-related and process related impurities are evaluated in the respective DS Sections. There is no need for further investigation of leachables based on the results of the extractables studies.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Most of the analytical procedures included in the FP specification are also used for DS testing and therefore, reference is made to the respective drug substance parts. As regards the provided data on analytical procedure validation, usage of FP samples is sufficiently covered.

The same reference standards are used for both active substance and finished product. Reference is therefore made to the active substance section.

The provided batch data comprising FP batches manufactured between 2005 and 2023 were found complying with the acceptance criteria being in place at the time of analysis. These FP batches were manufactured using the commercial process but varying batch sizes. However, batch data are missing for two of the three PPQ lots. Moreover, it is unknown, which FP batches have been used in the 'Recurrent pericarditis' clinical studies and whether batch data have been presented. This should be clarified. (**OC**)

Stability of the product

In the precedent MAA in 2007 and based on the 'primary stability' data a FP shelf life of when stored at 2-8 C was concluded. Besides long-term stability data, stability data obtained under accelerated conditions were presented.

In accordance with the post-approval stability protocol and stability comment, supportive stability data were generated from the annual stability batches encompassing 2008-2023 (except 2010 and 2014).

Since the FP manufacturing process remained unchanged since precedent approval in 2007, these stability data can be taken into account.

Stability data from batches (commercial scale, ½ commercial scale) of finished product stored for under long term conditions according to the ICH guidelines were provided. The batches of rilonacept medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In general, samples were tested for the FP shelf-life specifications. The analytical procedures used are stability indicating. However, since testing the amount of endotoxin is usually conducted at least at the end of shelf life the Applicant should consider including the parameter into the FP shelf-life specification as well as to revise the stability testing plan respectively. (**OC**)

Based on the available data no significant changes have been observed. The lyophilized drug product in its commercial CCS demonstrates sufficient stability when stored. Respective stability data from long-term storage conditions remain within pre-defined acceptance criteria.

Photostability had already been assessed in the previous MAA in 2007. It was concluded to include the statement 'Keep the vial in the outer carton in order to protect from light' into the SmPC.

In-use stability, i.e. stability of the FP after reconstitution with WFI has been adequately addressed in Section 3.2.P.2.6. Based on the data, the following statement is (already) included in the SmPC: 'The prepared solution may be kept at room temperature (15 °C to 25 °C) but protected from light. From a microbiological safety point of view, the product should be used as soon as possible after reconstitution with water for injection - within 4 hours after reconstitution - because it does not contain a preservative.'

Post approval change management protocol(s)

N/A

Adventitious agents

No raw materials of direct human/animal origin are used during DS / DP manufacturing. FBS (covered by EDQM TSE Certificates of Suitability) was used at the developmental cell bank level. Only materials with indirect source of animal origin are used during production. Risk regarding TSE is adequately addressed and is considered negligible for these materials.
The extent of virus testing of the cell banks (MCB, WCB, EOPCs) is in accordance with ICH Q5A and considered adequate.
The extent of routine testing of unprocessed bulk harvest for adventitious viruses is adequate.
Three steps have been investigated in virus validation studies. Virus validation reports representative for the P4 process could not be located and should be provided to resolve issues discussed below. **(OC)**
. Clarification is requested on virus carry-over runs. **(OC)**. Concerning viral filtration, the information provided is currently not considered sufficient. Clarification is requested whether a post filtration flush and pressure release occurs during manufacturing. **(OC)** Significant flux reduction was seen for some runs, and information is requested on the virus stocks used for spiking the filtration runs. **(OC)** Clarification is requested how (filter load) potentially caused by freezing/thawing are excluded **(OC)** and on representativeness of the filter load material (P3 vs. P4 material), which was used for small scale model qualification / virus validation. **(OC)**
. Clearance for small non-enveloped model viruses such as MMV is not considered optimal, particularly, as virus validation of this step is currently not considered representative for the manufacturing process. The risk assessment concerning retrovirus like particles is deemed adequate.

. Risk assessment for Parvoviridae (and other small non-enveloped viruses) removal during full-scale manufacturing process should be provided. **(OC)**

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The application for Rilonacept finished product containing rilonacept as active substance is not approvable from a quality point of view since one major objection (MO) has been identified. The MO pertains to the pharmaceutical form of the finished product which is different between the eAF and the provided Module 1 and Module 3 documents. In addition, a number of other concerns have been noted which need to be addressed by the Applicant. These deficiencies are described in detail in the assessment report and are reflected in the LoQ below.

Manufacture of the drug substance is described with sufficient detail including flow chart and process controls performed during upstream and downstream processing. Only few comments or requests for clarification are made. Drug substance manufacture is a continuation of manufacture of rilonacept by an established process initially used to produce the product Arcalyst. By comparison of the process flow and IPCs used for the former product Arcalyst and those used for this current product only very minor adaptations are noted that reflect evolution of a process over time. Therefore, no new process validation was performed. However, it is expected that process verification data of continued process verification are provided to reflect the process in its entirety up to today.

Similarly, characterisation data are those of the formerly produced DS used in Arcalyst. Characterisation is performed with a high level of depth and a large number of orthogonal methods to cover chemical, physical and biological characteristics of the DS. Since DS manufacture is a continuation of manufacture of rilonacept for the former product Arcalyst, clarification is requested on continuation of the manufacture and qualification of the reference standard and on the use of a two-tiered system for reference standards to avoid drift in quality attributes.

The DS specification and analytical methods are largely equivalent to the formerly produced DS used in Arcalyst, except for some method changes. Still, some updates to the analytical methods are requested, as not all methods are considered state-of-the-art. The atypically large amount of commercial manufacturing batch data available shows consistent manufacturing control, as well as is supporting the stability of rilonacept.

Finished product information provided on product development, process development, manufacture and process control is considered generally acceptable. Rilonacept finished product specification is largely equivalent to those for the former FP Arcalyst and is considered sufficient to control drug product quality.

Currently, neither the release nor the stability data for two full-size PPQ batches and most of DP batches used in pericarditis studies have been provided by the Applicant.

The lyophilized drug product in its commercial CCS demonstrates sufficient stabilityover the claimed shelf-life . Respective stability data from long-term storage conditions remain within pre-defined acceptance criteria.

A MO has been raised with regards to the missing information on the manufacture and quality of the solvent that should be provided as part of the Module 3 and subjected to assessment before the marketing authorisation can be positively concluded. Additionally, the correct pharmaceutical form as stated on the MAA form should be updated across the PI texts.

The suitability of the proposed drug product for self-administration is questioned. The Rapporteur also covers this aspect in the Quality report but proposes that the issue is raised in the Clinical part of the report. The rapporteur concern is endorsed.

The stability data for the drug product are presented but final conclusions are depending on the responses to the rapporteurs` raised concerns.

3.2. Concerning adventitious agents safety a few issues are raised. Non clinical aspects

Rilonacept is a fusion protein that blocks interleukin-1 (IL-1) signalling by acting as a soluble decoy receptor that binds IL-1α and IL-1β and prevents their interaction with IL-1 cell surface receptors.

Rilonacept has been developed for the treatment of recurrent pericarditis, and it has obtained Orphan Designation in treatment of idiopathic pericarditis on 6 Jan 2021 (EU/3/20/2390). Marketing authorization in the EU is being sought specifically for the treatment of idiopathic recurrent pericarditis and reduction in the risk of recurrence. Pericarditis is an inflammation of the multi-layered sac that surrounds the heart. It is a life-threatening and chronically debilitating disease involving chest-pain, changes in electrocardiogram, pericardial effusion, and the risk of developing cardiac tamponade and constrictive pericarditis, which can lead to clinical circulatory collapse.

Rilonacept (Rilonacept Regeneron, previously Arcalyst) was approved in the EU under Exceptional Circumstances (EU/1/09/582/001) on 23 Oct 2009 for the following indication:

Rilonacept Regeneron is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older.

The marketing authorization was voluntarily withdrawn by the MAH for commercial reasons on 25 Oct 2012.

Pharmacodynamic, pharmacokinetic and toxicological properties of rilonacept have been described extensively in this previous procedure (EU/1/09/582/001). Therefore, the Applicant has not provided additional studies. The carcinogenicity potential has been reviewed with an up-to-date literature research.

3.2.1.1. Primary pharmacodynamic studies

The pharmacology of rilonacept was characterised extensively in the previous marketing authorization procedure. Rilonacept was shown to have similar binding to human and cynomolgus macaque IL-1β, IL-1α and the endogenous receptor antagonist of IL-1 receptors, IL-1ra, but a lower affinity for murine IL-1β, IL 1α and IL-1ra. A murine analogue (mIL-1 Trap) was generated and engineered using murine IL-1 receptor genes and Fc domain in a manner mimicking the design of the human version. The binding affinities of mIL-1 Trap for murine IL-1 cytokines were of a similar order to those of rilonacept for the human and monkey ligands. No specific binding was observed for any of a standard panel of human or monkey tissues upon visualisation with secondary reagents and chromogenic substrate.

No specific binding was observed for any of a standard panel of human or monkey tissues.

3.2.1.2. Secondary pharmacodynamic studies

Rilonacept blocked the production of IL-6 in response to human IL-1β *in vivo* (mouse). mIL-1 Trap was active in a mouse model of collagen-induced arthritis, in which it blocked the development of arthritic joints and prevented cartilage erosion in the hind limb joints. Neointimal hyperplasia, induced by ligation of a carotid artery in mice, was also prevented by mIL-1 Trap. Rilonacept was immunogenic in two strains

of mice and one of rats. There was no evidence that rilonacept activates complement-dependent or antibody-dependent cytotoxicity Fc effector functions.

3.2.1.3. Safety pharmacology programme

No adverse effects of rilonacept were observed in safety pharmacology evaluations following repeated dosing of cynomolgus monkeys via intravenous or subcutaneous routes of administration at doses up to 60 mg/kg or 100 mg/kg, respectively.

3.2.2. Pharmacokinetics

The pharmacokinetics of rilonacept were investigated in mice, rats and cynomolgus monkeys following single subcutaneous and intravenous administration at doses between 0.3 and 10 mg/kg. Although anti-IL-1 Trap antibodies eventually developed in mice, rats and monkeys, they did not occur early enough to influence the conclusions from single-dose pharmacokinetic studies.

Traditional absorption, distribution, metabolism, and excretion (ADME) studies were not performed, which is acceptable for a glycoprotein. The bioavailability of approximately 60 and 70% following SC administration of rilonacept in rats and monkeys, respectively, supported the clinical use of this route of administration. After IV administration, the decline of the rilonacept in serum is biphasic. The terminal half-lives were 61, 38 - 57, and 64 hours in mice, rats and monkeys, respectively, compared with approximately 1 week in humans. The pharmacokinetic indices of mice, rats and cynomolgus monkeys were similar between males and females within a given species.

Rilonacept was not found in the amniotic fluid or foetal plasma of monkeys, but the samples were collected more than fifty days after the last dose. Antibodies to rilonacept were found in the foetal serum and it is assumed that these were derived from the maternal circulation. It is not known if rilonacept is excreted in the milk.

3.2.3. Toxicology

3.2.3.1. Single dose toxicity

Specific single-dose toxicology studies were not conducted and the CHMP accepted that they were not likely to contribute to the safety evaluation of rilonacept.

3.2.3.2. Repeat dose toxicity

The safety studies include repeated-dose toxicity with periods of recovery in cynomolgus monkeys, and developmental and reproductive toxicity studies in cynomolgus monkeys and mice; The choice of the cynomolgus monkey was justified on the basis of a tissue cross-reactivity study; there was also no evidence of binding to either monkey or human tissues, indicating a low potential for off-target effects.

The most notable toxicological findings when rilonacept was administered SC in the 6-week and 3-month toxicology studies in cynomolgus monkeys were injection site reactions. These reactions, which are thought to be immune-mediated pathologic sequelae rather than a direct effect of the drug, largely resolved during recovery time off drug. Clinically relevant drug concentrations were not maintained over the course of these studies because of an anti-drug antibody response in over 90% of the monkeys that increased drug clearance. Therefore, higher dose and more frequent administration strategies were used in the 26-week studies to increase exposure. Large but relatively infrequent IV doses were administered to achieve high Cmax concentrations with the recognition that drug levels would be low for much of the treatment period because of accelerated clearance.

In a second study, the magnitude of SC dose and frequency of administration were increased to override the antibody response, resulting in sustained drug levels throughout the treatment period. In the 6-month IV study, doses up to 100 mg/kg once every two weeks, which was the highest dose tested, were administered without reaching the NOAEL, although one animal at 100 mg/kg was killed in extremis in week 26 following a urinary tract infection and a few animals had sporadic episodes of emesis.

In the 6-month SC study, doses between 15 and 60 mg/kg were administered three times weekly. There was no signal of an increased rate of infections in animals treated with drug. Drug administration in the two high dose groups of 40 and 60 mg/kg resulted in toxicity, which is considered to have resulted at least in part from an anti-drug immune response. The findings in the 15 and 25 mg/kg three times weekly groups did not preclude administration of drug up to these doses in humans. In the 25 mg/kg group of the 6-month SC toxicology study, mean peak plasma rilonacept levels 24 hours after the first and third doses within the first week were approximately 260 µg/mL and 620 µg/mL, respectively. Twenty-four hours after the last dose and in the presence of antibodies, the mean peak plasma level was approximately 200 µg/mL. Although there was a decrease in mean peak plasma level between the third and the last doses because of circulating antibodies, the mean peak plasma level of rilonacept in monkeys exceeds that of the human single-dose PK with a safety factor of around 4 - 8. Also, the dosage of 25 mg/kg three times per week administered SC (75 mg/kg/week), exceeds the currently planned weekly SC dose in humans for recurrent pericarditis (160 mg/week or 3.2 mg/kg /week for a 50 kg human) with a margin of more than 20.

3.2.3.3. Genotoxicity

Rilonacept is a protein that contains no reactive linker molecules and therefore no genetic toxicology studies have been carried out in accordance with ICH S6(R1) guidance. A review of the manufacturing process did not suggest the potential presence of any impurities likely to be genotoxic.

3.2.3.4. Carcinogenicity

No carcinogenicity tests have been conducted with rilonacept. The absence of carcinogenicity studies was considered acceptable for a monoclonal antibody with a well-known safety profile.

The Applicant provided an up-to-date literature search from peer-reviewed publications about the carcinogenic potential of rilonacept and its molecular pathway as requested in the Scientific Advice (EMA/SA/0000103922): The data indicate that IL-1 is involved in tumor induction, growth and progression when activated. A pro-tumorigenic effect of inhibiting IL-1 has not been described. Based on observations from clinical trials, it was suggested that inhibition of IL-1 might be a therapeutic approach for the treatment of certain cancers. Although clinical data have not yet demonstrated clear anti-tumor effects of other IL-1 inhibitors, namely canakinumab and anakinra, positive trends have been observed in these studies; therefore, it can be considered that the carcinogenic potential of IL-1 pathway inhibition is likely to be very low. There is, moreover, no reason to suppose that rilonacept is likely to have proliferative or mitogenic actions that would suggest a need for further investigation.

However, treatment with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies. This information has been included in the SmPC, section 4.4.

3.2.3.5. Reproductive and developmental toxicity

The toxicological program concerning reproductive toxicity is acceptable, except for the lack of information on placental transfer. The pharmaceutical company Regeneron has committed 2009 in a FUM to conduct an additional embryo-fetal development toxicity study in the Cynomolgus monkey to

investigate this along with exposure data to the conceptus and measurement of hormonal level to the adults. It is not known if rilonacept is excreted in the milk.

3.2.3.6. Local tolerance

Local tolerance was assessed by evaluation of the injection site responses during the repeat-dose toxicity studies. Inflammatory changes were seen at the injection sites in the repeat-dose toxicity studies; during the recovery period, these changes were almost completely reversed. Additional studies of local tolerance were not considered necessary by the CHMP.

3.2.3.7. Other toxicity studies

Since blockade of IL-1 might potentially affect immune function, an assessment of immune function and potential serum complement activation was included as a component of the 6-month SC toxicology study in cynomolgus monkeys: the NK activity of peripheral blood mononuclear cells (PBMC) was examined as a measure for assessing drug-induced immunotoxicity. Rilonacept did not appear to affect adversely or enhance NK activity.

Phototoxicity

No phototoxicity studies were performed.

3.2.4. Ecotoxicity/environmental risk assessment

Due to the peptide structure of rilonacept no environmental risk assessment is considered necessary according to the relevant guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr).

3.2.5. Discussion on non-clinical aspects

Pharmacodynamics, pharmacokinetics as well as toxicology of rilonacept have been described and discussed extensively in the previous market authorization procedure. Further investigations regarding reproductive and developmental toxicology have also been the subject of a FUM.

The current MAA has been submitted based on Article 10(3) of directive 2001/83/EC (hybrid application) with indication for the treatment of idiopathic recurrent pericarditis. The Reference Product is Rilonacept Regeneron, approved under Exceptional Circumstances (EU authorisation number EU/1/09/582/001) for the Treatment of CAPS, including FCAS and MWS in adults and children aged 12 and older, which was granted on 23 Oct 2009 and withdrawn on 25 Oct 2012 by the MAH for commercial reasons.

The posology, patient age range and dosing regimen of the proposed product are the same with the reference product. Hence, the safety margins from the toxicology studies remain unchanged while assuming there are no alterations in drug product quality and that the scientific bridge between the product is established. This is also noted in the CHMP SA. The proposed chronic treatment is supported by 6-month repeat-dose toxicity study in cynomolgus monkeys from the previous application.

In accordance with the SA of the CHMP and the pre-submission meeting with the Rapporteurs it was concluded that there is no need to submit Module 4 but the application can be cross-referenced to the previous MAA. The previous authorisation was based on full new and independent data. For the first EU approval the non-clinical study package was considered adequate, and it is considered also sufficient for MAA for pericarditis indication.

IL-1 is a key cytokine in inflammatory reaction and due to that in inflammatory diseases. Rilonacept was designed to block inflammation caused by the cytokine IL-1. Rilonacept blocks IL1 signalling by acting as a soluble decoy receptor that traps both IL1α and IL1β ligands and prevents their interaction with IL1

cell surface receptors. The Applicant has stated that: "although the pathogenic mechanism of recurrent pericarditis is not completely understood, there is a growing body of evidence that IL1α and IL-1β may be key mediators of multiple autoinflammatory syndromes including RP and that targeting this cytokine may provide important benefits". This concept formed the biological basis for the further clinical development.

Since the current application proposes a different indication from the reference product, this would usually require new primary PD studies in animals. However, as this is a hybrid application and based on the MoA of rilonacept and what is already known from the non-clinical studies performed, the Applicant was recommended to provide required non-clinical data from the published literature. An article from an academic non-clinical trial (Mauro, A, Bonaventura, A, Vecchié, A. et al. The Role of NLRP3 Inflammasome in Pericarditis: Potential for Therapeutic Approaches. J Am Coll Cardiol Basic Trans Science. 2021 Feb, 6 (2) 137–150. https://doi.org/10.1016/j.jacbts.2020.11.016) has been submitted as part of updated non-clinical package for the current application.

The authors have pointed out that acute pericarditis represents a stereotypical response to an acute injury of the mesothelial cells of the pericardium, the trigger being a virus or cellular debris. Those triggers might activate NLRP3 inflammasome – a macromolecular intracellular complex to sense stress or injury and trigger local or systemic inflammatory response through release of proinflammatory cytokines, including IL-1β. IL-1α is another isoform of the IL-1 family, released during cellular injury and triggers the same inflammatory signalling. No direct demonstration of the presence of the NLRP3 inflammasome in the pericardium during an acute episode of pericarditis had been provided before. The study aimed to:

*Detect the presence of the NLRP3 inflammasome in human pericarditis samples;

*Develop an innovative mouse model of acute pericarditis secondary to NLRP3 inflammasome activation.

*Evaluate whether an inhibitory strategy against the inflammasome itself or cytokines involved in the activity of the inflammasome (IL-1α, IL-1β) could be beneficial as a future treatment in patients with pericarditis.

The human samples were obtained from chronic pericarditis patients experiencing an acute flare or from autopsies. The used mouse model was CD1 with adult male mice and the acute pericarditis was generated by Zymosan A that was injected into the mice pericardial space (the agent is a known agonist of the TLR-2 that leads to the activation of NLRP3 inflammasome.)

Treatment was based on 1 of the 6 different intraperitoneal injections with ibuprofen (100mg/kg/day), colchicine (100 µg/kg/day), NLRP3 inflammasome inhibitor (100mg/kg/day), anakinra (100mg/kg/2x in a day), recombinant murine IL-1 trap (a fusion protein mouse homologue of rilonacept; 1, 5, 30mg/kg day every 48h) or vehicle NaCl.

Results showed that the human NLRP3 inflammasome protein expression was detected in all pericardial samples with acute flare of chronic pericarditis. In mice, Zymosan A did induce pericarditis. Also, IL-1α and IL-1β were expressed higher. Effects of IL-1 blockade indicated that treatment with anakinra twice daily (100mg/kg) attenuated pericardial effusion by 13%, IL-1 trap given every 48h reduced pericardial effusion by 43%, 35% and 33% at all 3 doses tested (1, 5, and 30 mg/kg). IL-trap consistently reduced pericardial thickening and the formation of the inflammasome was significantly reduced. The authors admit that this acute inflammatory model may not be representative of the chronic pericarditis as it was conceived to explore the pathophysiological events occurring in acute pericarditis, and not to explore long-term effects as in chronic pericarditis.

Regarding pharmacokinetic profile of the substance there are no new studies, and the pharmacokinetics study package was deemed sufficient during the previous application.

The Applicant has not provided any new toxicology studies as the toxicology package was also deemed sufficient during the last application with one follow-up measure remaining and also, as agreed during the pre-submission meeting regarding the non-clinical submission strategy. However, the Applicant was asked to discuss in the MA documentation available reproductive toxicity studies and to include any pregnancies, lactating/breast feeding information from the post-marketing experience. Also, discussion on available juvenile toxicity studies as invited.

Regarding the reproductive toxicology, the Applicant has summarised data in the SmPC as follows:

"*a prenatal and postnatal reproductive toxicology study, in which mice were dosed subcutaneously with a murine analogue of rilonacept at doses of 20, 100 or 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area), there were no effects on fertility and reproductive performance in male and female mice.*

In an animal reproduction study, subcutaneous administration of rilonacept to pregnant monkeys during the period of organogenesis was complicated by losses of rilonacept exposure as the study progressed, due to anti-rilonacept antibody formation at all doses, but a dose-related increase in exposure was still evident. There were no treatment-related effects on foetal 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 foetuses at doses approximately 2 times the MRHD and higher, that slightly exceeded incidences in both control animals and the historical control database. A study of embryo-foetal development was conducted with rilonacept in monkeys at doses up to approximately 4 times the human dose. Decreases in β-estradiol levels were seen in the treated groups, the significance of this finding is unknown."

Of note, during the recurrent pericarditis clinical studies, two events of pregnancy were reported during the Long-Term Extension period of the Phase 3 study RHAPSODY (KPL-914-C002 study). Both patients stopped the treatment. One of the participants withdrew from the study and the other stopped treatment but completed the follow-up visits. No reported adverse outcomes were noted with these two pregnancies. There were 4 post-marketing reports of pregnancy with no reported adverse outcomes. More information is in the clinical part of the report.

Regarding juvenile toxicity, the previous MA documentation provided information that in the chronic repeat-dose toxicology study of rilonacept administered to cynomolgus monkey by the intravenous route, the animals ranged between 3 and 6 years of age at study initiation. This age range in monkeys corresponds to adolescence in humans. Particularly, sexual and skeletal maturation are still ongoing in monkeys at that age (cf. ICH S11 "Non-clinical safety testing in support of development of paediatric pharmaceuticals"). Therefore, the available toxicity data of rilonacept in monkeys support its use in adolescents, which is also in agreement with the previously approved European therapeutic indication that covered adults and children aged 12 years and older. It would have been more appropriate to include this discussion in the non-clinical documentation for the current application, as indicated in the CHMP SA and at the pre-submission meeting, but no further concerns are raised on this. To note that with the current application the use of rilonacept to treat children of 12 years and older is not clinically well justified and a as B/R MO has been raised.

There were following non-clinical FUMs that the Applicant agreed to complete after approval of Rilonacept Regeneron:

*FUM 14: Updated reports on long-term stability of rilonacept upon frozen storage to be provided when available with due date Q2 2010;

*FUM 15: Report of an additional embryo-foetal developmental toxicity study in cynomolgus monkeys to investigate placental transfer, exposure of the conceptus and measurement of hormonal levels in the adults to be provided when available with the due date Q4 2010.

The FUM14 was submitted, assessed and regarded as fulfilled. With regards to the FUM 15 the latest update from the Applicant prior to withdrawal of the MA from EU was that the study report was to be available by the end of 2012 and the interim report was planned to be available prior to 30 Sept 2012. From this there seems to be a notion that the studies had at least been started prior to withdrawal. However, the MAA was subsequently withdrawn and the data were never submitted in the EU. Therefore, a non-clinical MO is raised by the CHMP as this information remains relevant also for the proposed application.

The CHMP SA has also requested an updated assessment of the carcinogenic potential of inhibitors of the IL-1 pathway, outlining also the specific criteria for the literature search. The data presented in the MA documentation is unfortunately rather scarce and there is no reasoning why or how the selected publications were chosen. However, the issue is not further pursued.

IL-1 is known to exert a critical function in malignancies, influencing the tumor microenvironment and promoting cancer initiation and progression. Thus, it orchestrates immunosuppression recruiting pro-tumor immune cells of myeloid origin. Furthermore, IL-1 can be directly produced by tumor cells in a positive feedback loop and it contributes to the failure of targeted therapy [Gelfo 2020]. These pro-tumorigenic functions of IL-1 suggest that inhibition of this cytokine may rather be beneficial than detrimental in patients with cancer. The Applicant has additionally provided a summary of findings of the two IL-1 inhibitors approved in the EU – canakinumab and anakinra. A pro-tumorigenic effect of inhibiting IL-1 has however not been described. As a caution, there is a statement proposed in the SmPC stating that treatment with immunosuppressants may result in an increase in the risk of malignancies. This is supported.

The data of the additional embryo-fetal development toxicity study in the Cynomolgus monkey have not been included in the non-clinical package and therefore the information on placental transfer is lacking **(OC)**.

It would be also helpful to include any post-marketing data with pregnant and lactating /breast-feeding woman.

3.2.6. Conclusion on non-clinical aspects

The pharmaceutical company Regeneron has committed 2009 in a FUM to conduct an additional embryo-fetal development toxicity study in the Cynomolgus monkey to investigate this along with exposure data to the conceptus and measurement of hormonal level to the adults. It is not known if rilonacept is excreted in the milk. Further investigations have also been the subject of a FUM.

The data of the additional embryo-fetal development toxicity study in the Cynomolgus monkey have not been included in the non-clinical package and therefore the information on placental transfer is lacking.

3.3. Clinical aspects

The legal basis of this marketing authorisation application for Rilonacept is Article 10(3) of Directive 2001/83/EC, a so-called "hybrid" application to the reference medicinal product Rilonacept Regeneron.

Rilonacept Regeneron (previously ARCALYST, EMEA/H/C/001047), is an IL-1α and IL-1β inhibitor which was approved under exceptional circumstance in the EU on 23 October 2009 for the treatment of cryopyrin-associated periodic syndromes (CAPS).

The marketing authorisation for Rilonacept Regeneron has been withdrawn at the request of the marketing-authorisation holder in the EU on 24 October 2012 for commercial reasons.

Two clinical studies, i.e. the Phase 2 study (C001) and the RHAPSODY Phase 3 study (C002), have investigated the use of rilonacept among 111 patients in the recurrent pericarditis indication.

Table 2: Studies Included in the Summary of Clinical Safety

Study Number	Study Design	Population	Starting Dose	N (Total)	N (Adult)	N (Paediatric)	Data Cutoff Date/Study Status
C001	Single-active-arm Phase 2 study	Participants with idiopathic recurrent pericarditis or recurrent post-pericardiotomy syndrome (adult and paediatric)[a]	Initial 320 mg SC; 160 mg SC q.w. (adults) Initial 4.4 mg/kg (320 mg max) SC; 2.2 mg/kg (160 mg max) SC q.w. (paediatrics)	25	25	0	Completed 17 May 2019
C002	Phase 3 double-blind, placebo-controlled, randomised withdrawal study with Long-term extension 05 Sep	Participants w/ recurrent pericarditis (adult and paediatric)[b]	Loading dose = 320 mg SC; 160 mg SC q.w.(adults) Initial 4.4 mg/kg (320 mg max) SC; 2.2 mg/kg (160 mg max) SC q.w. (paediatrics)	86	79	7	31 Aug. 2020 05 Sep. 2023
Total Participants in the Integrated Safety Group				111	104	7	N/A

[a] No paediatric participants ultimately enrolled.
[b] In C002, 7 paediatric participants refer to adolescent participants (13 to 17 years of age)
max = maximum; N/A = not applicable; q.w. = once weekly; SC = subcutaneous
FOOTNOTE: The exposures in this Integrated Safety Group regarding study C002 are derived from the RI and RW periods only, exclusive of the LTE. LTE safety data are reported separately.

3.3.1. Exemption

This is a hybrid application, thus, reference must be made to a product (the reference medicinal product) which is or has been authorised in the Union. This condition is fulfilled.

The reference medicinal product needs to be approved based on a complete dossier, i.e., reference can only be made to the dossier of a reference medicinal product for which a marketing authorisation has been granted in the Union in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC. If not longer authorised, it should not have been withdrawn due to safety reasons. This condition is fulfilled. The reference medicinal product (Rilonacept Regeneron, EMEA/H/C/001047) is no longer authorized in the Union and was withdrawn from the EU for commercial reasons. No reference medicinal product batches were placed on the Union market.

According to the applicant, the proposed drug product is identical to the reference medicinal product (Rilonacept Regeneron, EMEA/H/C/001047) having the same composition, manufacturing process, strength, route of administration and dosing with the only difference in indication applied for. There is no direct comparison of pharmacokinetics of the proposed product made to the reference medicinal product through bioavailability studies and the Applicant's approach to bridge to the reference medicinal product is established based on a quality comparison and a scientific rationale/justification covering the comparison of achieved exposure levels in different patient populations and medicinal product quality attributes.

The adequacy of the bridge will be further assessed based on the responses to the concerns outlined in the LoQ.

3.3.2. Clinical pharmacology

To support the application, the Applicant has submitted one open-label phase 2 study in patients with recurrent pericarditis (RP) (KPL-914-**C001**) as well as one phase 3 efficacy and safety study in RP patients (KPL-914-**C002**). Both studies C001 and C002 provide PK data. Moreover, data on C reactive protein (CRP) were generated, which is considered for evaluation of the pharmacodynamic (PD) effect in patients with RP.

The KPL-914-PopPK-RP study was conducted with data from the above-mentioned studies C001 and C002 to perform an exploratory graphical analysis of the serum concentration-time profile of rilonacept and to develop a population PK (popPK) model for rilonacept to describe the serum concentration-time data. See discussion on popPK model below.

Pharmaceutical development

No studies were provided in the context of pharmaceutical development.

According to the SmPC, the medicinal product is intended for self-administration by the patients if the physician deems it appropriate and provides medical follow-up if necessary. Considering the reconstitution procedure required prior to administration (withdrawal of 2.3 mL of WFI solvent, injection into the vial, waiting until reconstitution finished, withdrawal of up to 2.0 mL reconstituted drug product, administration) the presentation of the product is not considered appropriate to ensure drug product quality at the time of administration especially in view of microbiological safety. Furthermore, due to the extensive handling instructions to be done by non-professionals patient safety might be jeopardised.

The EPAR for Rilonacept Regeneron (EMEA/541561/2009) does not discuss the issue in detail and does not refer to a drug utilization study. Appropriate handling is crucial for efficacy and safety and the 12-17 years age group is not covered by the patient population with CAPS.

Study C002 in the RP programme included self-administration of the study drug by the participants, and the efficacy and safety results gained are based on the proposed handling of the drug product. Self-administered injections made up >95% of administrations for each part in Study C001 and ranged from 87.54% to 96.15% in Study C002.

Nevertheless, it should be noted that in the clinical study, all items needed for the self-administration are provided to the study participants, but these are not contained in the carton for the product to be marketed. In real life, the patient should obtain all these items either from the healthcare professional or from the pharmacy, the feasibility of which is unclear. Thus, the suitability of the proposed drug product for the self-administration is currently questioned.

The Applicant is asked to provide data demonstrating appropriate handling of study drug upon self-administration for the whole target group of patients, e.g. by providing data from a drug utilization study and/or by providing robust data from post marketing experience relevant for patients with RP. In this regard the currently proposed "Instructions for use" should be updated and simplified as well as additional pictures for handling steps be added. **(OC)**

3.3.2.1. Pharmacokinetics

In context with the previous marketing authorization (indication for various Cryopyrin-associated periodic syndromes [CAPS]), relevant PK data were submitted from two studies with healthy subjects (Studies IL1T-RA-0401 and -0402) as well as from a study with rheumatoid arthritis patients (IL1T-RA-0004).

These data are not discussed in detail in this assessment report, as they were already previously assessed. The following overview of PK data from the above-mentioned studies is taken from the EPAR of Rilonacept Regeneron (EMEA/541561/2009, from previous CAPS indication, product no longer authorised):

Study Ref. No.	Study Objective	Study Design	Subject No. (M/F) Type Age: Mean (Range)	Treatments (Dose, Dosage Form, Route)	Dose Group	Mean Parameters* (+/- SD) Cmax/Dose (kg/L)	Tmax (hr)	Cl (mL / (day x kg))	Terminal Half-Life (day)
IL1T-RA-0004, Part A and B	Evaluate efficacy, PK, and safety	Parallel	No. Subjects: 107 (25 in Part A single dose, 82 in Part B multiple dose) Part A: Age Range: 37-72 Age Mean: 53 Gender: F= 18 (72%), M= 7(28%) Part B: Age Range:23-74 Age Mean: 55 Gender: F= 67(82%), M= 15(18%)	Multiple weekly SC injections: Placebo, 50, 100, 200, 400, 800µg/kg	Mean of All Dose Groups	4.11 (1.4)	89 (27)	19.9 (10.3)	7.69 (1.52)
					50	4.35 (1.3)	90 (36)	18.8 (3.4)	8.15 (1.69)
					100	3.00 (0.59)	96 (34)	24.1 (4.5)	6.67 (0.40)
					200	3.73 (0.85)	96 (34)	22.5 (11.2)	8.96 (1.51)
					400	4.94 (1.3)	78 (12)	12.0 (2.2)	7.28 (0.41)
					800	4.53 (2.2)	84 (24)	22.1 (2.0)	7.37 (2.23)
IL1T-RA-0401	Evaluate PK parameters after SC injection and compare two formulations	Parallel	No. Subjects: 103 Age Range: 19-69 Age Mean: 38.2 Gender: F= 55 (53.4%), M= 48 (46.6%)	Single SC injection: Placebo, 50, 80, 104, 120, 160, 240, 320mg	Mean of All Dose Groups†	3.83 (1.1)	84 (36)	22.8 (6.5)	6.31 (1.18)
					50	2.92 (1.0)	98 (37)	29.8 (14.2)	6.91 (1.54)
					80	4.54 (0.97)	61 (12)	20.2 (4.2)	6.42 (0.94)
					104	3.55 (1.06)	92 (34)	22.0 (4.9)	6.85 (0.86)
					120	3.18 (1.22)	96 (44)	28.1 (8.6)	6.12 (1.53)
					160	4.11 (0.73)	67 (11)	23.7 (4.4)	5.25 (1.51)
					240	3.68 (1.21)	120 (48)	21.0 (5.5)	6.13 (0.83)
					320	4.39 (0.94)	66 (12)	17.7 (4.1)	6.32 (1.03)
IL1T-RA-0402	Evaluate PK parameters after IV infusion	Parallel	No. Subjects: 28 Age Range: 19-58 Age Mean: 40 Gender: F= 18 (64.3%), M= 10 (35.7%)	Single IV infusion: 100, 300, 1000, 2000mg	Mean of All Dose Groups	14.9 (2.60)	ND	10.3 (1.7)	7.48 (1.07)
					100	15.1 (2.1)	ND	9.8 (7.4)	7.54 (1.66)
					300	15.8 (1.5)	ND	9.3 (1.5)	7.60 (1.19)
					1000	12.1 (0.8)	ND	12.2 (1.6)	7.28 (0.84)
					2000	16.6 (3.1)	ND	9.7 (1.6)	7.49 (0.74)

Source: Population Pharmacokinetic Analysis Report, Tables Y.5, Y.6, Y.10, and Y.14
ND Tmax calculations were not performed for this single-dose study.
* Dose- and weight-adjusted PK parameters from the non-compartmental analyses conducted for the Population Pharmacokinetic Report.
† Calculated values omit the 50 mg dose cohort which utilized P2 DP and analysis was not relevant to the comparison of P1 and P3.

In the following, the PK data from the newly submitted studies KPL-914-C001 and KPL-914-C002 are discussed.

Study *KPL-914-C001*

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

For details on study design and methods, please see efficacy part.

Methods

Analytical methods

Method validation

Quantitation of rilonacept serum concentrations
An enzyme-linked immunosorbent assay (ELISA) was used to quantitate total IL-1 Trap in human serum. Standards, controls and samples are added to the plate (coated with REGN514), and IL-1 Trap captured on the plate is detected using a different, non-competing biotinylated mouse anti-IL-1 Trap monoclonal antibody (Biotin-REGN739), followed by NeutrAvidin conjugated with horseradish peroxidase (NeutrAvidin-HRP). A luminol-based substrate specific for peroxidase is then added to achieve a signal intensity that is proportional to the concentration of total IL-1 Trap. The validation experiments were conducted from May 07 through May 25, 2018.

Standards and quality controls were prepared in neat human serum at 50X of their final assay concentrations. The standard curve (50X) ranges from 5 µg/mL (ULOQ) to 0.078 µg/mL (LLOQ). The final concentrations (after 50X dilution; 2% human matrix) were 100 ng/mL (ULOQ), 50 ng/ml, 25 ng/ml, 12.5 ng/ml, 6.25 ng/ml, 3.13 ng/ml, and 1.56 ng/ml (LLOQ) *plus* a zero sample. The following five validation QCs were prepared (50X of their nominal concentration): ULOQ: 5 µg/mL; HQC: 3.75 µg/mL; MQC: 1 µg/mL; LQC: 0.225 µg/mL, and LLOQ: 0.078 µg/mL.

The method satisfied all specified acceptance criteria set forth in the Validation Protocol IL1T-AV-18095. However, it is noted that the method to quantitate rilonacept in human serum does not include a step to remove ADA from the samples. Thus, the negative correlation between ADA titre and rilonacept serum concentration might reflect the competition of ADAs with the antibodies used in the ELISA detection method rather than a "true" reduction of serum rilonacept levels. This should be discussed by the Applicant (**OC**). Moreover, long-term stability results should be submitted (**OC**).

Quantitation of rilonacept anti-drug antibodies (ADAs)

Rilonacept (IL-1 Trap) antibodies in human serum were determined by a non-quantitative, titer-based electrochemiluminescent bridging assay, which involves prior acid treatment of serum samples to dissociate antibody:drug complexes to improve ADA detection in the presence of drug molecules.

REGN739, a mouse anti-IL-1 Trap/rilonacept monoclonal antibody, is used as a positive control. Biotinylated IL-1 Trap (Bio-IL-1 Trap or Bio-REGN4) and ruthenium-labeled IL-1 Trap (Ru-IL-1 Trap or Ru-REGN4) are used as bridge components.

The method involves three tiers:

- Initial screening assay: Identification of potentially ADA-positive samples
  Samples and controls are diluted in acetic acid and then further diluted with a Tris-base solution containing Bio-IL-1 Trap and Ru-IL-1 Trap. Samples and controls are then added to a streptavidin-coated MSD microplate, which captures the Bio-IL-1 Trap and binds the immune complex (Bio-IL-1 Trap: ADA: Ru-IL-1 Trap). The bound complexes are detected by an electrochemiluminescent signal (ruthenium label).
- Confirmation assay: Test for inhibition of a positive response by excess unlabeled drug
  In this assay, the same procedure is used. Duplicate samples are incubated with two Tris-base solutions containing Bio-IL-1 Trap and Ru-IL-1 Trap (one without unlabeled IL-1 Trap and one with unlabeled IL-1 Trap) to evaluate the competition effect of the unlabeled IL-1 Trap on the assay response.
- Titer assay: Assess levels of ADA in positive samples.
  Samples are serially diluted in the negative control serum (NQC) prior to acidification. Multiple

dilutions of each sample are analyzed to determine the maximum dilution (titer) which is still above the titer cut point for the assay. Positive quality controls (PQCs) were prepared in NQC serum using REGN739 at 50X concentration: HQC (25 000 ng/mL), MQC (2 500 ng/mL) and LQC (25 ng/mL) yielding final concentrations of 500 ng/mL, 50 ng/mL and 0.5 ng/mL, respectively. A 4-parameter logistic (4PL) equation was applied to the responses of the QC dilution sets.

Ten validation parameters were selected to evaluate the performance of this assay as follows: (1) Screening Cut Point, (2) Confirmation Cut Point, (3) Sensitivity, (4) Dilution Linearity, (5) Drug Tolerance, (6) Precision, (7) Recovery, (8) Analyte Stability, (9) Robustness and (10) Ruggedness.

150 individual naïve human serum samples were analyzed, with and without drug (IL-1 Trap), to determine a screening cut point factor (CF), a confirmation cut point (CCP) and a titer cut point factor (TCF). The sensitivity of the assay in neat serum is based on the calculated sensitivity values for the monoclonal antibody positive control (REGN739) and app for the monkey anti-IL-1 Trap polyclonal antibody.

The drug tolerance of the assay, in neat serum, based on the calculated DTL values using 250 ng/mL of either the monoclonal antibody positive control (REGN739) or the monkey anti-IL-1 Trap polyclonal antibody. Additional development experiments also demonstrate that, using 100 ng/mL of REGN739 and the monkey anti-IL-1 Trap polyclonal antibody, DTL values.

Bioanalytical sample analysis

Quantitation of rilonacept serum concentrations
For bioanalytical sample analysis, the standard curve comprised the same concentrations as described above for method validation. As quality controls, HQC, MQC and LQC with a final concentration of 75, 20, and 4.5 ng/ml were used. Standards, QCs and study samples were run in duplicate.

The %AR (analyte recovery; 11 plates) ranged from 94% to 101% for the non-zero standards and QCs (CV%: 1 – 11%). Incurred sample reanalysis (ISR) with 30 samples from the KPL-914-C001 study (~10% of the total rilonacept samples) passed the acceptance criteria (variability <30%; passing rate: 100%). No sample reanalysis was required for the total rilonacept assay. Total rilonacept levels were measured in serum samples from a total of 26 subjects. The overall plate passing rate was 100% (all 11 plates passed). 18 samples from plate 390490 were rejected due to "PI Authorized Rejection". The exact reasons should be provided (**OC**).

Quantitation of rilonacept anti-drug antibodies (ADAs)
Serum samples from 26 subjects were assessed for the presence of ADA. Eighteen (18) ADA assay plates were analyzed in the study (6 plates for screening assay, 6 for confirmation assay and 6 for titer assay). The plate passing was rate 100%. CV% ranged from 11 to 13% (NQC, LQC, MQC and HQC). For the discussion of the results, please see safety section below.

- **Pharmacokinetic Variables**

In study KPL-914-C001, serum concentrations (mainly C_{trough} values) were determined and followed throughout the course of the study. For PK parameters like $C_{max,ss}$ or $AUC_{0-T,ss}$, please see predictions in the section on the Population PK Study KPL-914-PopPK-RP below.

- **Statistical methods**

Only standard descriptive parameters (e.g., SD, SEM) were determined.

Results

Serum concentration-time profile

The mean concentration time profile showed moderate to high variability (%CV: 30.1 – 69.2 %) between subjects across the duration of the study. Following the 320 mg loading dose, no additional accumulation of rilonacept was observed by a maintenance dose of 160 mg/week (median concentration: ~30,000 ng/mL over the first 6 weeks). The steady-state concentration from week 6 to 21 yielded median concentrations of 34,250 ng/mL, 33,150 ng/mL, and 31,000 ng/mL for weeks 6 – 9, 13 – 15, and 21, respectively.

The mean ± standard error of the mean (SEM) rilonacept concentration-time profile and individual rilonacept serum concentration values are shown in **Figure 2** below.

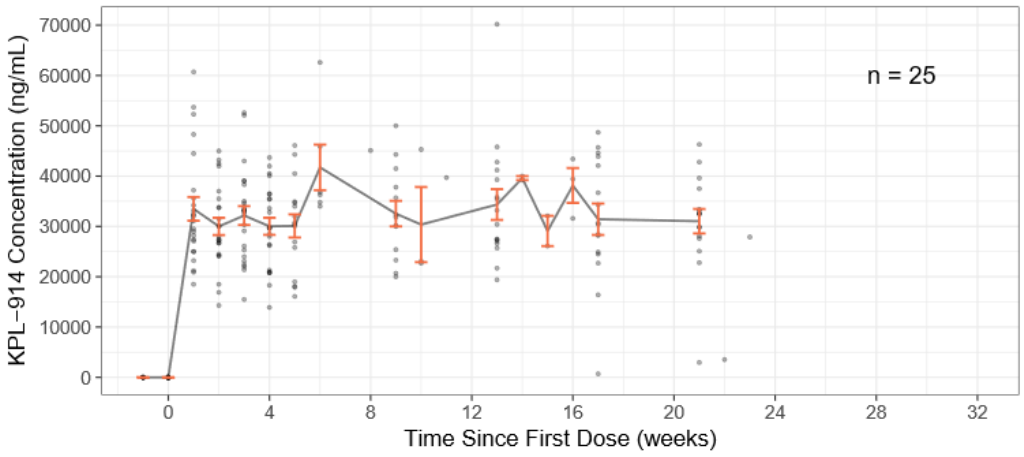


Figure 2: Linear +/- SEM Rilonacept Serum Concentration-time Profiles – Study C001 (semi log representation not shown here)

Comparison of Rilonacept Serum Concentrations in RP and CAPS Subjects

The Applicant has compared the mean, SD, and %CV of rilonacept concentrations sampled every third week from Study C001 (RP), and from the blinded parts of Regeneron Study IL1T-AI-0505 (CAPS). A moderate-to-high variability in rilonacept serum concentrations was observed for both RP and CAPS subjects.

For each time point, mean rilonacept concentrations observed in subjects with CAPS were 5 – 30% lower than those observed in subjects with RP. The Applicant assumes that this difference might be due to a different bioanalytical method and a different matrix (plasma) used to quantitate rilonacept in the CAPS subjects in study IL1T-AI-0505. Thus, a direct cross-study comparison of absolute concentrations is difficult.

Study *KPL-914-C002*:

A Phase 3 double blind, placebo-controlled, randomised withdrawal study with an open-label extension, to assess the efficacy and safety of rilonacept treatment in adult and paediatric subjects with RP. A secondary objective of the study was to characterise the PK profile of rilonacept in subjects with RP.

Methods

Analytical methods

Method validation

Quantitation of rilonacept serum concentrations and of rilonacept anti-drug antibodies (ADAs)
The method validations for quantitation of rilonacept in human serum as well as for rilonacept ADAs were the same as described above for study KPL-914-C001.

Bioanalytical sample analysis

Quantitation of rilonacept serum concentrations
The concentrations of standard curve and quality control samples were the same as describe above in the section on study KPL-914-C001. Standards, QCs and study samples were run in duplicate.

The %AR (analyte recovery; 21 plates) ranged from 95% to 102% for the non-zero standards and QCs (CV%: 1 – 11%). The overall plate passing rate was 95%, since one of the 22 plates (#509766) did not meet the run acceptance criteria (reason: %AR for QC(s) did not meet assay specification). One plate (#515902) was considered incomplete as no data were generated from it. No incurred sample reanalysis (ISR) was conducted with samples from study KPL-914-C002. Instead, the Applicant refers to the ISR performed in study KPL-914-C001 (see above).

Total rilonacept levels were measured in serum samples from a total of 82 adult subjects and 4 paediatric subjects. Sample reanalysis was performed on 3 samples from 1 subject.

Quantitation of rilonacept anti-drug antibodies (ADAs)
Serum samples from 82 adult and 4 paediatric subjects were assessed for the presence of ADA. Thirty (30) ADA assay plates were analyzed in the study (12 plates for screening assay, 12 for confirmation assay and 6 for titer assay). The plate passing was rate 97% (i.e., one plate failed). The provided reason for the failure of one plate was "CV% counts for QC(s) did not meet assay specification". CV% ranged from 4 to 10% (NQC, LQC, MQC and HQC). For the discussion of the results, please see safety section below.

Detection of anti-rilonacept neutralizing antibodies (NAbs)

Method validation

Rilonacept (IL-1 Trap) neutralizing antibodies in human serum were determined by a non-quantitative, electrochemiluminescent (ECL) bridging immunoassay, which involves prior an acid-dissociation-extraction procedure to dissociate drug-NAb complexes to allow increased detection of NAbs in the presence of free drug. The NAb are further captured with biotin-conjugated rilonacept and subsequently detected using Sulfo-Tag conjugated recombinant human IL-1β (rhIL-1β) allowing for ECL detection proportional to the amount of NAb present in the sample.

REGN739, a mouse anti-IL-1 Trap/rilonacept monoclonal antibody, is used as a positive control. Biotinylated IL-1 Trap (Bio-IL-1 Trap or Bio-REGN4) and ruthenium-labelled IL-1 1β (Ru-IL-1β) are used as bridge components.

Nine validation parameters were selected to evaluate the performance of this assay as follows: (1) Precision, (2) Assay Cut Point, (3) Sensitivity, (4) Drug Tolerance, (5) Target Interference, (6) Selectivity, (7) Stability, (8) Robustness and (9) Ruggedness.
50 individual naïve human serum samples were analysed to determine an assay cut point factor. The sensitivity of the assay was determined. The drug tolerance of the assay, in neat serum, using either HPC (5000 ng/mL) or LPC (1000 ng/mL) monoclonal antibody positive control (REGN739). It is noted

that this does not cover the actual serum levels of rilonacept observed in the clinical studies (predicted C_{max} = 32.1 µg/mL), and the potential impact of rilonacept interference on nAb assay performance should be discussed (**OC**). Target interference assessments demonstrated that no interference was observed with recombinant human interleukin 1β and 1α in the concentration range of 1 to 1000 ng/mL at the HPC or LPC level.

Bioanalytical sample analysis

Forty-eight (48) samples were assessed for the presence of nAbs. Forty-two (42) samples we determined to be negative, and six (6) samples were determined to be positive. The plate passing was rate 100%. CV% of NQC, LQC, HQC signal was within acceptance limits ≤ 20.0%.

- **Pharmacokinetic Variables**

In study KPL-914-C001, serum concentrations were determined and followed throughout the course of the study. For PK parameters like $C_{max,ss}$ or $AUC_{0-\tau,ss}$, please see predictions in the section on the Population PK Study KPL-914-PopPK-RP below.

- **Statistical methods**

Only standard descriptive parameters (e.g., SD, SEM) were determined.

Results

Rilonacept Serum Concentration-time Profiles

86 subjects (37 M/49 F) were enrolled, 79 subjects (35 M/44 F) completed period 1 (RI), 60 subjects (28 M/32 F) completed period 2 (RW), and 74 subjects (34 M/40 F) initiated period 3 (LTE).

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 12 (RI period) with steady state being reached between week 3 and 4. Significant reductions in rilonacept serum concentrations were observed at 2 weeks after the end of the RI period in subjects randomised in the RW period to receive QW SC injections of placebo. Individual rilonacept serum concentrations of paediatric subjects, where rilonacept was dosed according to body weight, were within the range of the adult subjects. However, this observation is based on a limited sample of 7 paediatric subjects. The mean (± SD) rilonacept C_{trough}-time profiles and the individual subject values during period 1 (RI) and period 2 (RW) are shown in **Figure 3**.

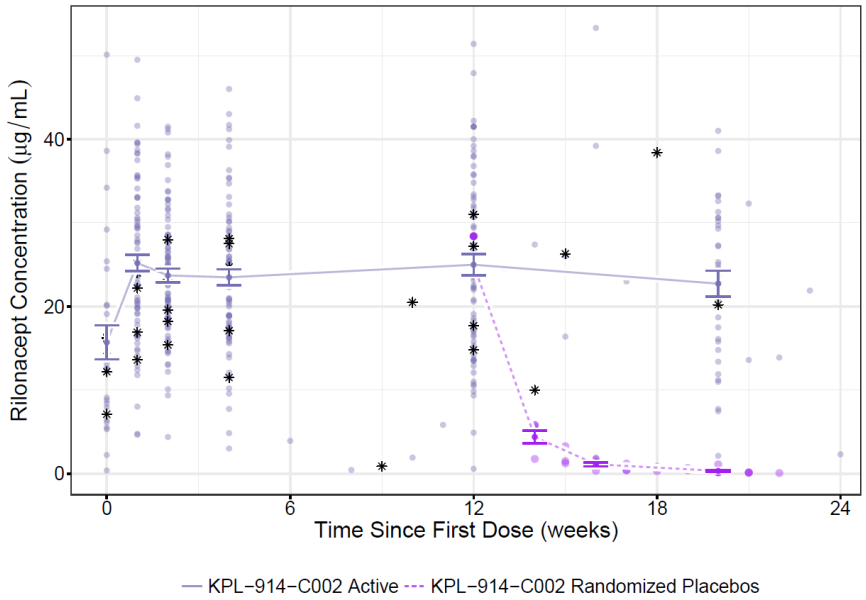


Figure 3: Mean (± SEM) and Individual Adult and Paediatric Subject Rilonacept Serum C_{Trough}-time profiles in the Run-In and Randomised Withdrawal of study C002 - Lines represent the mean serum concentration coloured by treatment (Active or Placebo) as indicated in the legend. Vertical bars represent the standard deviation, symbols represent the observed data, the lighter lilac line and symbols represent the observed data following randomisation to placebo and were excluded from the mean and SD calculations. Black asterisk symbols represent observed data from paediatric subjects (age <18 years). Note: Data were truncated at 24 weeks, and BLQ data (<0.078 µg/mL) were excluded from the figure.

The results from the paediatric population (n=7), where rilonacept was dosed according to body weight, were within the range of the adult subjects. However, only 7 paediatric subjects were included, which limits the informative value of the paediatric data.

KPL-914-PopPK-RP study (population pharmacokinetic model)

The final popPK model for rilonacept in RP patients was a one-compartment model with first-order elimination and first-order input. Body weight (normalized to a weight of 80 kg) was a significant covariate on clearance and volume with estimated exponents. The resulting impact of very low or very high body weight on exposure in adult patients with flat dosing (LD: 320 mg and MD of 160 mg) remains unclear but should be shown and discussed with respect to safety and efficacy. (OC)

In addition, the popPK analysis revealed that relative bioavailability was different between the two studies (41% higher in study KPL-914-C001 compared to study KPL-914-C002). This needs be explained and discussed. (OC)

3.3.2.2. Pharmacokinetic Conclusion

C_{trough} values were analysed for study C001 as well as for the run-in and the randomized withdrawal period of study C002. The results show that the loading dose of 320 mg is sufficient to achieve the target plasma concentration, which is the maintained by a dose of 160 mg/week without any signs of further accumulation. The results from the paediatric population in study C002, where rilonacept was dosed according to body weight, were within the range of the adult subjects. However, only 7 paediatric subjects were included, which limits the informative value of the paediatric data. As expected, in the randomized withdrawal period of study C002, the serum concentrations declined in the placebo group, approximately confirming the half-life of about 7 days. There seem to be differences in bioavailability between study C001 and C002 that should be discussed by the Applicant (**OC**). Moreover, the impact of

very low or very high body weight on exposure in adult patients with flat dosing (LD: 320 mg and MD of 160 mg) should be discussed with respect to safety and efficacy (**OC**).

3.3.2.3. Pharmacodynamics

Results from previous marketing authorization:

Pharmacodynamics was already extensively characterized in context of the previous marketing authorization to treat CAPS. The following description of the results is taken from the EPAR of Rilonacept Regeneron (EMEA/541561/2009):

Mechanism of action:
Binding of IL-1 by Rilonacept blocks the bioactivity of the bound cytokine. Because of its structure, the Fc portion of rilonacept provides the basis for dimerization and a long circulating half-life. Rilonacept has a pharmacokinetic half-life of approximately seven days.

Free cytokine levels have not been measured before or after rilonacept administration. In contrast, cytokine complexes with rilonacept, i.e. Il-1ß bound to rilonacept (IL-1ß complex levels) and total IL-1ra levels (free and captured) were measured in four PD studies as well as in the pivotal CAPS study.

It was considered plausible that, due to the stoichiometry of the complexes, total IL-1ra instead of bound IL-1ra was measured. Unfortunately, no baseline values of free cytokines before treatment (neither IL-1ß nor IL-1ra) were measured in the studies. Complexes with IL-1ra generally comprised less than 15% of the total during active dosing, while IL-1β complexes comprised considerably less than 1% of the total. Thus, the vast majority of the rilonacept in serum is present as free rilonacept.

The IL-1ß complex levels were in the range of 1-4 pM except in CAPS patients where markedly higher levels of 19 pM (up to 66 pM) were measured. This was supposed to reflect the proposed IL-1β overproduction resulting from the cryopyrin mutations underlying CAPS.

Total IL-1ra levels determined in different studies after rilonacept were in the range of 6.6 – 22.5 nM, which exceeds the IL-1β complex levels in RA subjects by 1000-fold or more. There was no evidence for a relationship between dose (rilonacept concentrations at the respective time points) and either IL-1ß complex levels or total IL-1ra levels. This is not surprising since the rilonacept concentrations are at any time very high compared to the affinity to the cytokines so that it has to be assumed that the cytokines are almost completely bound at any time and dose. Therefore, the bound cytokine levels appear to reflect the total amount of cytokine present in serum at the respective time point and do not serve as a biomarker for the response.

Primary and Secondary pharmacology
Rilonacept tended to normalize the levels of a variety of different acute phase markers and hematological measures in essentially all of the RA studies. In one study, there were statistically significant decreases in CRP, erythrocyte sedimentation rate (ESR), and white blood cells, and there were trends to decrease platelets and rheumatoid factor (RF). Statistically significant decreases in CRP were evident in the 25 mg and 100 mg dose groups; administration of 50 mg also resulted in decreases that were numerically, but not statistically, significant. There was no conclusive evidence that administration of 100 mg rilonacept weekly gave a maximal response across all measured biomarkers.

In part A of the pivotal CAPS study CRP decreased from high baseline values of 20.1 mg/l to normalized mean values of 1.3 mg/l. Similarly, SAA levels decreased from high baseline values of 49.5 mg/l to normalized mean values of 2.5 mg/l. Immunogenicity (development of anti-rilonacept antibodies) appeared to be very high in the multiple dose studies performed. In two out of 17 paediatric patients

treated antibodies were found accompanied by a considerable and (at least in one patient) persistent decrease in rilonacept serum concentrations.

In the pivotal CAPS study, 43% of subjects (20 of 46) dosed with rilonacept for up to 24 weeks in Parts A and B of the study demonstrated a rilonacept-specific response in the anti-rilonacept antibody assay, respectively. The treatment profile (sequence of placebo and drug) of the patients did not determine either frequency or time point of the first appearance of antibodies. Of the 56 samples tested, ten samples from seven subjects were positive for neutralizing antibodies. Interestingly, five of the seven subjects who were positive for neutralizing antibodies tested negative for neutralization at a later time point. However, for safety considerations all (binding) antibodies are relevant, whereas the discrimination between binding and neutralising antibodies might be of importance in terms of efficacy reduction. Further investigations of immunogenicity in patients who have a reduction in efficacy are planned.

Two potential pharmacodynamic interactions were identified: Firstly, it is known from experience with another drug that blocks IL-1 (anakinra) that concomitant administration with a TNF-blocking agent has been associated with an increased risk of serious infections and an increased risk of neutropenia. Thus, the concomitant administration of rilonacept with TNF-blocking agents may also result in similar toxicities and should be avoided.

Secondly, the concomitant administration of rilonacept with other drugs that block IL-1 (anakinra) has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of rilonacept and other drugs that block IL-1 should be avoided.

Results from current application

For studies C001 and C002, C-reactive protein (CRP) is going to be discussed as main PD parameter and as marker of inflammation, which is commonly elevated in participants with RP, correlating with disease activity. All other endpoints (pericarditis pain etc.) are addressed in the efficacy section below.

Study KPL-914-C001

Details on this study, incl. design and methodology are presented in the efficacy part. Participants enrolled in Parts 1 and 4 represent a population that is most aligned with the inclusion and exclusion criteria for the population in the C002 phase 3 study. The primary endpoint for Parts 3 and 5 was disease activity after corticosteroid taper in participants with corticosteroid-dependent idiopathic RP or recurrent post-pericardiotomy syndrome.

In the following, C-reactive protein (CRP) will be discussed as primary PD endpoint. Information at baseline and during treatment was collected to assess treatment response after initiation of rilonacept in symptomatic participants.
Mean CRP levels decreased from baseline after the first rilonacept dose in all study parts, although the decreases were greater in parts 1 and 4 than in parts 2, 3 and 5. This is due to higher baseline levels in parts 1 and 4, because per protocol, these parts required elevated CRP >1 mg/dL. The greatest mean changes from baseline occurred in part 1. Reductions in mean CRP levels were maintained throughout the Treatment Period and the extension period (EP). At the final visit, CRP levels were normal (≤0.5 mg/dL) for 10 of 11 (90.9%) subjects in part 1 and all subjects in the other study parts.

Persistent CRP normalization was defined as CRP ≤0.5 mg/dL at 2 consecutive visits with no abnormal value (>0.5 mg/dL) thereafter. Among subjects with abnormal CRP levels at baseline (>0.5 mg/dL), the proportion of subjects with persistent CRP normalization was 9/12 (75%) during both the Treatment

Period and the entire study for part 1. Due to the low number of subjects with abnormal CRP levels (n≤1) in the other parts of the study (part 2: n=1; part 3: n=0; part 4: n=1; part 5: n=0), these data are not considered meaningful and are not shown in detail in this overview.

The median time to CRP normalization (CRP ≤0.5 mg/dL) was 9.0 days for Parts 1 and 2, 8.0 days for Part 4, and not estimable for Parts 3 and 5. The first post study-drug dose CRP measurement occurred at visit 2, i.e., 1 week after the first (loading) study drug dose.

Study KPL-914-C002

Details on this study, incl. design and methodology are presented in section 3.4 (clinical efficacy). In study C002, a 12-week single-blind run-in period (treatment with 160 mg rilonacept SC weekly) was used to stabilize and taper background pericarditis medications. This was followed by 1:1 randomization (rilonacept 160 mg SC weekly *vs.* placebo) of the clinical responders (NRS ≤2.0; CRP ≤0.5 mg/dL). This event-driven double-blind randomized withdrawal period was decisive for the primary efficacy endpoint and was followed by an up to 24-month open-label long-term extension with 160 mg of rilonacept SD weekly. The primary endpoint of this study (time to pericarditis recurrence) is discussed below in the efficacy section. In the following, only change in CRP levels is discussed as pharmacodynamics parameter.

Run-in period

Sixty-nine subjects had a baseline CRP value ≥0.5 mg/dL. In the run-in period, 68 of these subjects (98.6%) achieved CRP normalization. Median time to CRP normalization was 7 days – see **Table 1** below:

Table 1: Summary of CRP Normalization during the RI Period (Run-in Analysis Set)

Parameter	**Run-In (N = 86)**
Number of subjects with a baseline CRP measurement ≥ 0.5 mg/dL	69
Number of subjects with CRP normalization	68 (98.6)
Number of subjects censored (without normalization) and censoring reason	1 (1.4)
Completing RI period without CRP normalization	1 (1.4)
No CRP normalization on or before treatment discontinuation	0
Time to CRP normalization (days)	
25th Percentile (95% CI)	5.0 (4.0, 5.0)
Median (95% CI)	7.0 (5.0, 8.0)
75th Percentile (95% CI)	8.0 (8.0, 14.0)
CI = confidence interval; CRP = C-reactive protein; RI = run-in	

CRP levels decreased rapidly following the first administration of study drug, with substantial reduction (to ~1 mg/dL) as early as day 4 – see **Figure 4** below.

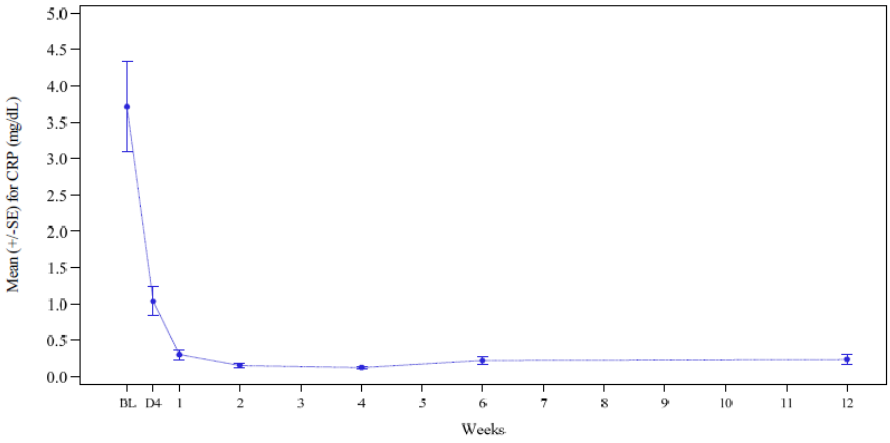


Figure 4: Mean CRP over Time during the Run-in Period (Safety Analysis Set)

Randomized withdrawal (RW) period

Median time to CRP ≥1 mg/dL was not estimable in the rilonacept arm due to the low number of subjects with CRP >1 mg/dL. However, it was 6.9 weeks in placebo subjects. At week 16, the percentage of subjects with CRP ≥1 mg/dL was 75.1% in the placebo group and 12.8% with rilonacept – see **Table 2**.

Table 2: Time to C-reactive protein level ≥1 mg/dL: RW Period (ITT Analysis Set)

	Randomized Withdrawal	
	Rilonacept (N = 30)	**Placebo (N = 31)**
Number of subjects with events (CRP ≥1 mg/dL)	3 (10.0)	25 (80.6)
Number of subjects censored	27 (90.0)	6 (19.4)
Time to CRP ≥1 mg/dL (Weeks)[a]		
25th Percentile, 95% CI	NE (8.3, NE)	3.7 (2.1, 4.6)
Median, 95% CI	NE (NE, NE)	6.9 (4.0, 10.1)
75th Percentile, 95% CI	NE (NE, NE)	15.1 (9.1, 32.0)
Hazard ratio (KPL-914 vs placebo), 95% CI[b]	0.07 (0.02, 0.22)	
Two-sided p-value[c]	<0.0001	
Percentage of subjects with CRP ≥1 (mg/dL) and 95% CI[a]		
Week 8	3.7 (0.5, 23.5)	52.9 (36.5, 71.2)
Week 16	12.8 (4.3, 35.2)	75.1 (58.3, 89.1)
Week 24	12.8 (4.3, 35.2)	81.4 (63.5, 93.9)
Week 36	12.8 (4.3, 35.2)	93.8 (76.4, 99.5)

CI = confidence interval; CRP = C-reactive protein; ITT = intent to treat; ORT = oral rescue therapy.

[a] Kaplan-Meier method used to estimate the survival functions for each treatment arm.
[b] Calculated based on a Cox proportional hazards model with treatment as covariate and stratified by oral corticosteroid use at run-in baseline.
[c] Two-sided p-value is from the log-rank test stratified by oral corticosteroid use at run-in baseline.

The central laboratory CRP levels were collected at fixed intervals, i.e., they may not reflect changes due to pericarditis recurrence. All subjects had CRP ≤0.5 mg/dL at RW baseline. The placebo group had higher baseline CRP levels than the rilonacept group (0.26 vs. 0.10 mg/dL).

Long-term extension (LTE) period

In the LTE period, subjects were reviewed at 18 months after their most recent recurrence (qualifying episode for original enrolment or recurrence in RW requiring bailout rilonacept, whichever was later), referred to as the "18-month decision milestone". During this visit, it was decided based on clinical status to (1) continue rilonacept on study, (2) suspend rilonacept for off-treatment observation (rescue allowed) or (3) discontinue the study.

After the 18-month decision milestone, the majority of subjects (>90%) who remained on treatment had CRP levels ≤0.5 mg/dL. The proportion of subjects with CRP ≤0.5 mg/dL was 100% (n=20), 96.7%

(n=29), 91.3% (n=21), 93.8% (n=15) and 100% (n=7) at 0, 12, 24, 36 and 48 weeks after the 18 month decision milestone, respectively. The one pericarditis recurrence among the 33 subjects who remained on therapy as well as the 6 recurrences among the 8 subjects who suspended rilonacept for observation, were all associated with CRP elevation.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

The ELISA analytical method to quantitate rilonacept in human serum has met all specified acceptance criteria from the validation protocol IL1T-AV-18095. However, as the method does not include a step to remove ADA from the samples, the observed negative correlation between ADA titre and rilonacept serum concentration might reflect the competition of ADAs with the antibodies used in the ELISA method rather than a "true" reduction of serum rilonacept levels. This should be discussed by the Applicant (**OC**).

The bioanalytical assay performed consistently with good precision and accuracy in both study C001 and C002. However, the Applicant should provide more details on the reasons for the "PI authorized rejection" of 18 samples from plate 390490 in study C001 (**OC**). Moreover, the applicant should specify how long the samples were stored in studies C001 and C002 and provide the long-term stability results (analyte in biological matrix) for rilonacept ELISA (**OC**).

It is noted that, in both the rilonacept and the ADA quantitation method, selectivity in diseased matrix (serum from RP patients) was not assessed, which should be justified **(OC)**. Furthermore, not all the critical reagents used in sample analysis from studies C001 and C002 were listed for both rilonacept and ADA quantitation methods. This information should be provided by the applicant **(OC)**.

The validated drug tolerance in the nAb assay does not cover the actual serum levels of rilonacept observed in the clinical studies (predicted C_{max} = 32.1 µg/mL), which may lead to interference with nAb assay performance **(OC)**.

Clinical PK information on rilonacept is mostly from efficacy and safety studies with sparse (C_{trough} only) sampling, and the evaluation of PK relies heavily on popPK analysis. In both study C001 and in the run-in period of study C002, the mean concentration (C_{trough}) *vs.* time profiles indicate that the loading dose of 320 mg is already sufficient to achieve the target plasma concentration, which is the maintained by a dose of 160 mg/week without any signs of further accumulation. The totality of the PK data across both studies C001 and C002 indicates that the systemic exposures of rilonacept for subjects with RP are similar with levels observed in CAPS subjects. The PK parameters CL/F and V/F derived from the PopPK model were similar across the CAPS, gout and RP subjects, demonstrating that the PK of rilonacept is not affected by these specific disease states.

As expected, in the randomized withdrawal period of study C002, the serum concentrations declined in the placebo group and the kinetics approximately confirms the half-life of about 7 days, which had been determined in the previous development programme for CAPS.

The results from the paediatric population, where rilonacept was dosed according to body weight, were within the range of the adult subjects. However, these data should be interpreted with caution due to limited number of studied subjects (n=7) and sparse PK sampling. The reference medicinal product was authorized in EU under exceptional circumstances with one of the special obligations to further study steady-state exposure in paediatric subjects. The applicant should clarify if the PK study to investigate rilonacept steady state in paediatric population imposed as a special obligation on the reference medicinal product was ever performed and submit the study report (**OC**)**.**

The mean trough concentrations were generally comparable between subjects in study KPL-914-C002 and CAPS, but subjects with recurrent pericarditis in study KPL-914-C001 appeared to have higher

rilonacept concentrations throughout the study than the previously studied CAPS. Moreover, there seem to be differences in bioavailability between study C001 and C002 (mean plasma concentrations in study C002 are lower than in study C001), which is confirmed by the popPK analysis (bioavailability by 41% higher in study KPL-914-C001 compared to study KPL-914-C002). The potential mechanism or cause for this should be discussed both from clinical and product quality perspective (**OC**). The applicant should provide for the paediatric population aged 12 to 17 years a comparison of predicted exposure metrics (C_{max}, C_{trough}, T_{max}, $AUC_{0-\tau}$, AR C_{max}, AR $AUC_{0-\tau}$, $t_{1/2}$) between children with RP and CAPS receiving rilonacept (a) and a comparison of the observed mean c_{trough} levels by all treatment weeks between adults and children 12-17 years based on clinical data from study C002 (b) (**OC**).

Moreover, it is not understood why exposure metrics were predicted only for subjects from study C002 and not for subjects from study C001. That should be further clarified and same model predicted PK parameters (C_{max}, C_{trough}, t_{max}, $AUC_{0-\tau}$, AR C_{max}, AR $AUC_{0-\tau}$, $t_{1/2}$) provided for subjects in study C001. Higher predicted exposure as compared to subjects in study C002 should be discussed related to safety and efficacy (**OC**).

The popPK analysis revealed that body weight influences clearance and volume of distribution of rilonacept. The resulting impact of body weight on exposure in adult patients with flat dosing (LD: 320 mg and MD of 160 mg) was shown for 50% of the patients (in the range of 25th to 75th weight percentile: 66-97 kg) and deemed not clinically relevant. The impact with regard to safety and efficacy should also be shown for extreme weights seen in adults (at least in the range observed in the study: 50 – 169 kg) receiving flat doses. The results should be discussed related to efficacy and safety. In addition, due to the body weight-based dosing in adolescents, in a 50 kg adolescent, the dose will only be 69 % of the dose of an adult with the same weight. The resulting differences in exposure should be discussed with respect to efficacy (**OC**). It is noted that ADA titer and CRP was reported to be a significant covariate on CL/F in CAPS patients but not in RP patients. The reasons for such differences should be discussed (**OC**).

In both studies, the participants or their caregivers were mostly able to administer the drug following the first injection by the healthcare professional and the second one under the guidance of the trained healthcare professional. Self-administered injections made up >95% of administrations for each part in Study C001 and ranged from 87.54% to 96.15% in Study C002. However, it is questioned whether the proposed product is suitable for the self-administration in clinical reality. Data from the drug utilisation study and/or post marketing experience would be informative.

Pharmacodynamics

Rilonacept blocks IL-1 signalling by acting as a soluble decoy receptor that binds IL-1α and IL-1β and prevents cytokine interaction with the cell surface receptor, attenuating inflammatory and other effects secondary to excess IL-1. Free cytokine levels have not been measured before or after rilonacept administration.

The pharmacokinetic (PK) and pharmacodynamic (PD) properties, focusing primarily on the impact of ADAs on the PK of rilonacept, were previously evaluated in healthy participants, in participants with CAPS, and in other diseases where IL-1β plays a role (rheumatoid arthritis, systemic juvenile idiopathic arthritis, chronic active gout, and well-controlled end-stage renal disease). The pharmacokinetics of rilonacept are linear and dose-proportional in healthy participants and in participants with CAPS, rheumatoid arthritis, gout, and end-stage renal disease. As with other large therapeutic proteins, rilonacept is expected to be cleared largely by proteolytic catabolism. The observed terminal half-life of rilonacept is approximately 6 to 8 days.

The PD effect of rilonacept administration on circulating CRP levels and other pericarditis manifestations in the broader context of recurrent pericarditis events was evaluated in the C001 and C002 studies and

is discussed further under these studies. However, a side-by-side comparison of weekly CRP levels for ADA negative and ADA positive participants should be provided (**OC**).

The CSR states that blood samples for central assessment of biomarkers were performed, but it does not define which biomarkers in addition to CRP were measured and what were the results. This should be clarified **(OC)**.

In clinical studies, the use of rilonacept has been associated with increases in total, HDL and LDL cholesterol. Data from C002 showed that there was some increase in the lipid levels, including significant increase of mean triglycerides at week 24 in the randomized withdrawal period. It has been discussed that this change is based on the decrease of inflammation (which caused initial lipid lowering), not by any direct effects from rilonacept to the lipid metabolism. No further investigation on the potential mechanism for lipid profile changes has been performed and this is considered acceptable. The aspect of lipid profile change and subsequent lipid profile monitoring during rilonacept treatment is adequately addressed in SmPC.

Rilonacept, as an interleukin-1 (IL-1) inhibitor, is not metabolized via the cytochrome P450 (CYP450) system, making it less prone to conventional drug-drug interactions. Based on the mechanism of action, there is potential for additive effects with other immune modulating drugs, and this is adequately described in the SmPC.

A separate population PK study (KINIK202002) was performed concurrently in Study KPL-914-C002 subjects. Based on the report, serum drug concentrations are comparable to previously studied populations. No assessment on the relationship between plasma concentration and effect/safety was performed, although it was evident that most of the pericarditis recurrences occurred while the plasma concentrations were low (mainly based on placebo group, mean individual predicted concentration prior to recurrence 1.251.25 µg/mL).

3.3.4. Clinical efficacy

3.3.4.1. Dose response studies

No dose finding studies specific for RP were conducted.

The rilonacept dosing regimen used in the pivotal study was the same as the previously approved rilonacept dosing regimen for adult and paediatric subjects with CAPS; i.e., 320 mg SC loading dose (4.4 mg/kg in subjects ≥12 and <18 years old), followed by once weekly SC doses at 160 mg (2.2 mg/kg in subjects ≥ 12 and <18 years old). Reference is made to the Rilonacept Regeneron EPAR (EMEA/541561/2009).

In the rilonacept development program in CAPS, gout, rheumatoid arthritis, and other inflammatory conditions, more than 2000 subjects were exposed to rilonacept, including 1650 subjects receiving a rilonacept dose of 160 mg or higher. A total of 103 and 169 subjects were exposed to any rilonacept dose for at least 1 year or 6 months, respectively. As of March 2018, when the protocol was written, approximately 365 CAPS patients had been exposed to rilonacept in the postmarketing setting since 2008. The accumulated safety data supported the benefit/risk ratio for the rilonacept dose evaluated in subjects with recurrent pericarditis.

The same dose was investigated in the Phase 2 proof-of-concept study (KPL-914- C001). Study C001 was a Phase 2 open-label, single-active-arm, pilot study designed to explore the clinical and biochemical endpoints of pericarditis symptomatology and to collect inter-and intra-participant variability data on both at-baseline and on-treatment parameters. participants with different clinical features of patients with pericarditis. 1) Part 1 enrolled symptomatic participants with recurrent idiopathic pericarditis with

an elevated marker of systemic inflammation (CRP >1 mg/dL). 2) Part 2 enrolled symptomatic participants with recurrent idiopathic pericarditis with CRP ≤ 1 mg/dL which, in the opinion of the investigator, can be attributed to concomitant medications (e.g., corticosteroids) and with pericardial inflammation present on cardiac MRI confirmed by the imaging core lab. 3) Part 3 enrolled participants with corticosteroid-dependent recurrent idiopathic pericarditis not experiencing symptoms which would meet the diagnostic criteria for a pericarditis recurrence. 4) Part 4 enrolled symptomatic participants with recurrent post-pericardiotomy syndrome with an elevated marker of systemic inflammation (CRP >1 mg/dL). 5) Part 5 enrolled participants with corticosteroid-dependent recurrent post-pericardiotomy syndrome not experiencing symptoms which would meet the diagnostic criteria for a pericarditis recurrence. Exploratory analyses indicated that treatment with rilonacept was associated with

1. Resolution of pericarditis episodes as indicated by: a. Rapid and sustained reductions in participant-reported pericarditis pain using the 11-point pain NRS pain scale b. Improved participant physical and mental quality of life (QoL) using a global health instrument (PROMIS v1.2), c. Resolution or improvement in objective clinical manifestations of pericarditis, including pericardial effusions, rub, ECG changes, and CRP levels

2. Reduction in pericarditis recurrences as indicated by: a. Reduction in annualised incidence of pericarditis episodes while on rilonacept treatment during the study as compared to prior to the study. Interpretation of the data was hampered by the lack of a control group. Particularly, calculated incidence rates of pericarditis recurrences are prone to regression to the mean effects. However, based on these data the same dose was forwarded to be investigated in the pivotal phase 3 study (KPL-914-C002). As summarized above (PK), the rationale not to administer a reduced dose in low weight adults to achieve a dose matching with paediatric patients is not entirely clear but. Low weight adults may have a higher exposure than adolescents or adults at higher weight. Whether this is relevant for safety should be further addressed **(OC).**

Overall, the approach is acceptable. Feasibility of conducting a comprehensive dose finding programme in patients with RP is limited by the number of patients available and by variability associated with recurrent pericarditis events. Regarding non-specific safety, data available from other indications may be supportive. At the end concluding on a positive benefit risk balance of the dose based on the pivotal RHAPSODY trial may also serve to establish the proposed dose regimen.

3.3.4.2. Main studies

Study KPL-914-C001:

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

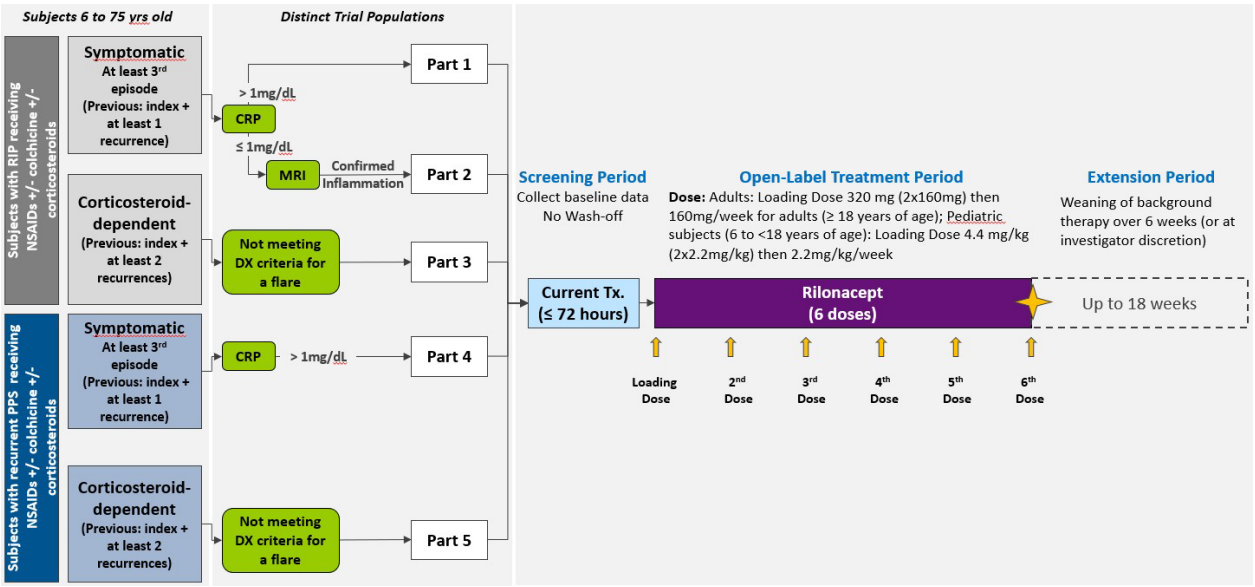
Study design

Study C001 consisted of 5 distinct parts enrolling different subsets of RP (see subjects below)

All subjects were treated with once-weekly (QW) SC-administered injections of rilonacept. In the Base Treatment Period, 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 enter the Long-term Extension Period (LTE) and receive an additional 18 weeks of rilonacept treatment up to week 24.

For embarking into the extension period treatment response was defined by the investigator as:

• Parts 1, 2, and 4: A clinically significant reduction in pericardial pain using the 11-point numeric rating scale (NRS), normal or near normal CRP levels, and/or absent or decreasing ECHO effusion at the End-of-Trial Visit
• Parts 3 and 5: Absence of pericarditis flare and feasibility to taper corticosteroids



Sparse sampling was collected for the analysis of rilonacept serum concentrations. In order to measure C_{trough}, blood samples were collected prior to the first dose and prior to each subsequent dose during the Base Treatment Period. Additional PK and ADA samples were collected from subjects in the Extension Period.

- **Study Participants**

Eligible subjects were adult (18 years or older) and paediatric (≥ 6 years old) subjects with history of idiopathic RP or RP due to PPS. Subjects with diagnosis of RP secondary to specific etiologies as predefined in the study protocol were excluded.

Subjects in the 5 different parts.

(1) Symptomatic subjects with idiopathic recurrent pericarditis (RP) with an elevated marker of systemic inflammation (CRP >1 mg/dL)
(2) Symptomatic subjects with idiopathic RP with CRP ≤1 mg/dL which, in the opinion of the investigator, could be attributed to concomitant medications (e.g., corticosteroids) and with pericardial inflammation present on cardiac MRI confirmed by the imaging core lab
(3) Subjects with corticosteroid-dependent idiopathic RP not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis
(4) Symptomatic subjects with recurrent post-pericardiotomy syndrome (PPS) with an elevated marker of systemic inflammation (CRP > 1 mg/dL).

(5) Enrolled subjects with corticosteroid-dependent recurrent PPS not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis.

Main Inclusion Criteria

Male or female, of any ethnic origin, 6 to 75 years of age, inclusive, and others with RP according to on of the 5 groups above.

- Treatments

Open label rilonacept, first dose at study site (visit 1), follow up doses were to be administered by subject or caregiver at the abdomen, thigh, or upper arm sites and were to be rotated.

In adult subjects (≥ 18 years old), rilonacept was administered as an initial loading dose of 320 mg SC on Day 0, delivered as 2 SC injections of 160 mg (2ml) each on the same day at 2 different sites, then 160 mg SC dosed once weekly for 5 subsequent weeks in the Treatment Period and continued at the same doses for 18 weeks in the EP.

Subjects aged 6 years to < 18 years were to receive an initial loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as 2 injections of 2.2 mg/kg each SC with a maximum single injection volume of 2 mL. Dosing continued with a once-weekly injection of 2.2 mg/kg SC, up to a maximum of 160 mg, administered as a single injection of up to 2 mL for 5 subsequent weeks in the Treatment Period and continued at the same doses for 18 weeks in the EP.

Rilonacept (KPL-914; ARCALYST) was manufactured by Regeneron (Tarrytown, NY) and provided as a lyophilized formulation.

Background Pericarditis Medication Requirements for All Parts:

Subjects included in Parts 1, 2, and 4 could be receiving stable doses of concomitant NSAIDs, and/or colchicine, and/or oral corticosteroid treatment in any combination. Subjects in Parts 3 and 5 had to receive corticosteroids at enrolment and had to be considered 'corticosteroid-dependent' (i.e., the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn).

For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, were to be continued at pre-study dose levels until after the Treatment Period was concluded at the Visit 7/End-of-Trial (EoT) visit if reduction was not considered medically indicated.

Compliance was assessed by the means of a medication diary. Subjects returned all used and unused medication to the Study site/Clinic for accountability and reconciliation.

- **Objectives**

The pilot study in subjects with idiopathic RP or PPS pericarditis was designed to assess improvement of pericarditis symptomatology with rilonacept administration, feasibility of weaning from corticosteroid while receiving rilonacept in subjects with corticosteroid-dependent idiopathic RP or PPS, and safety and rilonacept dose relationships.

Primary Objective for Parts 1, 2 and 4

• To collect inter- and intra-subject variability data on CRP measurements and the 11-point Numeric Rating Scale (NRS) instrument for assessment of pericardial pain in subjects with idiopathic RP or symptomatic recurrent PPS both at baseline and on treatment with rilonacept in order to inform power calculations for future trials in pericarditis

Primary Objective for Parts 3 and 5

• To evaluate feasibility of weaning from corticosteroids while receiving rilonacept in subjects with corticosteroid-dependent idiopathic RP or recurrent PPS

And additional secondary objectives

- **Outcomes/endpoints**

Primary Efficacy Endpoints

Parts 1, 2, and 4

Primary efficacy endpoints for Parts 1, 2, and 4 include inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with idiopathic RP or recurrent PPS both at baseline and while on active rilonacept treatment in order to inform power calculations for future trials in pericarditis.

Parts 3 and 5

The primary efficacy endpoint for Parts 3 and 5 is disease activity after corticosteroid taper in subjects with corticosteroid-dependent idiopathic RP or recurrent PPS.

- **Sample size**

The sample size was chosen on an empirical basis, based on RP prevalence and number of subjects needed to inform phase 3 planning in this condition. Approximately up to 40 subjects with idiopathic RP or recurrent PPS were to be enrolled as study subjects across all Parts.

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

- **Randomisation and Blinding (masking)**

It was an uncontrolled open label study.

- **Statistical methods**

Analysis was descriptive in nature.

Analysis population:

The safety population consisted of all subjects who received at least 1 dose of study drug. The safety population was used for all safety analyses.

The modified Intention to Treat (mITT) was the same as the safety population.

The Per-Protocol Population consisted of all subjects who received all 7 doses of study drug during the active Treatment Period and who were maintained at stable dose levels of concomitant pericarditis medications (NSAIDs, colchicine, and/or corticosteroids, if used during screening) according to study protocol without a major protocol deviation with potential impact on efficacy.

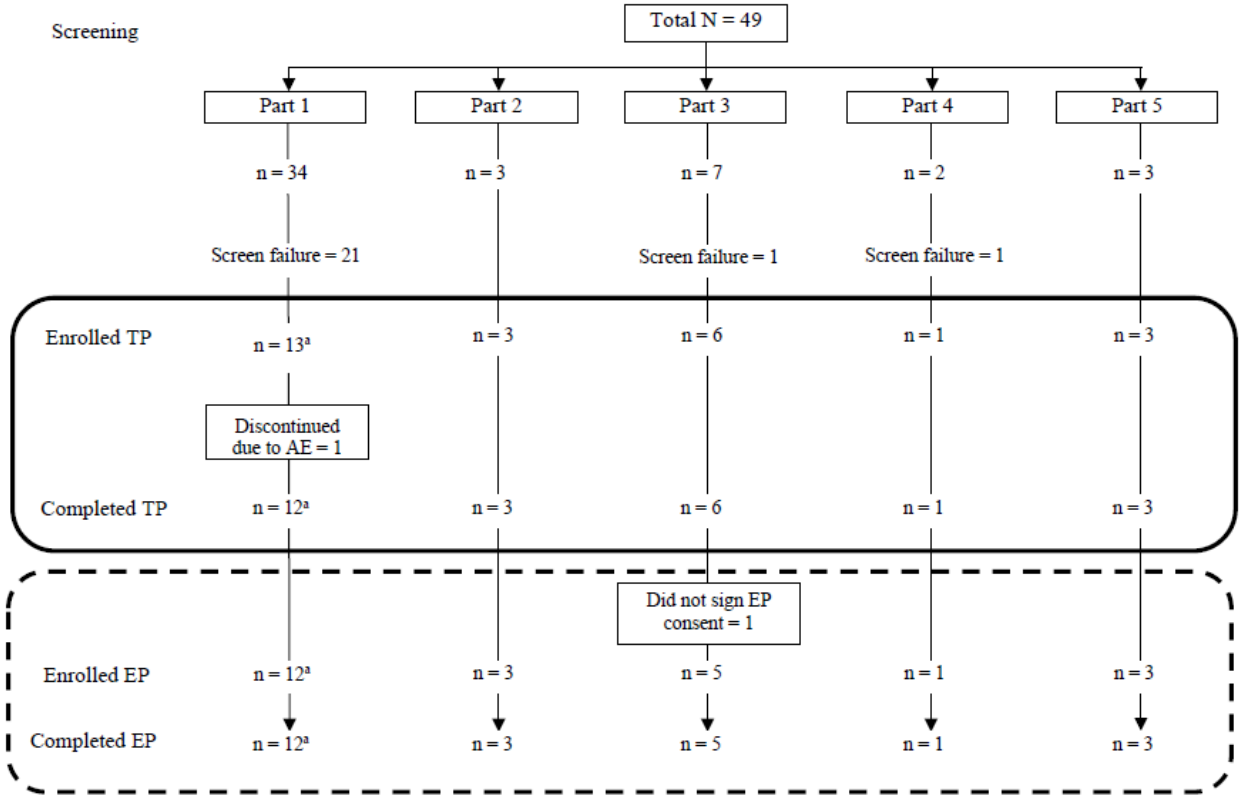
The Extension Period population consisted of all subjects who received at least 1 dose of the study drug during the EP. This population was used for analysis of select efficacy endpoints defined at final visit (Visit 8/Week 25). One subject was excluded from the EP population. The data collected during the EP for this subject was presented separately.

Results

Nine out of 14 study centres throughout the United States screened subjects and 7 sites enrolled at least 1 subject

- **Participant flow and Recruitment**

26 subjects were enrolled (25 unique subjects), and 24 subjects completed the study (10M/15F). Parts 1, 2, 3, 4, and 5 comprised 12, 3, 6, 1, and 3 participants in, respectively. Most screen failures were due to CRP levels not meeting Inclusion or Exclusion Criteria.



- [a]Overall, 26 patients were enrolled in the study but only 25 unique patients were included in the analyses (as presented by N=25 in efficacy and safety tables). Results from one subject, who was enrolled a second time as Subject are presented separately

- **Conduct of the study**

One subject was enrolled twice in the study. The second enrolment was excluded from the Safety, the mITT and the PP Population, and data for this subject was presented separately.

The original protocol was dated 25 September 2017. The protocol was amended 3 times, key changes are listed below.

Amendment 2 (14 February 2018): Parts 2, 3, 4, and 5 were added to study population

- The paediatric dosing regimen was added

Protocol deviations

Overall, 9 subjects had major protocol deviations. In addition, other major protocol deviations were reported in 12 subjects. The number and quality of protocol deviations are within the expected range and do not impact the ability to analyse and draw conclusions of the efficacy and safety data for the trial.

- **Baseline data**

Demographics

The mean age was 42.8 (SD 10.51) years (range: 26 to 62 years), i.e., all enrolled participants were adults. Slightly more female than male participants were enrolled (n = 15, 60.0% female) and the majority of participants were White (n=22, 88.0%). Baseline mean (SD) weight was 87.71 (16.725) kg (range: 58.1 to125.0 kg), and mean (SD) body mass index (BMI) was 30.900 (6.6851) kg/m2 (range: 22.49 to 52.71 kg/m2). The mean duration of disease was 2.20 (1.872, range: 0.2 to 7.9) years.

Of the 25 subjects, 22 (88%) were taking at least 1 medication for pericarditis at baseline. Three (12.0%) subjects were taking 1 medication for pericarditis, and 19 subjects (76%) were taking 2 or more different medications for pericarditis at baseline. Medications included: colchicine (80%), corticosteroids (60%), NSAIDs (48%), and aspirin (8%). All subjects in Parts 3 and 5 (corticosteroid-dependent idiopathic RP and PPS) were taking corticosteroids as required by the protocol.

Mean (SD) NRS scores at baseline were as follows: Part 1, 4.6 (1.68); Part 2, 4.7 (3.06); Part 3, 1.2 (0.75); Part 4, 4.0; Part 5, 2.0 (2.65). In Parts 1, 2, and 4 combined, 11 (68.8%) subjects reported NRS scores $\geqslant$4 compared with 1 (11.1%) subject in Parts 3 and 5 combined.

Mean (SD) CRP scores at baseline as assessed by central laboratory were as follows: Part 1, 4.907 (5.7686) mg/dL; Part 2, 0.460 (0.4424) mg/dL; Part 3, 0.232 (0.0975) mg/dL; Part 4, 1.140 mg/dL; Part 5, 0.097 (0.0503) mg/dL.

- **Numbers analysed**

25 unique subjects were analyzed. The following number of patients were included in the respective sets: mITT/Safety; PP

Part 1: 12; 7. Part 2: 3; 1. Part 3: 6; 6. Part 4: 1; 1. Part 5: 3; 2

- **Outcomes and estimation**

Primary Efficacy Endpoints

The primary endpoints for Parts 1, 2, and 4 were inter- and intra-subject variability estimates for CRP and the 11-point pain NRS, both at baseline and while on active rilonacept treatment, in symptomatic subjects with idiopathic RP or recurrent PPS.

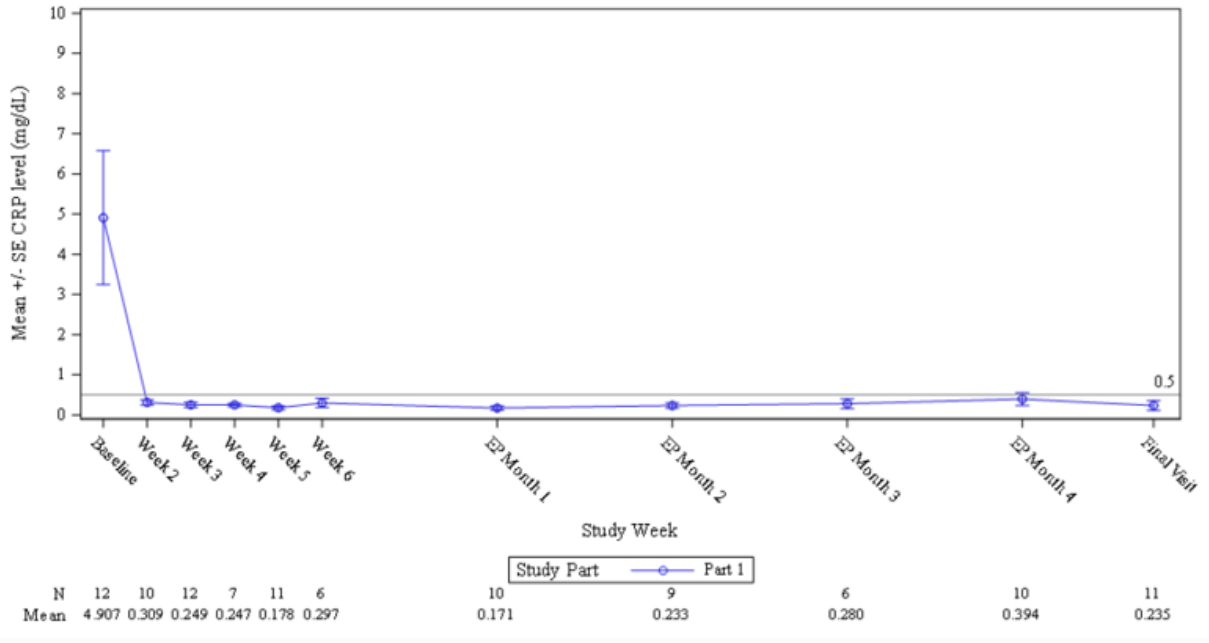
The primary endpoint for Parts 3 and 5 was disease activity after corticosteroid taper in subjects with corticosteroid-dependent idiopathic RP or recurrent PPS.

For a detailed description of results on C-Reactive Protein Levels Over Time see above (pharmacodynamics)

C-Reactive Protein

Mean CRP levels decreased from baseline after the first rilonacept dose in Part 1; by Week 2 mean CRP was < 0.5 mg/dL and remained below that threshold at all subsequent timepoints (Figure 5). CRP decreases were noted for all other Parts, though with the exception of Parts 1 and 4, decreases were trivial as baseline CRP levels were all below 0.5 mg/dL.

Figure 5: Mean ± SE CRP Levels Over Time – Study Part 1 (mITT Population)



EP = Extension Period; mITT = modified intent-to-treat; NRS = numeric rating scale; SE = standard error.

Inter- and Intra-participant Variability in CRP

The intra-participant variance is an estimate of the variability due to within-participant variability. For Part 1 participants' CRP values during the pretreatment period, this was 12.6852, which contributed for 39.8% (= 12.6852/31.8760) of the overall variance. During the on-treatment period, the within-participant variability only accounted for 0.16% (=0.0548/34.1994) of overall variance. This was likely due to different scales (original CRP values during pretreatment versus change from baseline during on treatment), as well as a homogeneous drop of CRP values in participants after receiving rilonacept.

Based on current study data, the overall SD for CRP changes was 5.8480, and for within-participant CRP variability, SD was 0.2341.

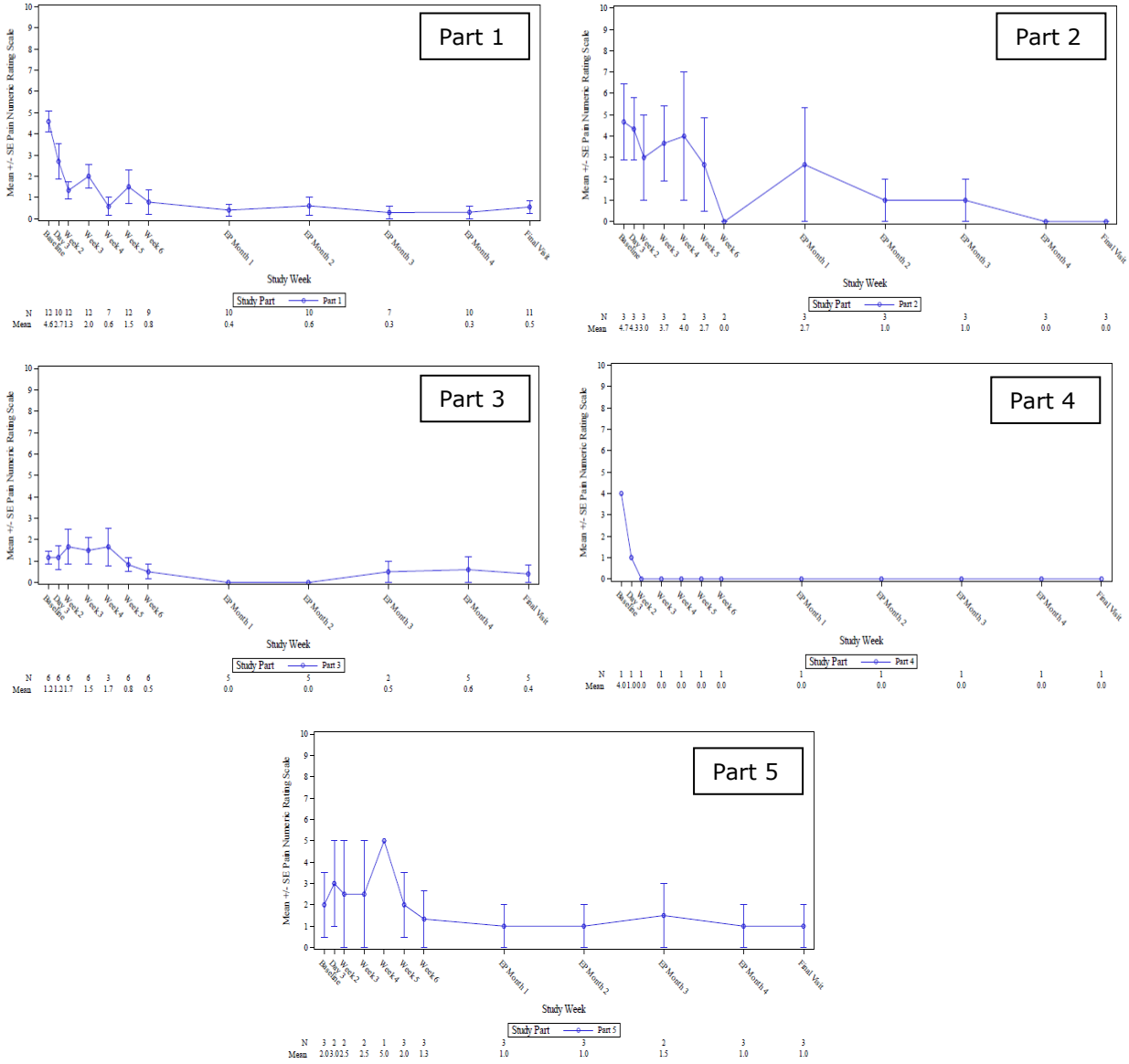
11-point pain NRS

Pericarditis pain was measured using the 11-point pain NRS. Subjects in Parts 1, 2, and 4 entered the study with symptomatic pericarditis episodes and therefore higher mean baseline pain levels compared to subjects in Parts 3 and 5, who entered the study without symptomatic episodes.

Mean pain levels, as measured by the patient-reported 11-point NRS, decreased from baseline at Week 2 in all parts of the study enrolling symptomatic patients with an acute RP episode. The average reduction in pain was 4 points on the NRS. The reductions in mean pain level were maintained throughout the 24-week combined base treatment and extension periods. In parts 1 and 4, reductions in average pericarditis pain were observed as soon as after the first (loading) dose of rilonacept, while the effect was somehow delayed in parts 2, 3 and 5. Overall, the decreases were greater for parts 1, 2, and 4 compared with parts 3 and 5. The greatest change from baseline occurred in part 1. The participants in parts 3 and 5 maintained low average pain and CRP levels despite tapering off the corticosteroids, while rilonacept treatment continued

At baseline, 66.7% of subjects in Parts 3 and 5 and no subjects in Parts 1, 2, and 4 had NRS scores ≤1 (= low pain level). At the final visit, NRS scores were ≤1 for all subjects in Parts 2 and 4, ~80% of

subjects in Parts 1 and 3; and 66.7% of subjects in Part 5. In the following figure, the development of NRS data over time is shown for each study part:



Inter- and Intra-subject variabilities in Pain NRS (only part 1)

The primary objective for Parts 1, 2, and 4 was to collect inter- and intra-subject variability data on CRP measurements and the 11-point NRS instrument for assessment of pericardial pain in subjects with idiopathic RP or symptomatic recurrent PPS both at baseline and on treatment with rilonacept.

The inter- and intra-subject SDs during pre-treatment in Part 1 were 1.6775 and 0.9845, respectively. The overall variance was 3.7832. At visit, for the pain NRS of part 1, the intra-subject variability was 0.9693, i.e., 25.6% of the overall variance of 3.7832. During the on-treatment period, the inter- and intra-subject SD for change-from-baseline values were 1.4131 and 1.3266, respectively. The overall variance was 3.7565. The intra-subject variance was 1.7598, i.e., 46.8% of the overall variance of 3.7565. Based on current study data, the overall SD for pain NRS changes was 1.9382, and for intra-subject pain NRS variability, SD was 1.3266.

Clinical response

Clinical response was defined as normal CRP (≤0.5 mg/dL) and pain NRS ≤2 at the same visit. Subjects fulfilling these criteria at study entry are presented as subjects with clinical response at baseline. Clinical response was observed in all study parts as early as Week 2. At the final visit, 80% of subjects in Part 1, 66.7% of subjects in Part 5, and all subjects in Parts 2, 3, and 4 demonstrated clinical response.

Other efficacy endpoints

Pericarditis signs

Documented pericarditis signs (recorded as "present" or "absent") included pericardial rub, typical pericarditis ECG changes (widespread ST elevation or PR depression based on local reads), fever (temperature ≥37.5° C), and presence of pericardial effusion on local ECHO evaluation.

At baseline, 12 out of 25 participants presented with 1 or more other pericarditis manifestations. Seven of 12 (58.3%) participants in Part 1 and 2 of 6 (33.3%) participants in Part 3 exhibited pericardial effusion; 2 of 12 participants (16.7%) participants in Part 1 exhibited pericardial rub; 2 of 12 participants [16.7%]) in Part 1 had widespread ST-segment elevation and 3 of 12 (25%) participants in Part 1 had PR depression on ECG.

These signs had generally resolved by the Interval Evaluation Visit: Pericardial rub and widespread ST-segment elevation were not observed in any Part; PR depression was observed in 2 subjects in Part 1, and pericardial effusion was observed in 1 subject each in Parts 1 and 3. By the final visit, PR depression and pericardial effusion were observed in 1 (9.1%) subject in Part 1, and pericardial effusion was observed in 1 subject (20%) in Part 3. Those effusions at final visit were commented by investigators as trivial/physiologic in the eCRF comment field.

ECHO Pericardial Effusion

At baseline, 7 subjects in part 1 and 2 subjects in part 3 exhibited a pericardial effusion. Of those, 6 (85.7%) subjects in part 1 did not have an effusion at the final visit. Of the 2 subjects in part 3, 1 still had an effusion and 1 had no data at the final visit. The subject who had no data at the final visit was a subject who elected not to enter the EP. His last available ECHO evaluation at V7/EoT was negative for pericardial effusion.

There appeared to be a positive correlation between CRP readings and pericardial effusion based on local ECHO readings for subjects in part 1 (CRP value at screening >1 mg/dL). For part 1, the association reached significance ($p<0.05$) at screening visit 1 ($p=0.0394$), at the interval evaluation visit ($p=0.0116$), at visit 7/end of TP ($p<0.0001$).

Recurrent pericarditis (RP) episodes during the study

One subject in part 1 had 1 RP episode during the study. No RP episodes were observed in the other study parts. Prior to the study, the mean (SD) number of pericarditis recurrences was 3.917 (3.6589). The annualized incidence of pericarditis during the study was a mean (SD) of 0.18 (0.620) for part 1 and 0 for all other study parts.

Cardiac MRI

Cardiac MRI with intravenous gadolinium was an optional assessment in the study, with exception of Part 2 subjects, where it was mandatory for assessment of subjects' eligibility. Presence of at least moderate delayed hyper-enhancement (DHE) was considered by central imaging core laboratory readers as clinically significant in contrast to mild DHE, which can be representative of prior recurrence and not reflect active disease/recurrence.

18 subjects (17 unique subjects) had ≥1 cardiac MRI assessment, and 11 subjects had baseline and final visit assessments. Treatment with rilonacept reduced pericardial inflammation on cardiac MRI as measured by improved pericardial DHE and pericardial effusion.

Among 9 subjects with presence of pericardial DHE at baseline (i.e., either mild, moderate or severe) and follow up cMRI, DHE improved or resolved in all but 2 subjects (DHE unchanged in part 2 and part 5). One subject in part 3 had no pericardial DHE at baseline and had mild DHE at the final visit. One subject in part 5 had myocardial DHE noted at the final visit, but baseline values were missing.

Seven subjects with MRI pericardial effusion at baseline had a follow up MRI. Pericardial effusion resolved in 6 subjects and decreased from very large to trivial/physiologic in 1 subject. One subject in part 3 had no pericardial effusion at baseline and trivial/physiologic pericardial effusion at the final visit.

Quality of Life Assessments Using PROMIS v1.2

Results in Global Physical Health

For subjects in Part 1 (N=12), the average baseline score for global physical health was 41.29, which is below the average in the US population (50). At the final visit, the average score for global physical health was 50.97, which was slightly better than the average of 50 in the US general population. The mean (SD) of change from baseline to final visit was 9.33 (4.544). The standardized effect size (mean change from baseline divided by standard SD) for within-subject comparison was 2.053. Mean global physical health scores increased from baseline to final visit in all the other groups, with the largest increase occurring in Part 2 (19.40).

Results in Global Mental Health

The average baseline-score for global mental health in Part 1 (N=12) was 46.38 (page 46), which was slightly below the average of the US general population. The average score at final visit (N=12) was 49.98, almost identical to the average of 50 in the US general population. The mean (SD) of change from baseline to final visit was 3.35 (5.653).

Study KPL-914-C002 (pivotal phase 3 study)

A Phase 3 double blind, placebo-controlled, randomised withdrawal study with an open-label extension, to assess the efficacy and safety of rilonacept treatment in adult and paediatric subjects with RP. A secondary objective of the study was to characterise the PK profile of rilonacept in subjects with RP.

Methods

- **Study design**

The study was conducted in Australia (6 centres), Italy (3 centres), Israel (10 centres), USA (39 centres).

The study was composed of the following three treatment periods (see also **Figure 6** below):

- **Period 1: Single-blind Run-In (RI) period (12 Weeks):** SC loading dose of 320 mg of rilonacept for adults and 4.4. mg/kg for paediatric subjects [≥12 and <18 years old], and 12 × QW maintenance SC doses of 160 mg for adults and 2.2 mg/kg for paediatric subjects.

  During the single-blind RI period, treatment with open-label rilonacept was administered, and subjects were tapered off background standard-of-care (SOC) therapy for pericarditis.

- **Period 2: Double-blind placebo-controlled Randomised Withdrawal (RW) period (event driven - 0 to 51 weeks):**

  During the RW period, eligible subjects were randomized 1:1 to double-blinded administration of study drug:

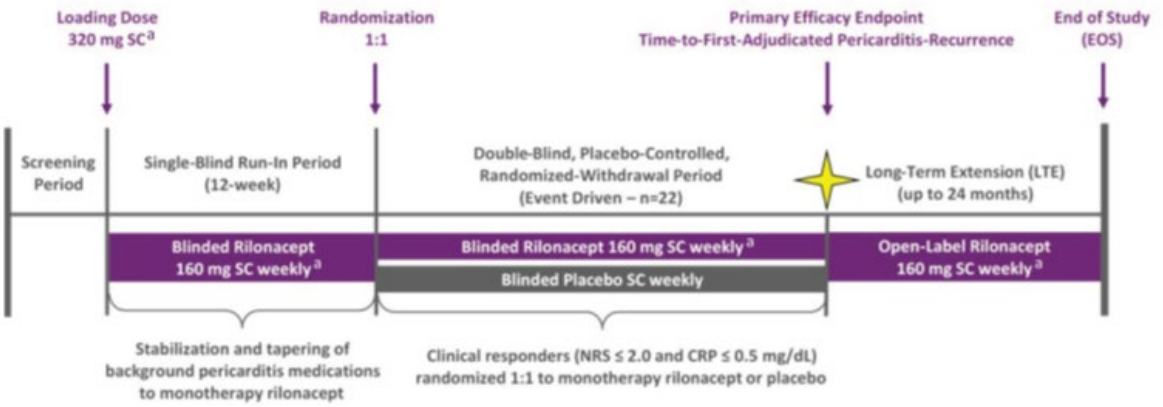
  • Rilonacept 160 mg (or 2.2 mg/kg in paediatric subjects ≥ 12 and < 18 years old) administered by subcutaneous (SC) injections once weekly OR

  • Matching placebo SC injections once weekly

  The RW period lasted until 22 independently adjudicated pericarditis cases had occurred.

- **Period 3: Long Term Extension Period (LTE) (up to 24 months; ongoing):** All subjects in the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) and subjects who successfully completed the RI period after closure of randomisation had the option to receive up to 24 months of open-label rilonacept (160 mg SC QW for adults and 2.2 mg/kg SC QW for paediatric subjects). The LTE is ongoing at the time of this submission.

Figure 6: Study Design



CRP = C-reactive protein; EOS = end of study; LTE = long-term extension; NRS = numerical rating scale; SC = subcutaneous
[a] Adult dose. The pediatric loading dose of rilonacept was 4.4 mg/kg SC, then 2.2 mg/kg SC once weekly throughout the RI period

For all subjects, serum samples were collected to quantify concentrations of rilonacept and ADAs.

- **Study Participants**

Key inclusion criteria (among others addressing informed consent, concerns on childbearing potential and birth control, immunization, adherence to study procedures and refraining from of major lifestyle changes)

- 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):

a. Pericarditic chest pain

b. Pericardial rub

c. New widespread ST-segment elevation or PR-segment depression according to ECG findings

d. Pericardial effusion (new or worsening)

- 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:

a. At least 1 day with pericarditis pain ≥4 on the 11-point NRS, AND

b. 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.

- **Treatments**

Rilonacept was provided as a lyophilized formulation for reconstitution and s.c. administration (for details see phase 2 study above).

Patients in the control group received matching placebo.

Dosing and administration

Patients received 320 mg SC loading dose (4.4 mg/kg in subjects ≥12 and <18 years old), followed by once weekly SC doses at 160 mg (2.2 mg/kg in subjects ≥12 and <18 years old).

The first study drug administration for adult and paediatric subjects at the RI baseline was prepared and administered by study site staff. The second injection was prepared and administered by the subject or the subject's caregiver after adequate training and under the supervision of study site personnel. Subsequent once weekly study drug doses were self-administered SC by the subject or administered to the subject by a trained caregiver as an outpatient administration if possible. If the subject or subject's caregiver was unable to prepare and inject the study dug, the subject may have received the injections at the study site or by a visiting registered nurse. No data were provided on whether patients were appropriately able to handle self-administration.

Background pericarditis therapy

Subjects were allowed to take concomitant stable NSAIDs and/or colchicine, and/or oral corticosteroid treatment in any combination

During a 1-week stabilization period of the RI, all SOC therapy was to remain stable. During the 9-week tapering period, SOC therapy was to be tapered and discontinued. During the 2-week monotherapy period, subjects were not allowed any SOC therapy, except for opioid analgesics if necessary.

During the RW period, no SOC therapy was permitted, with the exception of opioid analgesics if necessary.

Subjects who met the protocol criteria for bailout rilonacept upon pericarditis recurrence in the RW period of the study, regardless of treatment assignment at randomization, received open label rilonacept (loading dose of 320 mg SC followed by once weekly SC injections of 160 mg, or the corresponding paediatric doses). No less than 5 days after the most recent administration of study drug. Sequential ORT (i.e., analgesics, NSAIDs, colchicine) was also allowed at the Investigator's discretion.

It is not entirely clear from the study report which batches of the investigations drugs were used in RHAPSODY.

- **Objectives.**

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

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

- **Outcomes/endpoints**

Primary Efficacy Endpoint

The primary efficacy endpoint **was time to pericarditis recurrence (CEC-confirmed),** defined as the time from randomization to the date of the first pericarditis recurrence for each subject.

Pericarditis recurrence was defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis where applicable.

The CEC adjudicated potential cases on an ongoing basis, and used the following definitions to confirm pericarditis recurrence:

1. Re-appearance or worsening of typical pericarditis pain (with at least one pain NRS recording ≥4)

AND elevated CRP (≥1.0 mg/dL) either on the same day or separated by

no more than 7 days

OR

2. Re-appearance or worsening of typical pericarditis pain (with at least one pain NRS recording ≥4)

AND abnormal CRP (>0.5 mg/dL) either on the same day or separated by no more than 7 days

AND at least 1 supportive evidence of pericarditis as below

OR

3. Re-appearance or worsening of typical pericarditis pain (but no NRS scores being ≥ 4)

AND elevated CRP (≥ 1.0 mg/dL) not attributable to other causes

AND at least 1

supportive manifestation of pericarditis as below.

Supportive evidence (pericarditis manifestations):

− increased WBC count > UNL

− fever >38°C

− presence of pericardial rub

– ECG changes consistent with pericarditis

– new or worsening pericardial effusion on ECHO

– new or worsening pericardial inflammation on MRI or other imaging modality

Key Secondary Efficacy Endpoints

Key secondary endpoints for the RW period were as follows:

- Proportion of subjects who maintained 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 pericarditis pain is defined as non-missing NRS $\leq$ 2.
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGI-PS) at Week 16 of the RW period.

The following Patient- and Physician-Reported Outcomes were used

The Patient Global Impression of Pericarditis Symptoms (PGI-PS)

Physician Global Assessment of Pericarditis Activity (PGA-PA)

The SF-36 was was completed by subjects ≥18 years of age.

The 6-dimensional health state short form (SF-6D) derived from SF-36.

The European Quality of Life–Five Dimensions (EQ-5D-5L)

The Insomnia Severity Index (ISI)

Concerning additional secondary endpoints see results below.

- **Sample size**

For the purpose of sample size estimation, time to pericarditis recurrence was assumed to follow an exponential distribution. An event of interest was defined as a subject's first adjudicated recurrence of pericarditis. Given a 1-sided significance level of 2.5%, median time to event with placebo treatment of 8 weeks (based on rilonacept washout pharmacokinetics at steady state), and an assumed hazard ratio of 0.244, a minimum of 22 adjudicated pericarditis recurrence events was required to achieve 90% power. Thus, it was planned to randomize approximately 25 subjects per arm (a total of 50 subjects) to treatment. Considering 10% of subjects in the RI period were expected not to reach the RW period, approximately 56 subjects were planned to be enrolled in this study.

- **Randomisation and Blinding (masking)**

In the single-blind RI period, all subjects received blinded rilonacept at the same dose through Week 12; subjects were blinded to the time of transitioning to RW. Subjects who stopped background SOC pericarditis therapy and who achieved clinical response on rilonacept at RI Week 12/RW baseline were randomly assigned in a double-blind manner to receive blinded rilonacept or matching placebo using a 1:1 allocation ratio. Randomization was stratified to ensure balance of the treatment groups with respect to the various combinations of potentially prognostic factors. The randomization was stratified by 2 factors:

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

In the event of a pericarditis recurrence that met the criteria for bailout rilonacept, the subject was transitioned to open label rilonacept but remained blinded to his or her prior RW treatment assignment.

Site staff, CRO personnel, and the sponsor also remained blinded to treatment assignment. At the end of the RW period, subjects transitioned to open label rilonacept without being unblinded to their RW treatment assignment.

- **Statistical methods**

The following analysis populations were defined:

Intent to treat (ITT) analysis set: All subjects who were randomized in the RW period. The primary analysis for efficacy endpoints in the RW period was based on the ITT analysis set. Treatment comparisons for all ITT analyses was based on each subject's treatment assignment from randomization.
ITT Week 24 (week 16, week 8) analysis set: All subjects randomized at least 24 weeks (16 weeks, 8 weeks) before data cut-off. This analysis set was used for secondary efficacy endpoints measured at Week 24 (Week 16, Week 8) in the RW period.
Safety analysis set: All subjects who received at least 1 dose of study drug in the RI period. Safety analyses were based on the actual treatment a subject received.
Run-in analysis set (RIS): All subjects who received at least 1 dose of study drug in the RI period.
Long-term extension analysis set: All subjects who received at least 1 dose of study drug in the LTE period.
Per-protocol analysis set: A subset of the ITT analysis set excluding subjects with important protocol violations

There were 2 stratification variables for randomization: oral corticosteroid use at baseline (yes or no), and diagnosis of recurrent idiopathic pericarditis at RI baseline (yes or no). Strata were to be pooled in analyses stratified by these variables when a stratum had ≤ 5 events of interest

The primary efficacy endpoint was time to pericarditis recurrence. Subjects who did not have a CEC-confirmed pericarditis recurrence were censored at the date of the last available assessment for pericarditis recurrence during the RW period on or before data cutoff. Detailed censoring rules were specified in the SAP.

The log rank test was the primary method for the analysis of time to recurrence based on CEC confirmed events, stratified by the stratification variables for randomization. The ITT analysis set was the primary analysis set. Analysis based on the PP analysis set was considered as a sensitivity analysis. A sensitivity analysis was performed based on the Investigator's assessment of pericarditis recurrence.

Time to recurrence was summarized with the 25th, 50th (median), and 75th percentiles using the Kaplan-Meier method. The percentage of subjects with pericarditis recurrence and its 95% CI were calculated at Weeks 8, 16, 24, and 36 since randomization. The hazard ratio for rilonacept versus placebo and the corresponding Wald 95% CI was calculated based on a Cox proportional-hazards model with treatment as covariate, stratified by randomization strata.

Key secondary endpoints for the RW period were as follows:

- Proportion of subjects who maintained clinical response at Week 16 of the RW period. For this endpoint, the response rate and Clopper–Pearson 95% CI were obtained for each arm. The difference in response rates (rilonacept vs. placebo) and 95% CIs based on normal approximation were provided. The Cochran-Mantel-Haenszel (CMH) test was used to test the treatment effect, stratified by the stratification variables for randomization.
- Percentage of days with no or minimal pericarditis pain in the first 16 weeks of the RW period. No or minimal pericarditis pain is defined as non-missing NRS ≤ 2. This endpoint was analyzed with an analysis of covariance. In addition to treatment arm, the covariates included

stratification variables for randomization and RI baseline NRS weekly average in 2 categories, NRS ≤ 2 versus NRS > 2.

- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGI-PS) at Week 16 of the RW period. For this endpoint, the response rate and Clopper-Pearson 95% CI were obtained for each arm. The difference in response rates (rilonacept vs. placebo) and 95% CI based on normal approximation were provided. The CMH test was used to test the treatment effect, stratified by the stratification variables for randomization.

In order to control the overall 1-sided type I error rate at the 0.025 level, a gatekeeping procedure in combination with Hochberg's procedure was applied to testing the primary and key (major) secondary endpoints.

To the extent possible, attempts were made to minimize the amount of missing data through measures planned in the study. Unless otherwise specified, missing data were not imputed and only the observed data were used in the analyses. For the primary efficacy endpoint, time to pericarditis recurrence, subjects without a recurrence or lost to follow-up were censored at the last recurrence assessment. For the binary key secondary efficacy endpoints, missing data were considered as non-responders. For the continuous key secondary endpoint, percentage of days with pain NRS ≤2 in the first 16 weeks of the RW period, days with missing NRS values was counted as not meeting the NRS criterion.

Results

- **Participant flow and Recruitment**

Run in (RI) and Randomized Withdrawal (RW) period

Eighty-six subjects were enrolled in the study, and 79 subjects completed the RI period. Among the 7 subjects who did not complete the RI period, 4 (4.7%) discontinued due to an AE; 2 (2.3%) discontinued due to Investigator decision; and 1 (1.2%) discontinued for "other" reasons. Three subjects (3.5%) completed the RI period but did not meet the stringent protocol-defined clinical response criteria and thus did not enter the RW period: 2 due to CRP levels, and 1 due to pain score.

Of the 61 randomized subjects, 1 subject in the placebo group withdrew consent during the RW period, 1 subject completed the RW period but withdrew consent prior to participating in the LTE, and 59 subjects completed the RW period.

Seventy four of 75 eligible subjects continued into the LTE: Fifteen subjects went directly from the RI period to the LTE because, at that time, the protocol-specified 22 adjudicated pericarditis recurrence events had accrued.

Subject disposition for the run-in and the randomized withdrawal period is shown in **Figure 7** below.

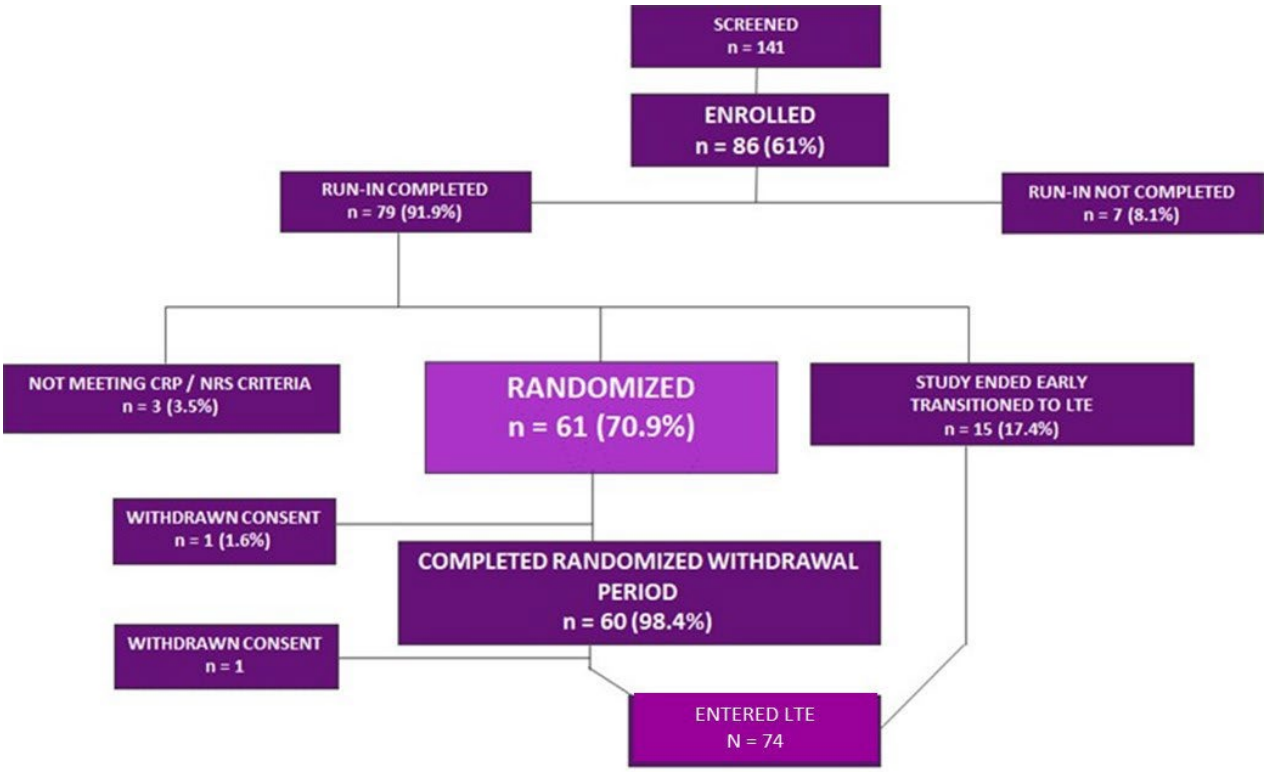


Figure 7: Disposition of subjects for run in and randomized withdrawal period of study C002.

Long-term extension (LTE) period

A total of 74 subjects, 59 from the RW and 15 from the RI Periods, transitioned to the LTE. The LTE at US sites was terminated after approximately 1 year, in April 2021, as planned, at the time of commercial launch of ARCALYST. Subjects in the US were required to end their participation in the LTE, transitioning either to commercial ARCALYST or to other standard of care treatment. The LTE continued outside of the US until its formal completion in June 2022.

Overall, 69 (93.2%) subjects completed the LTE period. Of the 5 subjects who discontinued the study early, 3 withdrew consent, 1 was lost to follow-up, and 1 was discontinued due to an SAE. The mean (SD) number of weeks subjects participated in the LTE was 74.8 (25.66).

Overall, 25 (33.8%) subjects completed the full 2-year planned treatment period of the LTE, and 49 (66.2%) subjects discontinued treatment early, i.e., prior to the 2-year planned duration. Of the 49 subjects who discontinued treatment early, 3 discontinued because of AEs (acute endocarditis, COVID pneumonia, fatigue), 2 for pregnancy, 2 subject decision, and 42 subjects reported "other" reasons.

When the LTE was closed in the US in April 2021, 32 US-based subjects switched to commercial ARCALYST, and 10 US-based subjects transitioned to standard of care, declining commercial ARCALYST (LTE).

Subject disposition for the LTE period is provided in Figure 8 below.

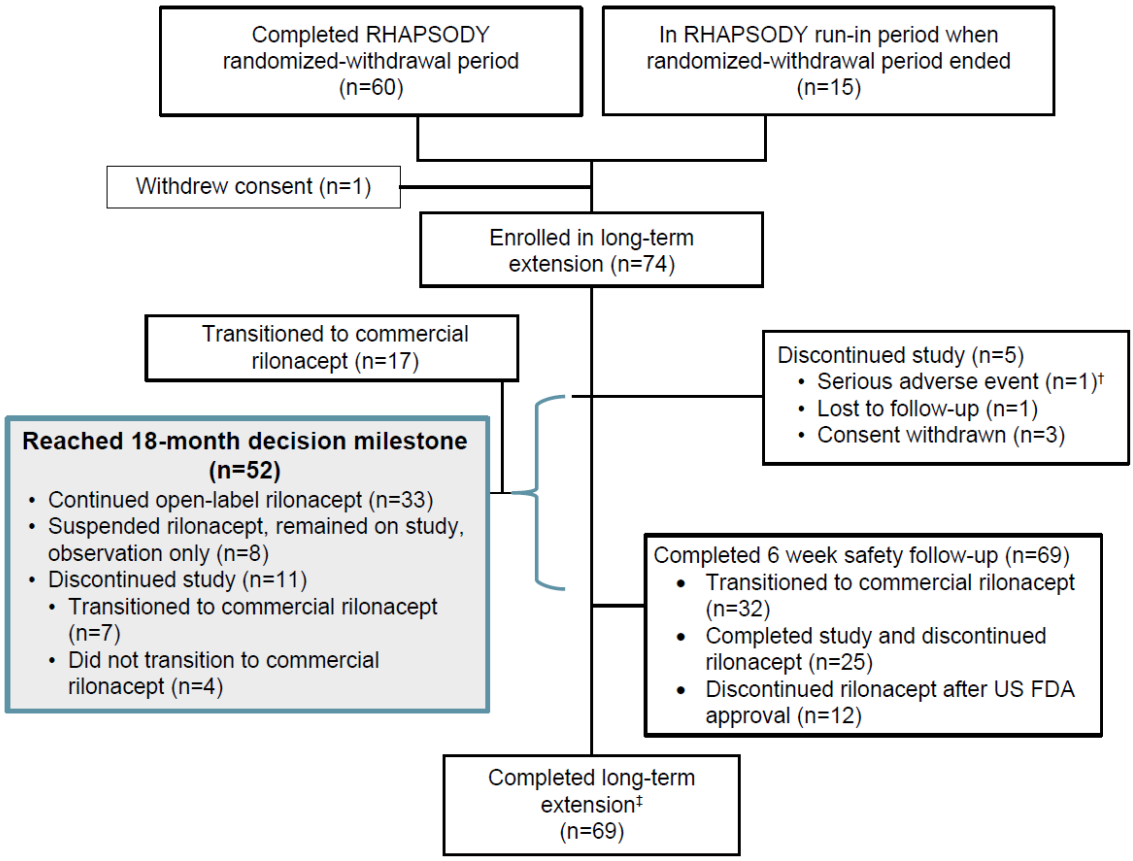


Figure 8: Disposition of subjects for the long-term extension (LTE) period of study C002.

The high number of patients not entering the RW period after RI was mainly not due to AEs or lack of efficacy but due to the protocol amendment 2. After achieving 22 events patients in the RI were offered to directly embark into the LTE. 15 of 86 enrolled patients did not enter the RW period due to achieving the predefined number of 22 events in the RW period were transferred directly to the LTE period.

- **Conduct of the study**

Changes in the Conduct of the Study or Planned Analyses

The original protocol (Version 1), dated 26 September 2018, was modified on 05 October 2018 (Version 1.1). This modification was not a formal amendment; administrative changes were made affecting an intentionally blank page, additions to the reference list.

Version 1.1 of the protocol was amended twice. Minor administrative and clerical changes were made with each amendment. Major changes to the protocol are outlined below:

Amendment 1, 12 April 2019

• Revised one of the criteria for permanent discontinuation of study drug • Added a baseline PK drug level measurement • Removed the 10-subject cap for the cardiac MRI Substudy • Revised the text regarding full physical examinations

Amendment 2, 10 March 2020

The following changes were made based on recommendations by the FDA from the Type B meeting (04 March 2020):

• The primary efficacy endpoint analysis triggered at 22 CEC-confirmed (adjudicated) pericarditis events. The requirement for 24 weeks of follow-up for all subjects was eliminated.

• Allowed subjects in the RI when randomization is closed and who met the definition of a clinical responder to directly enter the LTE period

• The LTE period was extended to 24 months, and the off-treatment observation follow-up was eliminated. Also allowed subjects to discontinue treatment, remain in the study for observation, and resume open label rilonacept in event of a subsequent recurrence

• Added an assessment in the LTE at 18 months from most recent recurrence.

• Increased enrolled population to up to 100 subjects and clarified exclusion language regarding antibiotic use

• Added additional secondary endpoints; made 16 weeks the primary time point in the RW for secondary endpoint and designated analyses at Weeks 8 and 24 as sensitivity analyses.

Changes due to COVID-19

In addition to the changes made in conjunction with the 2 protocol amendments, study conduct was altered to address health concerns arising from the COVID-19 pandemic.

In addition, some minor changes to the SAP and changes to the efficacy analyses of the LTE were implemented.

Protocol deviations

Randomized Withdrawal Period

Important protocol deviations were reported in subjects for whom study conduct was affected by COVID-19 modifications. 1 subject had an important deviation (non-COVID-19) that was considered to potentially impact efficacy analyses: dosing occurred outside of the ± 2-day window, and pericarditis recurred after missing 2 doses. This subject, who received placebo during the RW period, was not included in the per-protocol population.

During the LTE out of 74 patients 10 (13.5%) had at least one important protocol deviation, 8 with Missing endpoint assessments, and 1 with Study procedures/assessments and "other", respectively.

Overall, the protocol deviations reported do neither raise general concerns on the conduct of the study nor on the reliability of the overall results.

- **Baseline data**

Demographic and Other Baseline Characteristics

Selected demographic and baseline characteristics for the safety analysis set are shown in Table 3 and Table 4, respectively. Overall, more subjects (57.0%) were female. The majority of subjects were white (93.0%), with a mean age of 44.7 years. The majority of subjects were adults (79 of 86, 91.9%); 7 subjects (8.1%) were <18 years of age. Approximately half the subjects were using oral corticosteroids at baseline. The majority of subjects (84.9%) had been diagnosed with idiopathic recurrent pericarditis at baseline; 14.0% had post-pericardiotomy syndrome, and 1.2% had Dressler syndrome. Additional information is requested on the latter two groups **(OC)**. Mean disease duration was 2.41 years, and

mean number of pericarditis episodes per year was 4.42. In general, demographic and baseline characteristics were similar between subjects randomized to rilonacept or placebo in the RW period. Although all subjects met CRP and NRS pain score criteria at screening, changes in concomitant medications during screening resulted in some subjects having normal CRP and/or improved pain scores at baseline.

Of the 7 patients between 12 and 17 years included in the RI period only three entered the RW period.

Table 3. Demographic characteristics: Safety Analysis Set

Parameter	Run-in (N = 86)	Randomized Withdrawal		
		Rilonacept (N = 30)	Placebo (N =31)	Total (N = 61)
Sex, n (%)				
Male	37 (43.0)	14 (46.7)	15 (48.4)	29 (47.5)
Female	49 (57.0)	16 (53.3)	16 (51.6)	32 (52.5)
Race, n (%)				
White	80 (93.0)	28 (93.3)	28 (90.3)	56 (91.8)
Black or African American	5 (5.8)	1 (3.3)	3 (9.7)	4 (6.6)
Other	1 (1.2)	1 (3.3)	0	1 (1.6)
Ethnicity, n (%)				
Hispanic or Latino	1 (1.2)	0	0	0
Not Hispanic or Latino	85 (98.8)	30 (100)	31 (100)	61 (100)
Mean age, years (SD)	44.7 (16.1)	48.0 (15.7)	44.8 (14.5)	46.4 (15.1)
Age group, years, n (%)				
12-17	7 (8.1)	1 (3.3)	2 (6.5)	3 (4.9)
18-64	71 (82.6)	24 (80.0)	27 (87.1)	51 (83.6)
65-78	8 (9.3)	5 (16.7)	2 (6.5)	7 (11.5)
Mean body mass index (kg/m^2) (SD)	28.71 (8.1)	28.16 (6.6)	29.26 (8.9)	28.72 (7.7)

SD = standard deviation.

Table 4. Baseline characteristics: Safety Analysis Set

		Randomized Withdrawal		
Characteristic	**Run-in (N = 86)**	**Rilonacept (N = 30)**	**Placebo (N =31)**	**Total (N = 61)**
Oral corticosteroid use at baseline, n (%)				
Yes	41 (47.7)	13 (43.3)	14 (45.2)	27 (44.3)
No	45 (52.3)	17 (56.7)	17 (54.8)	34 (55.7)
Duration of oral corticosteroids before enrollment, n (%)				
< 4 weeks	24 (58.5)	8 (61.5)	9 (64.3)	17 (63.0)
4 to < 26 weeks	8 (19.5)	3 (23.1)	2 (14.3)	5 (18.5)
≥ 26 weeks	9 (22.0)	2 (15.4)	3 (21.4)	5 (18.5)
Recurrent pericarditis type, n (%)				
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's syndrome	1 (1.2)	1 (3.3)	0	1 (1.6)
Mean pericarditis duration, years (SD)	2.41 (3.1)	3.10 (4.4)	1.91 (2.1)	2.49 (3.5)
Mean number of episodes per year (SD)	4.42 (4.9)	4.37 (5.2)	4.33 (2.9)	4.35 (4.26)
Pericardial effusion (new or worsening), for qualifying episode, n (%)				
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)
Mean qualifying pain score on NRS (SD)	6.2 (1.8)	6.4 (1.7)	6.3 (1.9)	6.3 (1.8)
Mean qualifying CRP value, mg/dL (SD)	6.18 (6.68)	6.59 (7.30)	5.99 (5.10)	6.29 (6.23)

CRP = C-reactive protein; NRS = numerical rating scale; SD = standard deviation.

Long-term Extension Period

Of the 74 subjects who entered the LTE, 40 (54.1%) were female, and 34 (45.9%) were male. The majority of subjects (68/74, 91.9%) were white, and the mean (SD) age was 44 (15.6) years.

Prior and Concomitant Medications

In the safety analysis set, 90.2% of subjects took at least one prior medication, and 96.7% were taking at least one non-pericarditis concomitant medication at baseline.

Concomitant (background) pericarditis medications over time: At baseline, 79 subjects (91.9%) were taking background pericarditis medications. The number of subjects taking background pericarditis medications decreased steadily throughout the RI period. By RI Week 12, only 3 (3.8%) of 79 subjects were taking background pericarditis medications; these 3 subjects did not meet clinical response criteria and did not enter the RW period.

Mean overall treatment compliance during the study was 98.66% and was 99.30% during the RI period. Treatment compliance was similar for adult and paediatric subjects.

- **Numbers analysed**

All 86 subjects enrolled received at least 1 dose of study drug and were included in the run-in analysis set and safety analysis set. The numbers of subjects included in the ITT analysis sets for the RW period are shown in Table 5.

Table 5. Analysis Sets: Randomized Withdrawal Period

	Number of Subjects (%)		
Analysis Set	**Rilonacept**	**Placebo**	**Total**
ITT/randomized[a]	30 (34.9)	31 (36.0)	61 (70.9)
Week 8	27 (90.0)	31 (100)	58 (95.1)
Week 16	21 (70.0)	20 (64.5)	41 (67.2)
Week 24	17 (56.7)	15 (48.4)	32 (52.5)

ITT = intention to treat; RW = randomized withdrawal.
[a]ITT analysis set included all subjects who were randomized in the RW period. ITT analysis set was the same as the safety analysis set in the RW period. The denominator of the percentage was the number of subjects in run-in analysis set (86). ITT at Week 8, 16, and 24 included ITT subjects randomized 8, 16, and 24 weeks before the data cutoff, respectively. The denominator for the percentage is the number of subjects in the ITT analysis set.

Long-term Extension Period

Subjects who stopped background pericarditis medications and achieved clinical response on rilonacept monotherapy at RI Week 12 proceeded into the RW period ("Randomized"). Subjects who achieved clinical response on rilonacept monotherapy by the end of the RI period but did so after the event-driven RW period had closed (June 2022) were nevertheless given the option to participate in the LTE and receive open-label rilonacept without having proceeded through the RW period ("Not randomized").

All 74 subjects who entered the LTE period received at least 1 dose of study medication and were included in the LTE analysis set.

- **Outcomes and estimation**

Primary Efficacy Endpoint

Time to Pericarditis Recurrence in the Randomized Withdrawal Period

The time to pericarditis recurrence for the rilonacept treatment arm was significantly longer than for the placebo arm, with a hazard ratio of 0.04 (95% CI: 0.01; 0.18; Table 6); rilonacept reduced the risk of recurrence by 96%. These results are shown graphically in a Kaplan-Meier curve in Figure 9. Mean time to pericarditis recurrence was not estimable in the rilonacept group because there were too few recurrences. The median time to recurrence for subjects in the placebo arm was 8.6 weeks and was not estimable for the rilonacept arm.

By Week 8 of the RW period, the recurrence rates for the placebo and rilonacept arms were 49.6% and 0.0%, respectively. The recurrence rates increased to 73.4%, 80.1%, and 90.0% for the placebo arm and 4.3%, 4.3%, and 11.2% for the rilonacept arm at RW Weeks 16, 24, and 36, respectively, indicating that continued treatment with rilonacept resulted in a continued clinical response in subjects in the majority of subjects.

A majority of subjects randomized to the placebo arm (23/31 subjects, 74.2%) experienced a pericarditis recurrence event during the RW period, while only 2 of 30 subjects (6.7%) randomized to the rilonacept treatment arm experienced a recurrence event. The 2 events in the rilonacept arm were associated with temporary treatment interruptions of 1 to 3 doses.

Table 6: Time to Pericarditis Recurrence Based on CEC Adjudication (ITT Analysis Set)

	Randomized Withdrawal	
	Rilonacept (N = 30)	**Placebo (N = 31)**
Pericarditis recurrence categories, n (%)		
Number of subjects with events (pericarditis recurrence)	2 (6.7)	23 (74.2)
Recurrence without receiving ORT, corticosteroid or bailout rilonacept	2 (6.7)	22 (71.0)
Recurrence after receiving ORT/corticosteroid[a]	0	1 (3.2)
Recurrence after receiving bailout rilonacept	0	0
Number of subjects censored (without pericarditis recurrence)	28 (93.3)	8 (25.8)
Time to recurrence (weeks)[b]		
25th Percentile, 95% CI	NE (12.1, NE)	3.7 (2.1, 5.3)
Median, 95% CI	NE (NE, NE)	8.6 (4.0, 11.7)
75th Percentile, 95% CI	NE (NE, NE)	19.6 (9.1, NE)
Hazard ratio (KPL-914 vs placebo), 95% CI[c]	0.04 (0.01, 0.18)	
Two-sided p-value[d]	<.0001	
Pericarditis recurrence rate and 95% CI[b]		
RW Week 8	0.0 (0.0, 0.0)	49.6 (33.5, 68.3)
RW Week 16	4.3 (0.6, 27.1)	73.4 (56.0, 88.2)
RW Week 24	4.3 (0.6, 27.1)	80.1 (61.4, 93.5)
RW Week 36	11.2 (2.8, 39.0)	90.0 (68.0, 99.1)

CEC = clinical endpoint committee; CI = confidence interval; ITT = intent to treat; NE = not estimable; ORT = oral rescue therapy; RW = randomized withdrawal.

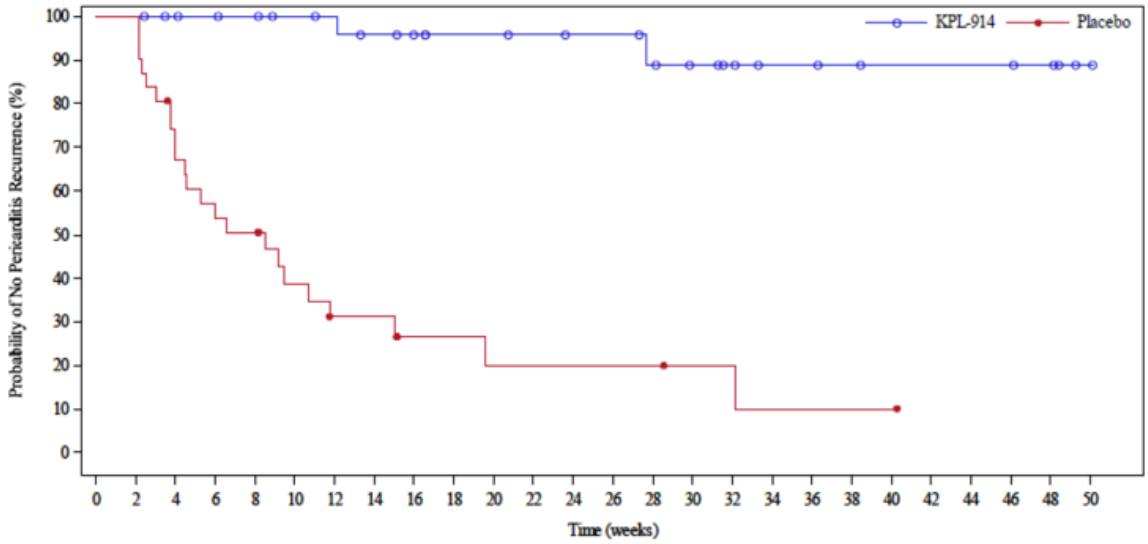
[a] Excluding subjects receiving ORT/corticosteroid while waiting for at least 5 days since previous administration of study medication before receiving bailout rilonacept or within 5 days prior to recurrence visit. No subject received corticosteroid as rescue medication.

[b] Kaplan-Meier method used to estimate the survival functions for each treatment arm.

[c] Calculated based on a Cox proportional-hazards model with treatment as covariate and stratified by oral corticosteroid use at run-in baseline.

[d] Two-sided p-value is from the log-rank test stratified by oral corticosteroid use at run-in baseline.

Figure 9: Kaplan-Meier Curves for Time to Pericarditis Recurrence Based on CEC Adjudication (ITT Analysis Set)

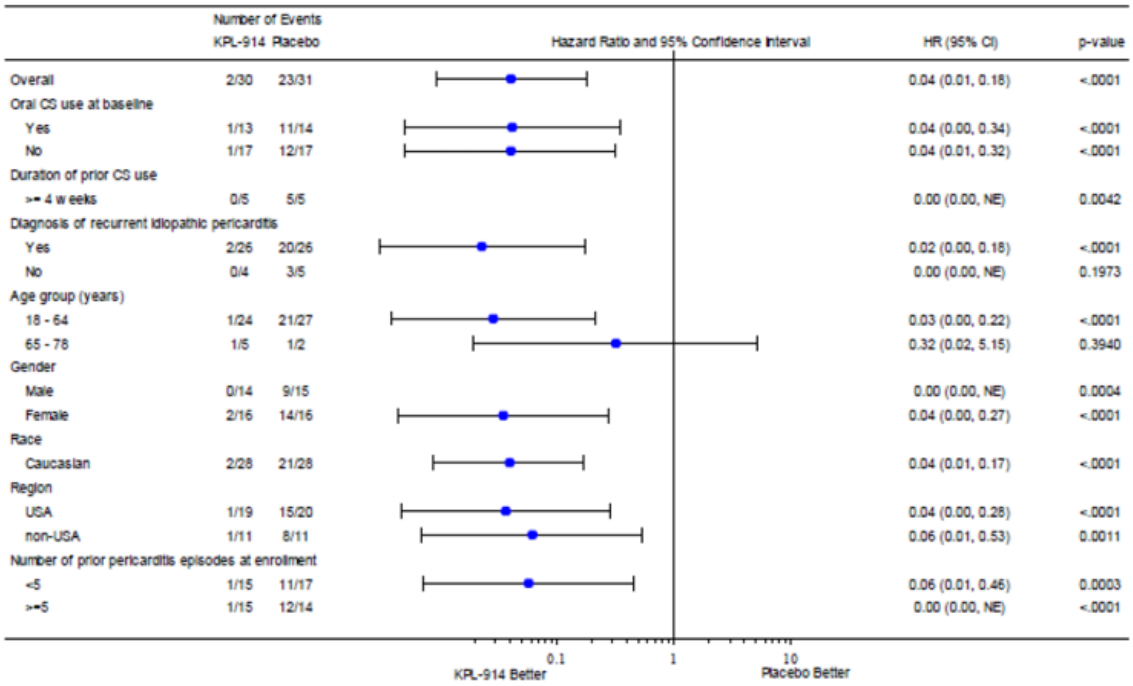


CEC = clinical endpoint committee; ITT = intent to treat.

The treatment effect may be somewhat lower in the proposed target group of patients. 7 out of 86 patients enrolled did not complete the run in. 15 of 86 enrolled patients did not enter the RW period due to having achieved the predefined number of 22 primary endpoint events (amendment 2) and were directly transferred to the LTE period. It is not entirely clear whether all of these 15 patients met the clinically defined response criteria.

A forest plot of the results for the primary efficacy endpoint for the following subgroups are shown in Figure 10: oral corticosteroid use at baseline and at ≥4 weeks at baseline; diagnosis of recurrent idiopathic pericarditis; age; sex; race; region; and number of pericarditis episodes. All subgroup analyses showed nominally a statistically significant result except for "no idiopathic pericarditis" and "age 65 to 78 years".

Figure 10: Forest Plot for CEC-adjudicated Time to Pericarditis Recurrence in the Randomised Withdrawal Period: Subgroup Analyses (ITT Analysis Set)



CEC = clinical endpoint committee; CI = confidence interval; CS = corticosteroid; HR = hazard ratio; ITT = intent to treat.

The results in the subgroup are overall consistent indicating a treatment effect of rilonacept. No numerically significant result could be demonstrated for patients above 64 years and patients with non-idiopathic RP.

No results were presented on efficacy for paediatric patients 12 – 17 years separately, only 3 out of 7 patients included in the RI period embarked the RW period.

Key Secondary Efficacy Endpoints

Proportion of subjects who maintained clinical response at Week 16 of the RW period
A key secondary efficacy endpoint was the proportion of subjects with maintenance of clinical response (defined as 11-point NRS ≤2.0 and CRP level ≤0.5 mg/dL) at week 16 of the randomized withdrawal period. Subjects who had a recurrence of pericarditis, used bailout rilonacept or rescue medications, discontinued study drug, or were lost to follow-up were considered non-responders.

Significantly more subjects in the rilonacept group maintained clinical response (17/21; 81.0%) at week 16 than in the placebo group (4/20; 20.0%) with the difference reaching statistical significance (p = 0.0002). A similar significant response was observed at Weeks 8 and 24. The results are shown in **Table 7** below.

Table 7: Maintained Clinical Response at RW Weeks 24, 16, and 8 (ITT Week 24, 16, and 8 Analysis Set)

Proportion of Patients Who Maintained Clinical Response [1]	Randomised Withdrawal Period	
	KPL-914	Placebo
RW Week 24 (ITT Week 24 Analysis Set), n	17	15
Number of Patients Maintained Response	13	3
Maintained Clinical Response and 95% CI, (%) [2]	76.5 (50.1, 93.2)	20.0 (4.3, 48.1)
Difference in Proportions and 95% CI [3]	56.5 (27.9, 85.0)	
Odds Ratio, 95% CI [4]	8.370 (1.317, 53.188)	
Two-Sided p-value [4]	0.0022	
RW Week 16 (ITT Week 16 Analysis Set), n	21	20
Number of Patients Maintained Response	17	4
Maintained Clinical Response and 95% CI, (%) [2]	81.0 (58.1, 94.6)	20.0 (5.7, 43.7)
Difference in Proportions and 95% CI [3]	61.0 (36.7, 85.2)	
Odds Ratio, 95% CI [4]	12.727 (2.438, 66.428)	
Two-Sided p-value [4]	0.0002	
RW Week 8 (ITT Week 8 Analysis Set), n	27	31
Number of Patients Maintained Response	21	8
Maintained Clinical Response and 95% CI, (%) [2]	77.8 (57.7, 91.4)	25.8 (11.9, 44.6)
Difference in Proportions and 95% CI [3]	52.0 (30.0, 74.0)	
Odds Ratio, 95% CI [4]	10.906 (3.051, 38.981)	
Two-Sided p-value [4]	<.0001	

[1] Clinical Response is defined as a weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS, CRP level ≤ 0.5 mg/dL, and on monotherapy of randomised study drug in that week. Patients who had recurrence, or used bailout rilonacept, or used rescue medication, discontinued double-blinded treatment, or lost to follow-up before the week were considered non-responders.
[2] Percentages are based on the ITT Weeks 24, 16, and 8 Analysis Sets which include participants randomised at least 24, 16, and 8 weeks before data cutoff, respectively. The exact 95% CI is calculated with randomisation strata pooled.
[3] Based on a normal approximation.
[4] 95% CI and p-value are analysed using a Cochran-Mantel-Haenszel (CMH) test adjusted by oral corticosteroid use and Diagnosis of Recurrent Idiopathic Pericarditis at RI baseline.
CI = confidence interval; RW = randomised withdrawal

Percentage of days with no or minimal pericarditis pain in the first 16 weeks of the RW period.
A key secondary endpoint was percentage of days in the RW period with pain ≤2 on the NRS (defined as no or minimal pericarditis pain) in the first 16 weeks. Subjects receiving rilonacept experienced significantly more days with no or minimal pericarditis pain during the first 16 weeks of the RW period than did subjects who received placebo. The least squares mean of days with no or minimal pericarditis pain in the first 16 weeks were 98.6% and 47.4% for subjects receiving rilonacept and placebo, respectively (p <0.0001) (see **Table 8** below). Results at week 8 (rilonacept: 97.9%; placebo: 57.3%) and week 24 (rilonacept: 100.6%; placebo: 48.7%) were consistent with those observed at week 16 (both p <0.0001).

Table 8: Percentage of Days with No or Minimal Pericarditis Pain in the Randomized Withdrawal Period

Time Point/Statistic	Randomized Withdrawal	
	Rilonacept	Placebo
In first 16 weeks (ITT Week 16 analysis set)[a]		
N	21	20
Mean	92.1	39.8
SD	13.52	35.06
Median	96.4	24.1
Minimum	41	4
Maximum	100	100
Least squares mean (SE)	98.6 (7.55)	47.4 (7.26)
Least squares mean difference (rilonacept – placebo), 95% CI	51.2 (34.5, 68.0)	
Two-sided p-value[b]	<0.0001	
In first 8 weeks (ITT Week 8 analysis set)[a]		
N	27	31
Mean	89.7	50.6
SD	20.65	33.59
Median	98.2	42.9
Minimum	4	0
Maximum	100	100
Least squares mean (SE)	97.9 (7.64)	57.3 (7.19)
Least squares mean difference (rilonacept – placebo), 95% CI	40.5 (25.3, 55.8)	
Two-sided p-value[b]	<0.0001	
In First 24 weeks (ITT Week 24 analysis set)[a]		
N	17	15
Mean	91.6	41.2
SD	11.29	35.23
Median	97.0	31.5
Minimum	61	4
Maximum	100	100
Least squares mean (SE)	100.6 (8.02)	48.7 (7.64)
Least squares mean difference (rilonacept – placebo), 95% CI	51.9 (33.8, 70.1)	
Two-sided p-value[b]	<0.0001	

CI = confidence interval; ITT = intent to treat; NRS = numerical rating scale; SD = standard deviation; SE = standard error.

[a] 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. Missing values in pain diary were counted as 0 day with no or minimal pain. Days of using oral rescue therapy or corticosteroid count as 0 day with no or minimal pain. If bailout rilonacept was used, each administration (loading dose or not) was counted as 7 days without qualifying no or minimal pain.

[b] Two-sided p-value was calculated using analysis of covariance with treatment, randomization strata and run-in baseline NRS weekly average category (NRS ≤ 2 versus NRS >2) as covariates.

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

RI period (other secondary efficacy endpoint)

The proportions of subjects with absent or minimal pericarditis symptoms as assessed by the PGI-PS were 18.1%, 89.5%, and 92.6% at RI baseline, Week 6, and Week 12, respectively. At Week 12, 54 (67%) of 81 subjects reported having no pericarditis symptoms.

Twi subjects entered LTE from RI on 27 April 2020 and 14 May 2020, respectively. They had PGA assessments on 29 Apr 2020 and 18 May 2020, respectively, which were accounted for in RI as shown in version 1 of the CSR. This was due to these subjects having no LTE start dates in the previous data cutoff. In the final DBL, both assessments were accounted for in the LTE period as both were performed in LTE period. Both subjects were later excluded from Week 12 in RI period.)

RW period (key secondary efficacy endpoint):
A key secondary efficacy endpoint was the proportion of subjects with no or minimal pericarditis symptoms at week 16, based on the PGI-PS. The PGI-PS is a single-item measure of the subject's impression of the overall severity of pericarditis symptoms (e.g., pain, dyspnoea, anxiety, fatigue or palpitations) at the time the questionnaire is administered, using a 7-point rating scale ranging from absent (no recurrent pericarditis symptoms) to very severe (recurrent pericarditis symptoms cannot be ignored).
At RW week 16, in a significantly higher proportion of subjects treated with rilonacept pericarditis symptoms were absent or minimal (17/21, 81.0%) than in placebo-treated subjects (5/20, 25.0%; p = 0.0006) – see **Table 9** below. Results observed at RW week 8 (rilonacept: 23/27, 85.2%; placebo: 10/31, 32.3%) and week 24 (rilonacept: 15/17, 88.2%; placebo: 3/15, 20.0%) were consistent with those observed at Week 16.

Table 9: Proportion of patients with absent or minimal pericarditis symptoms at RW Week 24, 16, 8 – ITT Week 24, 16, 8

Proportion of Patients with Absent or Minimal Pericarditis Symptoms based on the 7-point PGI-PS [1]	Randomised Withdrawal Period	
	KPL-914	Placebo
RW Week 24 (ITT Week 24 Analysis Set), n	17	15
Number of Patients with Absent or Minimum Pericarditis Symptoms	15	3
Absent or Minimal Pericarditis Symptoms and 95% CI, (%) [2]	88.2 (63.6, 98.5)	20.0 (4.3, 48.1)
Difference in Proportions and 95% CI [3]	68.2 (42.9, 93.6)	
Odds Ratio, 95% CI [4]	30.522 (4.262, 218.552)	
Two-Sided p-value [4]	0.0002	
RW Week 16 (ITT Week 16 Analysis Set), n	21	20
Number of Patients with Absent or Minimum Pericarditis Symptoms	17	5
Absent or Minimal Pericarditis Symptoms and 95% CI, (%) [2]	81.0 (58.1, 94.6)	25.0 (8.7, 49.1)
Difference in Proportions and 95% CI [3]	56.0 (30.6, 81.3)	
Odds Ratio, 95% CI [5]	10.000 (2.136, 46.826)	
Two-Sided p-value [5]	0.0006	
RW Week 8 (ITT Week 8 Analysis Set), n	27	31
Number of Patients with Absent or Minimum Pericarditis Symptoms	23	10
Absent or Minimal Pericarditis Symptoms and 95% CI, (%) [2]	85.2 (66.3, 95.8)	32.3 (16.7, 51.4)
Difference in Proportions and 95% CI [3]	52.9 (31.7, 74.1)	
Odds Ratio, 95% CI [5]	14.432 (3.439, 60.574)	
Two-Sided p-value [5]	<.0001	

[1] PGI-PS = Patient Global Impression of Pericarditis Severity
[2] Percentages are based on the ITT Weeks 24, 16, and 8 Analysis Sets which include participants randomised at least 24, 16, and 8 weeks before data cutoff, respectively. The exact 95% CI is calculated with randomisation strata pooled. Patients who had received bailout rilonacept or rescue medication before the timepoint were considered as non-responders.
[3] Based on a normal approximation.
[4] 95% CI and p-value are analysed using a Cochran-Mantel-Haenszel test adjusted by oral corticosteroid use at RI baseline.
[5] 95% CI and p-value are analysed using a Cochran-Mantel-Haenszel test adjusted by oral corticosteroid use and Diagnosis of Recurrent Idiopathic Pericarditis at RI baseline.
CI = confidence interval; ITT = intent-to-treat; RI = Run-in; RW = Randomised withdrawal

Other Secondary Endpoints:

Run-in Period

Clinical Response at Week 12

Among the 79 subjects who completed treatment through Week 12, 73 subjects (92.4%) achieved the rigid protocol definition of clinical response at this time point.

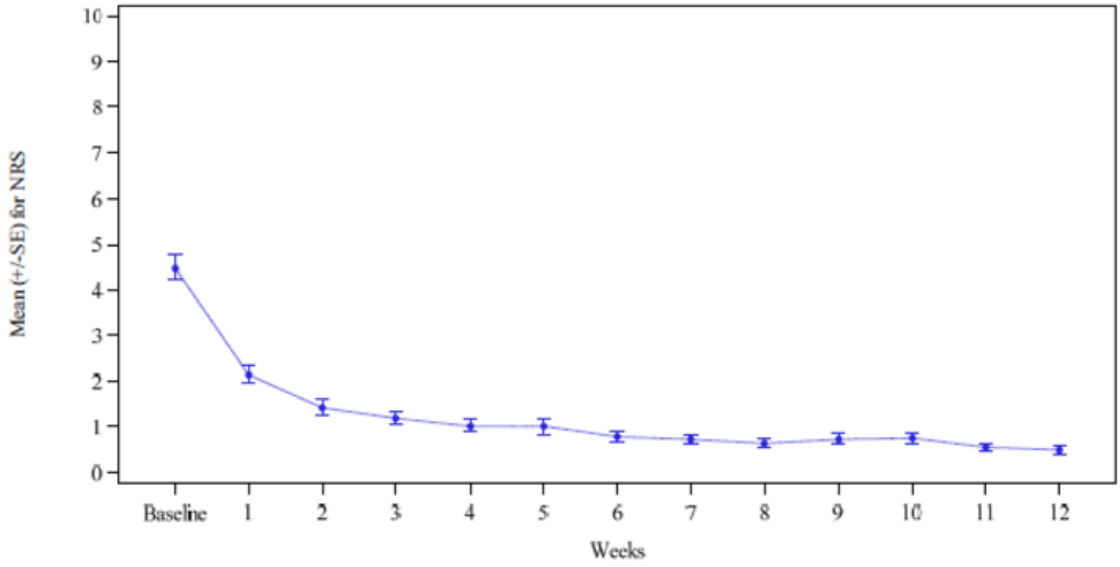
Clinical response was defined as a weekly average of daily pericarditis pain on the 11-point NRS ≤ 2.0, CRP level ≤ 0.5 mg/dL, on rilonacept monotherapy; all subjects who were randomized met formal Clinical Response criteria. Fifteen (17.4%) of 86 subjects transitioned directly from the RI period to the LTE, as randomization was closed. Four (4.7%) subjects discontinued treatment prior to Week 12. Six subjects did not meet the PP definition of CR at Week 12. Three of these subjects were not randomized; of the remaining 3 subjects, 1 was randomized because they met the protocol-defined criteria 2 days later (within the protocol-specified visit window), the remaining 2 transitioned directly to the LTE as noted above despite not meeting formal criteria for randomization. Of note, randomization was closed, as the study had accrued the requisite number of events.

NRS scores

Weekly pericarditis pain NRS scores throughout the RI period are displayed in Figure 11. In general, NRS pain scores decreased rapidly, beginning after the first rilonacept administration and were maintained through Week 12.

During the RI period, of 66 patients with a baseline NRS measurement ≥ 3, 65 (98.5%) achieved pain response (3-day rolling average NRS ≤ 2). The median time to pain response from first dose of rilonacept was 5 days (95% CI, 4.0–6.0).

Figure 11: Mean NRS Scores During the Run-in Period (Safety Analysis Set)

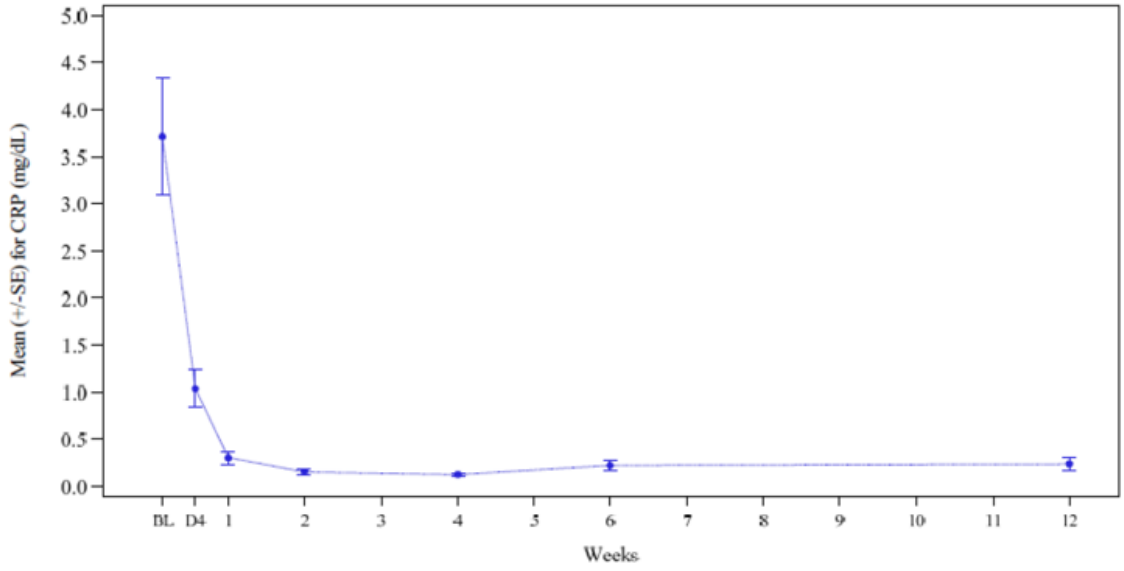


Bars are standard errors. NRS = numerical rating scale; SE = standard error.

Central laboratory CRP levels over time are displayed in Figure 12. CRP decreased rapidly following the first administration of study drug with a median time to normalisation from baseline of 7 days (i.e., prior to the second administration).

Sixty-eight patients had a baseline CRP value ≥ 0.5 mg/dL. During the RI period, 98.6% of these patients achieved CRP normalisation (CRP ≤ 0.5 mg/dL). Median time to CRP normalisation was 7 days. Time to Treatment Response was defined as time from the first dose to the first day of pain response 3-day rolling average NRS ≤ 2 and CRP ≤ 0.5 mg/dL within 7 days before or after pain response. A total of 77 patients out of 79 with either abnormal baseline NRS or CRP values (97.5%) achieved Treatment Response. The median time to treatment response was 5.0 days.

Figure 12: Mean C-Reactive Protein over Time during the Run-in Period (Safety Analysis Set)



CRP = C-reactive protein; SE = standard error.

Time to Treatment Response

Time to treatment response was defined as time from the first dose to the first day of pain (using NRS) ≤ 2 and CRP ≤ 0.5 mg/dL within 7 days before or after pain response. Treatment response day was the day of first pain response, whether before or after the CRP criterion was met.

A total of 77 subjects (97.5%) out of 79 with baseline NRS and CRP values achieved treatment response. The median time to treatment response was 5.0 (4.0; 7.0 Median 95% CI) days.

Pericardial Effusion and Pericarditis Manifestations

Table 10 summarizes pericardial effusion based on ECHO evaluated by the central laboratory during the RI period. "None or trivial/physiologic" is considered to be normal. At Week 12 of the RI period, all subjects had normal ECHO results. Of the post-baseline evaluations, only 1 subject had an effusion > trivial (a small effusion unchanged from baseline); no subjects had post-baseline effusion considered moderate or greater.

Table 10: Pericardial Effusion Assessment from Centrally Read ECHO during the Run-in Period (Run-in Analysis Set)

		Number of Subjects (%)
Visit (Number of Subjects with ECHO)	**Assessment**	**Run-in (N=86)**
Baseline (n = 85)	None or trivial/physiologic	74 (87.1)
	Small	9 (10.6)
	Moderate	1 (1.2)
	Large	1 (1.2)
	Very large	0
	NM/ND	0
Week 12 (n = 77)	None or trivial/physiologic	77 (100)
	Small	0
	Moderate	0
	Large	0
	Very large	0
	NM/ND	0
Worst post-baseline (n = 82)	None or trivial/physiologic	81 (98.8)
	Small	1 (1.2)
	Moderate	0
	Large	0
	Very large	0
	NM/ND	0

ECHO = echocardiogram; NM/ND = not measured/not done.

Of the 11 subjects who had an ECHO abnormality at RI baseline, 7 (63.6%) achieved resolution by Week 12 (Table 11). Six subjects had an ECG abnormality at RI baseline; all of these subjects achieved resolution at Week 12.

Table 11: Resolution of Pericarditis-Related ECHO and SCG Abnormalities at Week 12 of the Run-in Period (Run-in Analysis Set)

Visit/Parameter	Number of Subjects (%) Run-in (N=86)
RI baseline[a]	
Abnormal in ECHO	11 (12.8)
Abnormal in ECG	
Widespread ST-elevation	6 (7.0)
PR depression	6 (7.0)
Week 12[b]	
Resolution in ECHO	7 (63.6)
Resolution in ECG	
Resolution in widespread ST-elevation	6 (100)
Resolution in PR depression	6 (100)

ECG = electrocardiogram; ECHO = echocardiogram.
[a] Denominator is number of subjects who had an assessment at baseline.
[b] Denominator is the number of subjects who had an abnormality at baseline.

Table 12 shows the number of subjects with pericarditis manifestations at baseline and Week 12. Overall, the proportion of subjects with manifestations decreased from baseline to Week 12.

Table 12: Number of Subjects with Pericarditis Manifestations in the Run-in Period (Safety Analysis Set)

Visit/Category	n/m (%)[a] Run-in (N = 86)
Baseline	
Increased WBC count >ULN	21/76 (27.6)
Fever >38°C	2/85 (2.4)
Pericardial rub	14/86 (16.3)
Widespread ST-segment elevation and/or PR-segment depression	12/85 (14.1)
New or worsened pericardial effusion on ECHO	NA
Tamponade present	0/74 (0.0)
Baseline	
New or worsened pericardial inflammation on MRI or other imaging modality	28/30 (93.3)
Week 12	
Increased WBC count >ULN	2/79 (2.5)
Fever >38°C	0/80 (0.0)
Pericardial rub	1/71 (1.4)
Widespread ST-segment elevation and/or PR-segment depression	1/81 (1.2)
New or worsened pericardial effusion on ECHO	0/76 (0.0)
Tamponade present	0/77 (0.0)
New or worsened pericardial inflammation on MRI or other imaging modality	NA

[a] n = number of subjects with manifestations; m = number of subjects with assessment.
ECHO = echocardiogram; MRI = magnetic resonance imaging; NA = not applicable; ULN = upper limit of normal; WBC = white blood cell.

Time to Rilonacept and Tapering of Pericarditis Background Medications

Among the 79 subjects taking background pericarditis medications at baseline, 73 (92.4%) were able to discontinue background medications and achieved rilonacept monotherapy. Among the 5 subjects not discontinuing background medications, 1 subject discontinued study medication, and 1 subject did not discontinue background medications due to study site error. The median time from first dose of rilonacept to monotherapy was 7.3 weeks. Seventy-nine subjects were taking background pericarditis medications at baseline. By Week 8, 60.5% of subjects were not receiving background medications, and by Week 12, 97.5% were not receiving background medications (the 2 subjects still receiving background medications at Week 12 did not meet clinical response criteria and did not continue to the RW period). The number of background pericarditis medications also decreased at each time point during the RI period.

Randomized Withdrawal Period

Time to Pericarditis Pain ≥ 4

The time to pericarditis pain ≥ 4 on the NRS for the rilonacept treatment arm was significantly longer than the placebo arm, with a hazard ratio of 0.13 ($p < 0.0001$); rilonacept reduced the risk of experiencing pain ≥ 4 by 87%.

For subjects randomized to placebo, median time to NRS pain ≥ 4 was 4.1 weeks; median time for subjects receiving rilonacept was not estimable (25th percentile 33.1 weeks). At Week 16, the estimated proportion of subjects with NRS pain ≥ 4 was 15.0% in the rilonacept group, compared with 78.0% in the placebo group.

Oral Rescue Therapy, Corticosteroid Use, and Bailout

In the rilonacept treatment arm, 1 subject (3.3%) used ORT, and 1 subject received rilonacept bailout. In the placebo arm, 2 subjects (6.5%) used ORT, and 23 subjects (74.2%) received rilonacept bailout.

The odds ratio for the use of ORT, corticosteroids, or bailout rilonacept between treatments was 0.015 ($p < 0.0001$). One subject received bailout at 28.7 weeks in the rilonacept arm, median time to bailout was 4.57 weeks in the placebo arm. Nine subjects (29.0%) in the placebo group bailed out in ≤ 4 weeks into the RW period.

Regarding the C-RP related endpoints see above (Pharmacodynamics)

Patient reported outcomes

Assessments of Pericarditis Activity: PGA-PA

The PGA-PA is a single-item, clinician-reported outcome measure used to rate impression of the subject's overall pericarditis disease activity at the time the assessment is completed, using a 7- point rating scale ranging from absent to very severe (absent, minimal, mild, moderate, moderately severe, severe, very severe)

RI period:

The proportions of subjects with absent or minimal pericarditis symptoms as assessed by the PGA-PA were 10.6%, 94.8%, and 98.8% at RI baseline, Week 6, and Week 12, respectively. At Week 12, 59 (75.6%) of 78 subjects were reported by their study physician as having no pericarditis symptoms

RW period:

At RW Weeks 8, 16, and 24, 85.2%, 85.7%, and 88.2% of subjects randomized to rilonacept were reported to have absent or minimal symptoms, compared with 32.2%, 25%, and 20.0% of subjects randomized to placebo (before bailout), respectively. At each time point, rilonacept subjects were significantly more likely to report absent or minimal pericarditis symptoms ($p \leq 0.0002$).

Clarification is needed on the number of missing values at the different time points and on the validation of the PGA-PA (OC).

Additional Patient-Reported Outcomes

In addition to the PGI-PS, the SF-36, SF-6D, and EQ-5D-5L were used to assess adult subject's physical functioning, and mental well-being. The ISI was used to assess sleep disturbance and insomnia. There was a high number of missing data in the RW period at week 24 with only about half of the patients with values at baseline reporting back at week 24.

• The SF-36 and SF-6D

RI period:

Improvements from baseline were seen for both SF-36 composite measures and all 8 domains in adult participants. Mean scores for the physical and mental component scores improved from 35.6 and 44.0 at baseline to 49.2 and 53.4 at Week 12, respectively. - levels consistent with mean values for the general population. Scores for the individual domains were similarly improved at Week 12, ranging from 48.9 to 53.0. Greatest changes from baseline were seen for the bodily pain (34.1 to 53.0) and social functioning (36.6 to 51.6) domains. Similar results were seen for the SF-6D.

RW period:

Run-in period improvements in mean SF-36 scores at RW baseline were maintained in subjects on rilonacept at the RW Week 24 visit. Among adult subjects with pericarditis recurrence (2 rilonacept subjects, 22 placebo subjects), there was a worsening of SF-36 at the recurrence visit across all domains to scores similar to pretreatment scores at RI period baseline. Mean scores for placebo subjects at the pericarditis recurrence visit were 36.7 and 47.9 for the physical and mental component scores; these improved to 50.7 and 54.2, respectively by RW Week 24 following receipt of bailout rilonacept. (For each SF-36 composite measure and domain, a score of 50 represents a value consistent with the mean value for the general population.)

Results for change from baseline for SF-6D for the RW period and for subjects who experienced a recurrence of pericarditis during the RW period were consistent with results for the SF-36.

• EQ-5D-5L

RI period:

For the RI period, all 5 descriptive system dimensions of the EQ-5D-5L (scored as: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=extreme problems) were improved from baseline, with greatest mean changes seen for the pain/discomfort (–1.5) and usual activities (–1.1) dimensions. Mean index utility score, where a score of 1=perfect health, improved from 0.74 at baseline to 0.90 at Week 12. Mean visual analog scale score (0 = "worst health you can imagine", 100 = "best health you can imagine") improved from 57.7 at baseline to 79.5 at Week 12

RW period:

Run-in period improvements in mean EQ-5D-5L scores at RW baseline were maintained in subjects on rilonacept at the RW Week 24 visit. Among adult subjects with pericarditis recurrence (2 rilonacept subjects and 22 placebo subjects), there was a worsening of EQ-5D-5L scores at the recurrence visit across all 5 dimensions to scores similar to pretreatment scores at RI baseline recurrence returned to RW baseline levels by RW Week 24 following receipt of bailout rilonacept.

• Insomnia Severity Index (ISI)

RI period:

Mean total ISI score at RI baseline was 10.7 (indicating subthreshold insomnia), which improved at Week 12 to 5.6 (indicating no clinically significant insomnia). Categorical shifts from baseline to Week 12 for the 72 participants for whom results were available showed that 2 (2.5%) participants worsened by ≥1 level, 32 (40.5%) were unchanged, and 38 (48.1%) participants improved by >1 level.

RW period:

Mean total ISI scores at RW Week 24 were generally similar to those at RW baseline. Assessment at week 24 is hampered by a low number of reported results not allowing conclusions. Values for the total

score are available for 29 subjects in each group at RW baseline but only for n= 15 and n= 3 patients on rilonacept and placebo respectively at week 24.

- **Ancillary analyses**

Long term extension period of study Study KPL-914-C002

Upon completion of the RW period and the EORW visit, all participants who did not discontinue study drug had the option to continue treatment with open-label rilonacept in the LTE or to withdraw from the study. Participants in the RW period (including participants bailed out with open label rilonacept upon pericarditis recurrence) and participants who were in the Run-In period after closure of the RW period had an option to receive up to 24 months of open-label rilonacept 160 mg (or 2.2 mg/kg for paediatric participants) SC injections once weekly based on their clinical status and at the discretion of the Investigator, after signing LTE informed consent.

All 74 subjects who entered the LTE period received at least 1 dose of study medication and were included in the LTE analysis set. Of the 74 patients entering the LTE study only 52 (70.3%) were available for the 18 month LTE assessment.

Participants were reviewed again at 18 months after their most recent recurrence, (i.e., the qualifying episode for their original study enrolment prior to enrolling in the RI period or a recurrence in RW which was treated with bailout rilonacept, whichever was later, referred to as the 18-month Decision Milestone). During this visit the Investigator and participant decided based on clinical status 1) to continue rilonacept on study, 2) suspend rilonacept for off-treatment observation (rescue allowed), or 3) discontinue the study.

Efficacy outcomes during the LTE included annualized recurrence rate before and after the 18-month Decision Milestone and time to pericarditis recurrence after the 18-month Decision Milestone. PGIPS and PGA-PA were the secondary efficacy outcomes measures used to collect pericarditis symptoms at study visits. Patients assessed pain intensity using the pericarditis pain NRS only at the time of pericarditis recurrence. CRP levels were measured at baseline and every 12 weeks. Pericarditis recurrences in the LTE were Investigator-assessed. Data on pericarditis pain, CRP, ECG, physical exam (for pericardial friction rub), and echocardiogram (for pericardial effusion) were collected and were available for objective assessment relative to formal RHAPSODY RW period adjudication criteria.

Of the 52 participants who reached the 18-month Decision Milestone, all participants were clinically quiescent and had absent pericarditis symptoms. All but 2 participants were on rilonacept as monotherapy (i.e., taking concomitant colchicine); thus 50 of the 52 participants also met the criteria for Clinical Response (Treatment Response while on rilonacept monotherapy).

Of these 52 participants, 33 continued open-label rilonacept treatment, 8 suspended rilonacept but remained in the study for observation, and 11 discontinued the study (7 participants transitioned to commercial rilonacept and 4 did not).

Pericarditis Recurrence Before the 18-month Decision Milestone

Up to the 18-month Decision Milestone, the annualised incidence of pericarditis recurrence while on rilonacept treatment was 0.043 (95% CI, 0.0009, 0.125) events/patient-year. The mean (SD) number of episodes per year was 1.27 (0.562). The annualised incidence of pericarditis recurrence from LTE baseline up to the LTE 18-month Decision Milestone is summarised in Table 13.

Table 13: Annualised Incidence of Pericarditis Recurrence from LTE Baseline up to LTE 18-Month Decision Milestone (LTE Analysis Set)

	Total (N=74)
Total Number of Recurrences [a]	3
Total Participant Years	70.2
Annualised Incidence of Pericarditis Recurrence (95% CI)	0.043 (0.009, 0.125)
Average Number of Episodes per Year [b]	
n	3
Mean	1.27
SD	0.562
Median	0.98
Min	0.9
Max	1.9

CI = confidence interval; LTE = long-term extension; Max = maximum; Min = minimum; SD = standard deviation

Annualised Incidence of pericarditis recurrence = Total number of recurrences /Sum of participant years from LTE baseline up to LTE 18-Month date. Participant years is defined as the time from 1st dose date of LTE period to the date of End of Study, or data cutoff date, LTE 18-month date -1, whichever is earlier. The 95% CI was calculated using an exact method with Poisson distribution, Recurrences on or after LTE 18-month Decision Milestone dates were excluded.

Average number of episodes per year = number of events/duration of follow up in year.

Pericarditis Recurrence after the 18-month Decision Milestone

Amongst the 33 participants who continued rilonacept after the 18-month Decision Milestone, the annualised incidence of pericarditis recurrence while on rilonacept treatment was 0.041 (95% CI, 0.001, 0.227) events/patient-year (Table 13). One patient (recurrence rate, 3.0%) had an Investigator-assessed recurrence 23.4 weeks into the LTE, which met the RW period event adjudication criteria (NRS 8 and CRP 7.5 mg/dL). This event was associated with an intentional 4-week rilonacept treatment interruption 2 weeks prior to an elective surgery

Of the 8 participants who suspended treatment for observation after the 18-month Decision Milestone, 6 had an Investigator-assessed recurrence (recurrence rate, 75.0%) (Table 13). NRS scores were greater than 7, and CRP was greater than 1 mg/dL, thus meeting the formal RHAPSODY RW period event adjudication criteria).

During the post-treatment 6-week safety follow-up after cessation of study drug rilonacept, four additional Investigator-assessed pericarditis recurrences (NRS >6; CRP >1 mg/dL, meeting RHAPSODY RW period event adjudication criteria) were reported at 6 weeks. One additional participant was hospitalised due to acute endocarditis, leading to discontinuation of rilonacept.

The annualised incidence of pericarditis recurrence amongst these 33 participants who continued rilonacept of pericarditis recurrence after the LTE 18-month Decision Milestone is summarised in Table 14.

Table 14: Annualised Rate of Pericarditis Recurrence While on Treatment after LTE 18-Month Decision Milestone (LTE Analysis Set)

	LTE 18-Month Status	
	On-Treatment (N=33)	6-week Safety Follow-up (N=31)
Pericarditis Recurrence in LTE period based on Investigator's Assessment		
Total Number of Recurrences [a]	1	4
Total Participant Years [a]	24.5	27.1
Annualised Incidence of Pericarditis Recurrence (95% CI) [a]	0.041 (0.001, 0.227)	0.148 (0.040, 0.379)
Average Number of Episodes per Patient Year [b]		
n	1	4
Mean	1.63	1.16
SD	NA	0.177
Median	1.63	1.08
Min	1.6	1.0
Max	1.6	1.4

CI = confidence interval; EOS = end of study; LTE = long-term extension; Max = maximum; Min = minimum

[a] Annualised Incidence of pericarditis recurrence = number of recurrences in LTE periods for all participants/Sum of participant years in LTE periods for all participants. For participants who decided to continue in study off-treatment for observation, participant years calculated as treatment, minimum (EOS date, cutoff date, 1st dos date after observation -1) - LTE 18-Month Decision Milestone date +1; for participants who continued treatment, participant years calculated as minimum (EOS date, cutoff date) - LTE 18-Month Decision Milestone date +1; The 95% CI is calculated using an exact method with Poisson distribution.

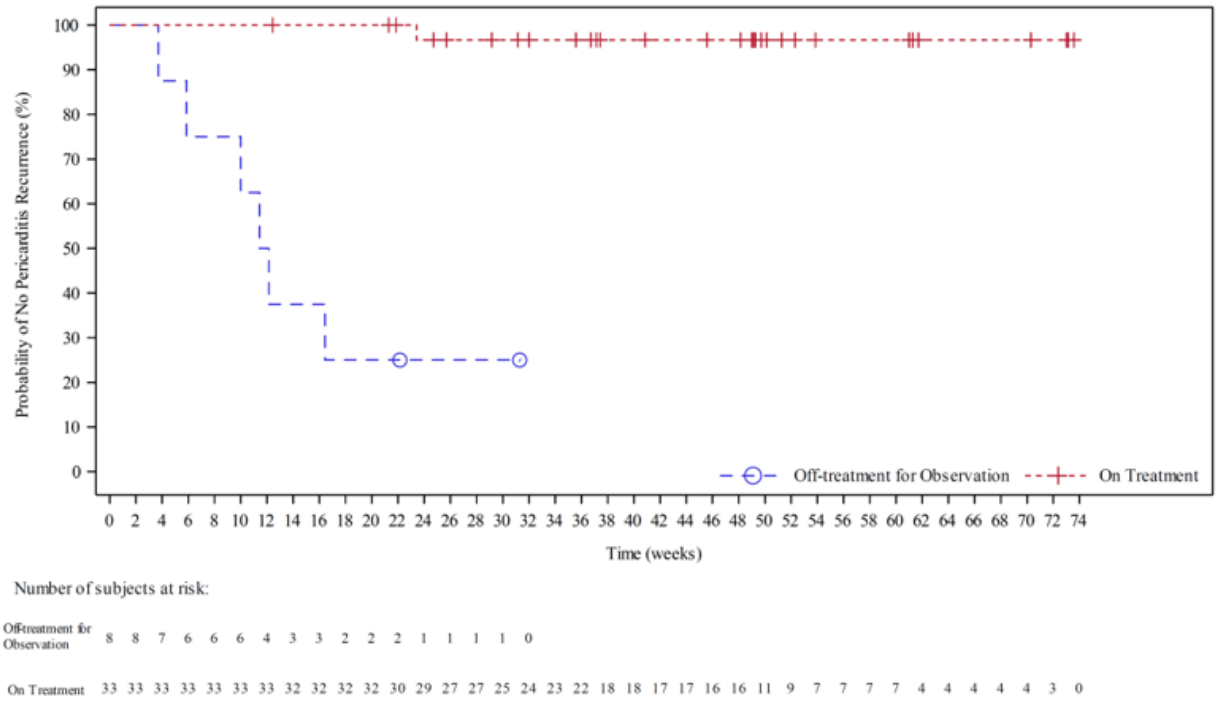
[b] Average number of episodes per year = number of events/duration of follow up in years.

Time to Pericarditis Recurrence After the 18-month Decision Milestone

The time to pericarditis recurrence by participant status (suspended treatment vs continued treatment at the 18-month Decision Milestone) is summarised in Table 14. The time to recurrence for participants who continued rilonacept treatment after the 18-month Decision Milestone was not estimable due to too few events. The time to pericarditis recurrence after the 18-month Decision Milestone in participants who suspended rilonacept therapy for observation was 11.8 weeks (hazard ratio, 0.02; P<0.0001). There was a 98% reduction in pericarditis recurrence risk among participants who continued rilonacept treatment after the 18-month Decision Milestone (n=33) versus those who suspended treatment for observation (n=8). These results are consistent with the magnitude of effect of rilonacept in the RW period (primary efficacy endpoint). A Kaplan-Meier curve of time to pericarditis is shown in Figure 13.

One patient experienced endocarditis not further specified here. As rilonacept, due to its mechanism of action, may be associated with infections, analyses on whether this was a case of bacterial endocarditis and whether rilonacept may have contributed to the outcome, should be clarified.

Figure 13: Kaplan-Meier Curve of Time to First Recurrence (LTE Analysis Set – Participants on Study After the LTE 18-month Decision Milestone)



LTE = long-term extension

Change in C-reactive Protein

Before the 18-month Decision Milestone, the proportion of patients on rilonacept treatment with CRP levels at/below 0.5 mg/dL or at/below 1 mg/dL at each study visit was 97.0% and 100%, respectively. The 3 Investigator-assessed pericarditis recurrences that were reported during this period were not associated with a CRP elevation (i.e., NRS only).

After the 18-month Decision Milestone, at every 12-week timepoint (when CRP was assessed), the majority of participants who remained on treatment remained at/below 0.5 mg/dL, ranging from 96.7% (n =29) at 12 weeks after the LTE 18-month Decision Milestone to 100% (n = 7) at 48 weeks after the LTE 18-month Decision Milestone. As mentioned previously, among the 33 participants who remained on therapy, the one pericarditis recurrence (in a patient who had an intentional 4-week rilonacept treatment interruption 2 weeks prior to an elective surgery) was associated with a CRP elevation. Amongst the 8 participants who suspended rilonacept treatment for observation, all 6 of the participants who had a pericarditis recurrence experienced a CRP elevation.

Investigator-assessed Pericarditis Recurrences During the LTE Period

Investigator-assessed pericarditis recurrences were reported for 15 participants during the entire LTE Period. The results the Investigator-assessed pericarditis recurrences were overall consistent with the results when applying the study criteria for pericarditis recurrence.

Patient-reported Outcome Measures during the LTE

Proportion of Participants with Absent or Minimal Pericarditis Symptoms Based on PGI-PS during the Long-term Extension Period

During the on-treatment period (open-label rilonacept) in the LTE prior to the 18-month Decision Milestone, pericarditis symptoms, as measured by the PGI-PS, remained low. Of the 52 participants

(70.3%) who reached the 18-month Decision Milestone visit, 92.2% (47/51) of participants reported absent/minimal pericarditis symptoms (PGI-PS score, 0 or 1). In addition to the lack of pericarditis symptoms by PGI-PS, all patients had normal CRP levels (i.e., less than 0.5 mg/dL), absent pericardial rub, normal electrocardiogram, and no pericardial effusion, demonstrating clinical quiescence after 18 months of rilonacept therapy.

After the 18-month Decision Milestone visit, among the 33 participants who continued rilonacept treatment (93.8% [30 of 32 participants with data available] had absent or minimum pericarditis symptoms at the 18-month Decision Milestone), over 90% of participants reported absent/minimal pericarditis symptoms through the 24-week assessment; thereafter, the number of participants at subsequent assessments was small (7 participants at 36 weeks and 4 participants at 48 weeks), but the trends of persistent low symptoms were maintained, suggesting continued clinical response while on continued rilonacept therapy

By contrast, among the 8 participants who suspended rilonacept treatment for observation, some increases in pericarditis symptoms by PGI-PS were noted at some scheduled follow up visits as well as during unscheduled pericarditis recurrence visits, as 75% of participants experienced pericarditis recurrence (6/8 participants – median time to event rate of 11.8 weeks) with substantial increases in NRS (and PGI-PS) noted at the time of recurrence. PGI-PS scores at scheduled visits after rescue therapy were improved.

A**ssessment of Pericarditis Activity – PGA-PA during the Long-term Extension Period**

During the on-treatment period (open-label rilonacept) in the LTE prior to the 18-month Decision Milestone, pericarditis symptoms, as measured by the PGA-PA, remained low (

Of the 52 participants (70.3%) who reached the 18-month Decision Milestone visit, 94.2% (49/52) of participants reported absent/minimal pericarditis symptoms.

After the 18-month Decision Milestone visit, among the 33 participants who continued rilonacept treatment (93.9% [31 of 33 participants with data available] had absent or minimum pericarditis symptoms at the 18-month Decision Milestone), all (100%) participants reported absent/minimal pericarditis symptoms through the 48-week assessment, suggesting continued clinical response while on continued rilonacept therapy.

By contrast, among the 8 participants who suspended rilonacept treatment for observation, some increases in pericarditis symptoms by PGA-PA were noted at some scheduled follow up visits as well as during unscheduled pericarditis recurrence visits, as 75% of participants experienced pericarditis recurrence (6/8 participants – median time to event rate of 11.8 weeks) with substantial increases in NRS (and PGA-PA) noted at the time of recurrence. PGA-PA scores at scheduled visits after rescue therapy were improved.

Psychometric evaluation report for the 11-point Pericarditis Pain Numeric Rating Scale (11-point NRS) and the Patient Global Impression of Pericarditis Severity (PGIPS) (KPL-914-C002)

A psychometric evaluation report has been provided (KPL-914-C002 Phase 3 Clinical Outcome Assessment Psychometric Evaluation Report; KP8279C | Version 3_0, 10 September 2020).

The Applicant has provided a validation report to evaluate the use of PPNRS and PGIPS as relevant measures for the primary and key efficacy analyses. Results supporting content validity were provided. In addition, data supporting in study validity within the pivotal trial KPL-914-C002 were provided on Test-retest reliability, Construct-related validity, Sensitivity to change and Score interpretation. There were some limitations regarding reliability, related to the restricted range of scores available.

Furthermore, the evaluation did not follow the pre-specified statistical analysis plan by also including data from RI Baseline and RI Week 6 in addition to data from the RW period only. The results provide reassurance on the reliability of the data generated with the PPNRS and PGIPS within the study. However, as a rule validation of PROs should be performed independently of the study where to be applied. It is not entirely clear from the documentation provided whether data on an external validation of PPNRS and PGIPS are available.

According to the validation a score of ≥2 would indicate mild to moderate pain for daily and weekly PPNRS; a score ≥7 would indicate severe pain for the daily PPNRS score. The threshold of 4 used in the pivotal trial KPL-914-C002 for decision making was not part of the validation.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15. Summary of Efficacy for trial KPL-914-C002 (RHAPSODY)

Title: A Phase 3 double blind, placebo-controlled, randomised withdrawal study with an open-label extension, to assess the efficacy and safety of rilonacept treatment in adult and paediatric subjects with RP. A secondary objective of the study was to characterise the PK profile of rilonacept in subjects with RP		
Study identifier	KPL-914-C002	
Design	Study C002 was multi-centre, event-driven Randomised withdrawal (RW) study designed to assess the efficacy and safety of rilonacept treatment in participants presenting with acute pericarditis recurrence.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Event driven 12 weeks 18 months, decision based withdrawal thereafter
Hypothesis	Superiority	
Treatments groups	Rilonacept	Rilonacept 320 mg SC loading dose (4.4 mg/kg in subjects ⩾12 and <18 years old), followed by once weekly SC doses at 160 mg (2.2 mg/kg in subjects ⩾12 and <18 years old). n= 30
	Placebo	Placebo, n= 31

Title: A Phase 3 double blind, placebo-controlled, randomised withdrawal study with an open-label extension, to assess the efficacy and safety of rilonacept treatment in adult and paediatric subjects with RP. A secondary objective of the study was to characterise the PK profile of rilonacept in subjects with RP			
Study identifier	KPL-914-C002		
Endpoints and definitions	Primary endpoint	pericarditis recurrence	Time to CEC confirmed Pericarditis Recurrence in the Randomized Withdrawal Period as defined by NRS ⩾4 AND elevated CRP (⩾1.0 mg/dL) Or NRS ⩾4 AND elevated CRP (⩾0.5 mg/dL) AND at least 1 supportive evidence of pericarditis Or Re-appearance or worsening of typical pericarditis pain (NRS s< 4) AND elevated CRP (≥ 1.0 mg/dL) AND at least 1 supportive manifestation of pericarditis
	Key Secondary confirmatory endpoint	Clinical response at week 16	Proportion of subjects who maintained clinical response at Week 16 of the RW period
	Key Secondary confirmatory endpoint	Days with no or minimal pericarditis pain	Percentage of days with no or minimal pericarditis pain in the first 16 weeks of the RW period. No or minimal pericarditis pain is defined as non-missing NRS ⩽ 2.
	Key Secondary confirmatory endpoint	PGI-PS at week 16	Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGI-PS) at Week 16 of the RW period.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Rilonacept }	Placebo	
pericarditis recurrence	Number of subject	30	31	
	Number of patients with events.	2	23	
	Time to recurrence (weeks, median)	NE	8.6	

Title: A Phase 3 double blind, placebo-controlled, randomised withdrawal study with an open-label extension, to assess the efficacy and safety of rilonacept treatment in adult and paediatric subjects with RP. A secondary objective of the study was to characterise the PK profile of rilonacept in subjects with RP				
Study identifier	KPL-914-C002			
	95% CI	NE	4.0; 11.7	
Effect estimate per comparison	Primary endpoint	Comparison groups		
		<Hazard ratio (95% CI)>	0.04	
		(95% CI)	0.01; 0.18	
		P-value (log rank test stratified by oral corticosteroid use at run-in)	< 0.0001	
	Confirmatory Secondary endpoints			
	Clinical response at week 16			
		Least squares mean difference	51. 2	
		(95% CI)	34.5; 68.0	
		P-value	< 0.0001	
	Days with no or minimal pericarditis			
		Odds ratio	10.000	
		(95% CI)	2.136; 46.826	
		P-value	0.0006	
	PGI-PS at week 16	Odds ratio	10.000	
		(95% CI)	2.136; 46.826	
		P-value	0.0006	

3.3.5. Discussion on clinical efficacy

A clinical development programme has been set up to support the following indication:

[Tradename] is indicated in adults and paediatric patients from 12 years for the treatment of idiopathic recurrent pericarditis and reduction in risk of recurrence.

The clinical development plan consists of 24 studies on different patient populations from which 2 studies (KPL-914-C002 and KPL-914-C001) were performed on recurrent pericarditis. Study KPL-914-C002 is the mainstay for efficacy results while KPL-914-C001 provides supportive data. Study KPL-914-C001 was a Phase 2 open-label, single-active-arm study of rilonacept in RP with a total of 25 adult participants enrolled.

Dose selection

No dose finding studies specific for RP were conducted.

The rilonacept dosing regimen used in the pivotal study was the same as the previously approved rilonacept dosing regimen for adult and paediatric subjects with CAPS; i.e., 320 mg SC loading dose (4.4 mg/kg in subjects ≥12 and <18 years old), followed by once weekly SC doses at 160 mg (2.2 mg/kg in subjects ≥12 and <18 years old). Reference is made to EPAR (EMEA/541561/2009).

In the rilonacept development program in CAPS, gout, rheumatoid arthritis, and other inflammatory conditions, more than 2000 subjects were exposed to rilonacept, including 1650 subjects receiving a rilonacept dose of 160 mg or higher. A total of 103 and 169 subjects were exposed to any rilonacept dose for at least 1 year or 6 months, respectively. As of March 2018, when the protocol was written, approximately 365 CAPS patients had been exposed to rilonacept in the postmarketing setting since 2008. The accumulated safety data supported the benefit/risk ratio for the rilonacept dose evaluated in subjects with recurrent pericarditis.

The same dose was investigated in the Phase 2 proof-of-concept study (KPL-914- C001). Study C001 was a Phase 2 open-label, single-active-arm, pilot study designed to explore the clinical and biochemical endpoints of pericarditis symptomatology and to collect inter-and intra-participant variability data on both at-baseline and on-treatment parameters. participants with different clinical features of patients with pericarditis. 1) Part 1 enrolled symptomatic participants with recurrent idiopathic pericarditis with an elevated marker of systemic inflammation (CRP >1 mg/dL). 2) Part 2 enrolled symptomatic participants with recurrent idiopathic pericarditis with CRP ≤ 1 mg/dL which, in the opinion of the investigator, can be attributed to concomitant medications (e.g., corticosteroids) and with pericardial inflammation present on cardiac MRI confirmed by the imaging core lab. 3) Part 3 enrolled participants with corticosteroid-dependent recurrent idiopathic pericarditis not experiencing symptoms which would meet the diagnostic criteria for a pericarditis recurrence. 4) Part 4 enrolled symptomatic participants with recurrent post-pericardiotomy syndrome with an elevated marker of systemic inflammation (CRP >1 mg/dL). 5) Part 5 enrolled participants with corticosteroid-dependent recurrent post-pericardiotomy syndrome not experiencing symptoms which would meet the diagnostic criteria for a pericarditis recurrence. Exploratory analyses indicated that treatment with rilonacept was associated with

1. Resolution of pericarditis episodes as indicated by: a. Rapid and sustained reductions in participant-reported pericarditis pain using the 11-point pain NRS pain scale b. Improved participant physical and mental quality of life (QoL) using a global health instrument (PROMIS v1.2), c. Resolution or improvement in objective clinical manifestations of pericarditis, including pericardial effusions, rub, ECG changes, and CRP levels

2. Reduction in pericarditis recurrences as indicated by: a. Reduction in annualised incidence of pericarditis episodes while on rilonacept treatment during the study as compared to prior to the study. Interpretation of the data was hampered by the lack of a control group. Particularly, calculated incidence rates of pericarditis recurrences are prone to regression to the mean effects. However, based on these data the same dose was forwarded to be investigated in the pivotal phase 3 study (KPL-914-C002). As summarized above (PK), the rationale not to administer a reduced dose in low weight adults to achieve a dose matching with paediatric patients is not entirely clear but. Low weight adults may have a higher exposure than adolescents or adults at higher weight. Whether this is relevant for safety should be further addressed **(OC).**

Overall, the approach is acceptable. Feasibility of conducting a comprehensive dose finding programme in patients with RP is limited by the number of patients available and by variability associated with recurrent pericarditis events. Regarding non-specific safety, data available from other indications may be supportive. At the end concluding on a positive benefit risk balance of the dose based on the pivotal RHAPSODY trial may also serve to establish the proposed dose regimen.

Design and conduct of clinical studies

The clinical program was mainly based on 1 controlled pivotal phase 3 study, study KPL-914-C002 (RHAPSODY) in patients with recurrent pericarditis.

Design

The study consisted of three periods:

- Period 1: Single-blind Run-In (RI) period (12 Weeks): SC loading dose of 320 mg of rilonacept for adults and 4.4. mg/kg for paediatric subjects [≥12 and <18 years old], and 12 × QW maintenance SC doses of 160 mg for adults and 2.2 mg/kg for paediatric subjects.

During the single-blind RI period, treatment with open-label rilonacept was administered, and subjects were tapered off background standard-of-care (SOC) therapy for pericarditis.

- Period 2: Double-blind placebo-controlled Randomised Withdrawal (RW) period (event driven - 0 to 51 weeks):

During the RW period, eligible subjects were randomized 1:1 to double-blinded administration of study drug:

· Rilonacept 160 mg (or 2.2 mg/kg in paediatric subjects ≥ 12 and < 18 years old) administered by subcutaneous (SC) injections once weekly OR

• Matching placebo SC injections once weekly

The RW period lasted until 22 independently adjudicated pericarditis cases had occurred.

- Period 3: Long Term Extension Period (LTE) (up to 24 months; ongoing): All subjects in the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) and subjects who successfully completed the RI period after closure of randomisation had the option to receive up to 24 months of open-label rilonacept (160 mg SC QW for adults and 2.2 mg/kg SC QW for paediatric subjects). The LTE is ongoing at the time of this submission.

Endpoints

The **primary efficacy endpoint** was time to pericarditis recurrence (CEC-confirmed), defined as the time from randomization to the date of the first pericarditis recurrence for each subject.

Pericarditis recurrence was defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis where applicable.

Diagnostic criteria used for pericarditis were according to ESC 2015, but recurrence was defined as having a new pericarditis episode with at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale (NRS) and C-reactive protein (CRP) value ≥1 mg/dL (either on the same day or separated by no more than 7 days) within 7 days prior to first study drug administration. This definition is not fully endorsed as it is less stringent than used in clinical practice and causes concerns with the selection of patient population. **(OC)**

Key secondary (confirmatory) endpoints for the RW period were as follows:
- Proportion of subjects who maintained 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 pericarditis pain is defined as non-missing NRS ≤ 2.
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point PGI-PS) at Week 16 of the RW period.

Additional secondary endpoints covered clinical response, CRP, pericarditis pain, signs and symptoms and different aspects of quality of life during the RI, the RW and the LTE period.

The design of the pivotal study was overall suitable to investigate efficacy in a controlled design and maintenance of efficacy up to 24 months by the means of the LTE including a milestone of 18 months where patients could opt for discontinuing therapy.

The definition of recurrence based on 3 different criteria reflects clinical judgement by considering worsening/re-appearance of pain associated with increases in CRP and, where applicable, additional supportive information. There are some points to be considered. Further information should be provided on how many recurrent events were diagnosed based on criterion 1., 2., or 3., respectively **(OC).**

A Psychometric evaluation report for the 11-point Pericarditis Pain Numeric Rating Scale (11-point NRS) and the Patient Global Impression of Pericarditis Severity (PGIPS) (KPL-914-C002) was provided to support the use of the 11 point NRS scale as part of the primary efficacy endpoint and the PBIPS as a confirmatory secondary endpoint. Overall, the results provide reassurance on the reliability of the data generated with the PPNRS and PGIPS within study KPL-914-C002. However, as a rule validation of PROs should be performed independently of the study where to be applied. It is not entirely clear from the documentation provided whether data on an external validation of PPNRS and PGIPS are available. This should be further discussed by the Applicant **(OC).** In addition, in the pivotal trial KPL-914-C002 an NRS threshold of 4 was used for decision making which should be further justified **(OC).**

Conduct

The rate of reported protocol violations was within the expected range, partly related to COVID-19 pandemia. Quality control measures were in place. No serious GCP issues were identified with the potential to affect the integrity of the study or with an impact of the conclusions on the benefit risk balance. Analyses covering the impact of the COVID19-pandemic were provided. Minor changes were included by informal changes and by Amendment 1. However, Amendment 2 by March 2020 implemented key changes to the conduct of the ongoing study and the evaluation of the primary endpoint in as such that the duration of the RW period, formerly 24 weeks, was deleted and the study became endpoint driven (22 events). Although the Applicant claims that the amendment was driven by a recommendation of the FDA, the Applicant should comment on the information available at the time of the decision to change the protocol and provide a sensitivity analysis on the primary and key secondary outcomes for patients randomized before and after Amendment 2 **(OC).**

After training and first administration of study drug by the study personnel, participants administered study drug on their own. Self-administered injections made up >95% of administrations for each part in Study C001 and ranged from 87.54% to 96.15% in Study C002. There are questions around the suitability of the drug product for self-administration **(OC)**.

Study size

Eighty-six subjects were enrolled in the study, 79 subjects completed the RI period. Three subjects (3.5%) completed the RI period but did not meet the stringent protocol-defined clinical response criteria and thus did not enter the RW period: 2 due to CRP levels, and 1 due to pain score.

Of the 61 randomized subjects, 1 subject in the placebo group withdrew consent during the RW period, 1 subject completed the RW period but withdrew consent prior to participating in the LTE, and 59 subjects completed the RW period.

Seventy four of 75 eligible subjects continued into the LTE: Fifteen subjects went directly from the RI period to the LTE because, at that time, the protocol-specified 22 adjudicated pericarditis recurrence events had accrued. It was a multinational study with a very low representation of patients from the EU,

only 3 out of 58 centres recruited in the EU (Italy). Transferability of the data to the EU population should be justified by the Applicant **(OC).**

Study population

The study enrolled patients with at least the second pericarditis recurrence with mainly idiopathic aetiology. The majority of subjects (84.9%) had been diagnosed with idiopathic recurrent pericarditis at baseline; 14.0% had post-pericardiotomy syndrome, and 1.2% had Dressler syndrome. Mean disease duration was 2.41 years, and mean number of pericarditis episodes per year was 4.42. Overall, slightly more subjects (57.0%) were female. The majority of subjects were white (93.0%), with a mean age of 44.7 years. The majority of subjects were adults (79 of 86, 91.9%); 7 subjects (8.1%) were <18 years of age. Although all subjects met criteria according to diagnostic criteria as set by the ESC (2015) at any time, patients had not necessarily to fulfil all of these criteria at the time of the recurrence of pericarditis. A high CRP value at baseline was among the inclusion criteria. Although this is not among the key criteria to establish the diagnosis of pericarditis, it is acceptable. CRP is clinically used to monitor patients with an established diagnosis.

Study population demographics were concordant with the demographics of the patient population in general, although concerns were raised for the baseline disease characteristics as relatively low number of participants compared to the literature presented with pericardial rub (16.3%), abnormal ECG (14.1%) and abnormal ECHO results (12.8%) **(OC).**

Of the 74 subjects who entered the LTE, 40 (54.1%) were female, and 34 (45.9%) were male. The majority of subjects (68/74, 91.9%) were white, and the mean (SD) age was 44 (15.6) years.

14.0% had post-pericardiotomy syndrome, and 1.2% had Dressler syndrome. Since for this subgroup the result for the primary efficacy endpoint did nominally not show significance, additional information should be provided on the reasons why 4 of the 13 patients enrolled with non-idiopathic pericarditis were not transferred to the RW period. **(OC)**

7 paediatric participants were included. Of these 7 patients between 12 and 17 years included in the RI period only three entered the RW period. Further information is requested on the reason for the high rate of adolescents not entering the RW period. Considering the low representation of paediatric patients with only 3 randomized, the Applicant should provide a thorough justification for including paediatric patients between 12 and 17 years into the indication **(MO on paediatric patients).**

Statistical considerations

The targeted estimand was not defined. However, the choices made for design and analysis suggest that the treatment effect regardless of treatment discontinuation, receiving ORT or corticosteroid, and bailout rilonacept was targeted (i.e. treatment policy strategy for all intercurrent events). This is acceptable.

The requirement that, in addition to observing 22 endpoint events, all patients need to be followed for at least 24 weeks was removed in a protocol amendment, which is acceptable as the study was still blinded.

The statistical methods were overall appropriate.

For the primary endpoint, standard time to event methods were used. The only censoring reason was not having a pericarditis at the date of the last available assessment for pericarditis recurrence during the RW period on or before data cutoff.

All subjects were followed for the duration of the RW period, unless they withdrew consent. The non-informative censoring assumption may be questioned for patients withdrawing consent, however, as

only 1 patient withdrew consent during the RW period, this is no relevant issue. Missing data handling for key secondary endpoints (non-response imputation for binary endpoints, days with missing NRS values counted as not meeting the NRS criterion) was conservative and is appropriate.

Randomization was stratified by corticosteroid use at baseline and diagnosis of recurrent idiopathic pericarditis. Randomisation stratification factors were taken into account in the analysis. If the number of events in a stratum was ≤ 5 or all subjects had the same response in a stratum, strata were pooled according to a pre-specified strategy. It is not clear whether this was needed, however, the approach is acceptable.

The multiplicity strategy ensured family-wise type 1 error control for the primary and key secondary endpoints.

Efficacy data

Primary Efficacy Endpoint, Time to Pericarditis Recurrence in the Randomized Withdrawal Period

The time to pericarditis recurrence for the rilonacept treatment arm was significantly longer than for the placebo arm, with a hazard ratio of 0.04 (95% CI: 0.01; 0.18); rilonacept reduced the risk of recurrence by 96%. Mean time to pericarditis recurrence was not estimable in the rilonacept group because there were too few recurrences. The median time to recurrence for subjects in the placebo arm was 8.6 weeks. By Week 8 of the RW period, the recurrence rates for the placebo and rilonacept arms were 49.6% and 0.0%, respectively. The recurrence rates increased to 73.4%, 80.1%, and 90.0% for the placebo arm and 4.3%, 4.3%, and 11.2% for the rilonacept arm at RW Weeks 16, 24, and 36, respectively. A majority of subjects randomized to the placebo arm (23/31 subjects, 74.2%) experienced a pericarditis recurrence event during the RW period, while only 2 of 30 subjects (6.7%) randomized to the rilonacept treatment arm experienced a recurrence event. Overall, the treatment effect can be considered clinically relevant.

Efficacy results were not presented according to widely acceptable criteria by ESC (2 out of 4 criteria: pericardial rub, pericarditis pain, ECG or ECHO signs of pericarditis) **(OC).** Most of the recurrences were based on CRP and NRS pain abnormalities with only a few cases due to changes in auscultatory, ECG or ECHO abnormalities.

The treatment effect may be somewhat lower in the proposed target group of patients if patients not completing the RI phase are taken into account. This should be further discussed and analysed by the Applicant in detail **(OC).**

Subgroup analyses by oral corticosteroid use at baseline and at ≥4 weeks at baseline; diagnosis of recurrent idiopathic pericarditis; sex; age 18 – 64 years; race; region; and number of pericarditis episodes showed nominally significant improvements for the primary endpoint event. Data for "no idiopathic pericarditis" and "age 65 to 78 years" were inconclusive probably due low numbers of subjects analysed. To further explore the results in these subgroups, analyses of efficacy or lack thereof should be provided for these subgroups included in the RI period, in the LTE period and in the phase 2 study. **(OC).** No results were presented on efficacy for paediatric patients 12 – 17 years separately, only 3 out of 7 patients included in the RI period embarked the RW period. Further justification is requested on inclusion of paediatric patients in the indication **(MO).**

Key secondary (confirmatory) efficacy endpoints

- Significantly more subjects in the rilonacept group maintained clinical response (17/21; 81.0%) at week 16 than in the placebo group (4/20; 20.0%, p = 0.0002). A similar numerically significant response was observed at Weeks 8 and 24. Consistent results were reported at weeks 8 and 24.

- Subjects receiving rilonacept experienced significantly more days with no or minimal pericarditis pain (≤2 on the NRS) during the first 16 weeks of the RW period than did subjects who received placebo. The least squares mean of days with no or minimal pericarditis pain in the first 16 weeks were 98.6% and 47.4% for subjects receiving rilonacept and placebo, respectively (p <0.0001). Consistent results were reported for weeks 8 and 24.

- At RW week 16, in a significantly higher proportion of subjects treated with rilonacept pericarditis symptoms (based on the 7-point PGI-PS) were absent or minimal (17/21, 81.0%) than in placebo-treated subjects (5/20, 25.0%; p = 0.0006). Consistent results were reported for weeks 8 and 24.

Other secondary efficacy endpoints

Run in period

Among the 79 subjects who completed treatment through Week 12, 73 subjects (92.4%) achieved the protocol definition of clinical response (weekly average of daily pericarditis pain on the 11-point NRS ≤ 2.0, CRP level ≤ 0.5 mg/dL) at this time point.

Time to treatment response was defined as time from the first dose to the first day of pain (using NRS) ≤ 2 and CRP ≤ 0.5 mg/dL within 7 days before or after pain response. A total of 77 subjects (97.5%) out of 79 with baseline NRS and CRP values achieved treatment response. The median time to treatment response was 5.0 (4.0; 7.0 Median 95% CI) days.

During the RI period, of 66 patients with a baseline NRS measurement ≥ 3, 65 (98.5%) achieved pain response (3-day rolling average NRS ≤ 2).

Sixty-eight patients had a baseline CRP value ≥ 0.5 mg/dL. During the RI period, 98.6% of these patients achieved CRP normalisation (CRP ≤ 0.5 mg/dL). Median time to CRP normalisation was 7 days.

Pericardial effusion, pericarditis associated ECG signs and other pericarditis manifestations as WBC counts >ULN, Fever > 38°C, and pericardial rub disappeared in almost all patients where present during the RI period. None of the patient had tamponade present at baseline, efficacy of rilonacept with respect to this manifestation is not known. The Applicant is asked to comment whether there is information, e.g. post marketing experience, as to whether rilonacept has any impact on tamponade. **(OC)**

Among the 79 subjects taking background pericarditis medications at baseline, 73 (92.4%) were able to discontinue background medications and achieved rilonacept monotherapy.

Randomized Withdrawal Period

The time to pericarditis pain ≥ 4 on the NRS for the rilonacept treatment arm was significantly longer than the placebo arm, with a hazard ratio of 0.13 (p < 0.0001); rilonacept reduced the risk of experiencing pain ≥ 4 by 87%.

In the rilonacept treatment arm, 1 subject (3.3%) used oral rescue therapy (ORT), and 1 subject received rilonacept bailout. In the placebo arm, 2 subjects (6.5%) used ORT, and 23 subjects (74.2%) received rilonacept bailout. The odds ratio for the use of ORT, corticosteroids, or bailout rilonacept between treatments was 0.015

Patient reported outcome data

Assessments of Pericarditis Activity: PGA-PA

RI period:

The proportions of subjects with absent or minimal pericarditis symptoms as assessed by the PGA-PA were 10.6%, 94.8%, and 98.8% at RI baseline, Week 6, and Week 12, respectively.

RW period:

At RW Weeks 8, 16, and 24, 85.2%, 85.7%, and 88.2% of subjects randomized to rilonacept were reported to have absent or minimal symptoms, compared with 32.2%, 25%, and 20.0% of subjects randomized to placebo (before bailout), respectively. At each time point, rilonacept subjects were significantly more likely to report absent or minimal pericarditis symptoms ($p \leq 0.0002$).

There are issues on the number of missing values and on the validation of the PGA-PA for patients with pericarditis to be clarified by the Applicant **(OC).**

SF-36 and SF-6D

RI period: Mean scores for the physical and mental component scores improved from 35.6 and 44.0 at baseline to 49.2 and 53.4 at Week 12

RW period: Among adult subjects with pericarditis recurrence (2 rilonacept subjects, 22 placebo subjects), there was a worsening of SF-36 at the recurrence visit.

Results for SF-6D were consistent.

EQ-5D-5L

RI period: All 5 descriptive system dimensions of the EQ-5D-5L were improved from baseline.

RW period: Among adult subjects with pericarditis recurrence (2 rilonacept subjects and 22 placebo subjects), there was a worsening of EQ-5D-5L scores at the recurrence visit across all 5 dimensions.

Insomnia Severity Index (ISI)

RI period: Mean total ISI score at RI baseline was 10.7 (indicating subthreshold insomnia) improved at Week 12 to 5.6 indicating no clinically significant insomnia).

RW period: Mean total ISI scores at RW Week 24 were generally similar to those at RW baseline.

Overall, the scores consistently indicated improvement in different domains associated with rilonacept therapy and worsening associated with recurrence of pericarditis. Only about 50% of patients with baseline RW values provided data at week 24. The reasons and the impact on the reliability of the results for all of the PRO should be explained and discussed by the Applicant. **(OC)**

Long term extension

Pericarditis recurrence before month 18. Up to the 18-month Decision Milestone, the annualised incidence of pericarditis recurrence while on rilonacept treatment was 0.043 (95% CI, 0.0009, 0.125) events/patient-year. The mean (SD) number of episodes per year was 1.27 (0.562). The results up to month 18 in the LTE period indicate maintenance of clinical efficacy in almost all of the patients being available for an assessment up to 18 months. Clarification is requested on 22 patients not available for the 18 months assessment and on the duration of treatment in 74 patients contributing to the assessment of annualized rates. **(OC)**

Pericarditis Recurrence after the 18-month Decision Milestone;

At month 18 patients could continue or discontinue active treatment. Amongst the 33 participants who continued rilonacept after the 18-month Decision Milestone, the annualised incidence of pericarditis recurrence while on rilonacept treatment was 0.041 (95% CI, 0.001, 0.227) events/patient-year. Of the 8 participants who suspended treatment for observation after the 18-month Decision Milestone, 6 had an Investigator-assessed recurrence (recurrence rate, 75.0%). During the post-treatment 6-week safety follow-up after cessation of study drug rilonacept, four additional Investigator-assessed pericarditis recurrences (NRS >6; CRP >1 mg/dL, meeting RHAPSODY RW period event adjudication criteria) were

reported at 6 weeks. Clarification is requested on one patient with endocarditis mentioned in the report as infections are a known AE of the treatment with Rilonacept **(OC)**.

MRI assessment

MRI assessment for pericardial inflammation was performed in a subpopulation of participants, but it is not clear from the protocol and study documents, how participants were chosen for this substudy. Summary of MRI results is not presented but is requested **(OC).**

3.3.6. Conclusions on clinical efficacy

Overall, clinical efficacy can be considered in adult patients with recurrent pericarditis. Data deriving from one pivotal trial are considered sufficiently robust, statistically compelling and clinically meaningful. Confirmation of the results can be derived from the uncontrolled phase 2 trial in a similar patient population.

There are several issues to be addressed (OCs).

Currently, the data presented are not sufficient to conclude on a demonstrated efficacy in the paediatric population **(MO)** and it should be further discussed whether this product should only be used in patients at high risk for recurrent pericarditis (**MO**)**.**

3.3.7. Clinical safety

The safety evaluation for the current MAA submission focusses mainly on exposure and safety data in the recurrent pericarditis (RP) target indication.

Two clinical studies, i.e. the Phase 2 study (C001) and the RHAPSODY Phase 3 study (C002), have investigated the use of rilonacept among 111 patients in the recurrent pericarditis indication.

The large clinical and post-marketing safety data pool for rilonacept in other indications is considered supplemental and supportive of a favourable safety assessment for the product.

Table 16 summarises studies C001 and C002. Both studies have been completed.

Table 16: Studies Included in the Summary of Clinical Safety

Study Number	Study Design	Population	Starting Dose	N (Total)	N (Adult)	N (Paediatric)	Data Cutoff Date/Study Status
C001	Single-active-arm Phase 2 study	Participants with idiopathic recurrent pericarditis or recurrent post-pericardiotomy syndrome (adult and paediatric)[a]	Initial 320 mg SC; 160 mg SC q.w. (adults) Initial 4.4 mg/kg (320 mg max) SC; 2.2 mg/kg (160 mg max) SC q.w. (paediatrics)	25	25	0	Completed 17 May 2019
C002	Phase 3 double-blind, placebo-controlled, randomised withdrawal study with Long-term extension 05 Sep	Participants w/ recurrent pericarditis (adult and paediatric)[b]	Loading dose = 320 mg SC; 160 mg SC q.w.(adults) Initial 4.4 mg/kg (320 mg max) SC; 2.2 mg/kg (160 mg max) SC q.w. (paediatrics)	86	79	7	31 Aug. 2020 05 Sep. 2023
Total Participants in the Integrated Safety Group				111	104	7	N/A

[a] No paediatric participants ultimately enrolled.
[b] In C002, 7 paediatric participants refer to adolescent participants (13 to 17 years of age)
max = maximum; N/A = not applicable; q.w. = once weekly; SC = subcutaneous
FOOTNOTE: The exposures in this Integrated Safety Group regarding study C002 are derived from the RI and RW periods only, exclusive of the LTE. LTE safety data are reported separately.

The pooled analysis of the safety data from both studies utilises the integrated safety group composed of all participants in studies C001, and the single-blind run-in (RI) and placebo-controlled randomised withdrawal (RW) periods of C002 exclusive of the open-label long-term extension (LTE).

Safety data from the open-label long-term extension (LTE) period of the Phase 3 study (C002) from an independent dataset are also presented as supportive information.

3.3.7.1. Patient exposure

In the two completed clinical studies in patients with recurrent pericarditis (RP), a total of 111 patients have received at least 1 dose of Rilonacept:

- 25 patients in the Phase 2 study (C001) and
- 86 patients in the RHAPSODY Phase 3 study (C002). Of these 86 patients, 74 transitioned into the open-label long-term extension (LTE) period, and 69 (93.2%) patients completed the open-label long-term extension (LTE) period of the RHAPSODY Phase 3 study (up to 2 years).

Table 17 presents information regarding treatment duration, compliance, and administration for the Safety Analysis Set of Phase 2 study (C001) and the Phase 3 study (C002) (RI, RW, LTE periods).

Table 17: Summary of Rilonacept/Placebo Exposure

Rilonacept/Placebo Treatment	Rilonacept	Placebo	All Participants	LTE Period Overall
	(N=111)[b]	(N=31)[a]	(N=111)[c]	(N=74)[g]
Treatment Duration (weeks)[d]				
n	111	31	111	74
Mean	24.69	9.88	27.46	68.13
SD	14.704	9.398	15.714	27.141
Median	23.86	6.71	24.14	54.21
Min	0.7	2	0.7	11
Max	62.4	40.1	67.4	105
Number of Administrations[e]				
n	111	31	111	74
Mean	24.7	9.7	27.4	66.2
SD	14.28	9.16	15.25	27.38
Median	25	7	25	54
Min	1	2	1	11
Max	63	39	68	105
Total Rilonacept Dose Administered (mg)[f]				
n	111	0	111	74
Mean	4102.1	NA	4102.1	10584.1
SD	2314.03	NA	2314.03	4364.24
Median	4000	NA	4000	8640
Min	312	NA	312	1760
Max	10400	NA	10400	16800

[a] Includes Study C002 placebo arm data from randomisation until bailout, treatment discontinuation + 6 weeks, end of study, or data cutoff, whichever occurs first.
[b] Includes all data for participants in Study C001 and all data for participants from RI and RW periods of Study C002 (excluding LTE period of C002). This also excludes data summarised in the Placebo column.
[c] Includes data for all participants from Study C001 and RI /RW periods of the Study C002 (Excludes LTE period).
[d] Treatment duration is defined as [minimum of (date of last study drug + 6, end of study date, date of cutoff) - date of first dose + 1)/7]. For participants randomised to placebo arm in Study C002, 1) duration of placebo treatment is defined as [minimum of (date of last placebo treatment + 6, end of study date, date of receiving rilonacept-1, data cutoff date) – date of first dose in RW period+1)/7; 2] duration of rilonacept treatment is the study overall treatment duration – duration of placebo treatment (also excludes LTE period).
[e] Number of administrations includes all administrations regardless of full amount or partial amount of syringe injected. The loading dose includes 2 injections and is counted as one administration.
[f] Total rilonacept dose administered (mg) = the sum of all doses received.
[g] Includes data from study C002 LTE period.
SD = standard deviation; Max = maximum; Min = minimum; NA = not applicable

Forty-four (44) participants completed the LTE period in Study C002, but did not complete the full 2-year LTE period. Of the 49 participants overall, who discontinued treatment in LTE period early, 3 discontinued because of TEAEs (acute endocarditis, COVID pneumonia, fatigue), 2 for pregnancy, 2 participant decision, and 42 participants reported "other" reasons. The Applicant should specify and discuss the possible safety issues, what were the "Other" reasons among all those who completed earlier the LTE period and among those who did not complete the full 2-year LTE period. (**OC**)

3.3.7.2. Adverse events

Adverse Events – Integrated Safety Group

The integrated safety data group is presented in Table 18 and includes the pooled safety data from the Phase 2 study (C001) and the single-blind run-in (RI) and double-blind, placebo-controlled randomised withdrawal (RW) periods of the RHAPSODY Phase 3 study (C002).

Notable TEAEs experienced by participants on Rilonacept vs. Placebo in the integrated safety group included injection site reactions (36.9% vs. 0%) and infections and infestations (31.5% vs. 9.7%) such as upper respiratory infection (22.5% vs. 0%), which encompasses the preferred terms nasopharyngitis, pharyngitis, pharyngitis streptococcal, rhinitis, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.

Table 18: Overview of Treatment-emergent Adverse Events – Integrated Safety Group

Category[d]	Placebo[a] (N=31) n (%)	Rilonacept[b] (N=111) n (%)	All Participants[c] (N=111) n (%)
Any Adverse Events	13 (41.9)	99 (89.2)	100 (90.1)
TEAEs[e]	13 (41.9)	98 (88.3)	99 (89.2)
TEAEs by Maximum Severity[f]			
Mild	9 (29.0)	68 (61.3)	66 (59.5)
Moderate	4 (12.9)	26 (23.4)	29 (26.1)
Severe	0	4 (3.6)	4 (3.6)
Drug-Related TEAEs[g]	1 (3.2)	68 (61.3)	68 (61.3)
Serious TEAEs (SAEs)	1 (3.2)	6 (5.4)	7 (6.3)
Drug-Related SAE[g]	0	1 (0.9)	1 (0.9)
TEAEs Leading to Dose Interruption	0	1 (0.9)	1 (0.9)
TEAEs Leading to Study Drug Discontinuation	0	5 (4.5)	5 (4.5)
Drug-Related TEAEs Leading to Treatment Interruption	0	1 (0.9)	1 (0.9)
Drug-Related TEAEs Leading to Treatment Discontinuation	0	4 (3.6)	4 (3.6)
TEAEs of Injection Site Reaction[h]	0	41 (36.9)	41 (36.9)
TEAEs of Malignancy (excluding basal cell carcinoma of the skin)	0	1 (0.9)	1 (0.9)
TEAEs of Infections and Infestations	3 (9.7)	35 (31.5)	37 (33.3)
TEAEs of Upper Respiratory Infection[i]	0	25 (22.5)	25 (22.5)

[a] Includes Study C002 placebo arm data from randomisation until bailout, treatment discontinuation + 6 weeks, end of study, or data cutoff, whichever occurs first.
[b] Includes all data for participants in Study C001 and all data for participants within the RI and RW periods of Study C002 excluding data from the placebo group. This also excludes C002 LTE period.
[c] Includes data for all participants from Study C001 and Study C002 excluding LTE period.
[d] Participants with multiple events are counted once in the same category.
[e] Treatment-emergent adverse events (TEAEs) are defined as AEs that start or increase in severity on or after the date of first dose and before 6 weeks after the last dose of study drug.
[f] Each participant has only been represented with the maximum severity.
[g] Related or possibly related, as assessed by the investigator.
[h] Injection Site Reaction is a category that encompasses the preferred terms erythema, swelling, pruritus, mass, bruising, inflammation, pain, oedema, dermatitis, discomfort, urticaria, vesicles, warmth, and haemorrhage.
[i] Upper Respiratory Tract Infection is a category that encompasses the preferred terms nasopharyngitis, pharyngitis, pharyngitis streptococcal, rhinitis, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.

The safety data from all study periods of the RHAPSODY Phase 3 study (C002) including the open-label long-term extension (LTE) period from an independent dataset are presented as supportive information and displayed within Table 19.

Table 19: Summary of TEAEs over the entire C002 Study

Category	Run-In	Randomised-Withdrawal Period		Overall (RI+RW)	Long-term Extension
no. (%)	(N = 86)	Rilonacept Before Bailout	Placebo Before Bailout	Rilonacept or Placebo	
		(N = 30)	(N = 31)	(N= 86)	(N = 74)
All adverse event [a]	70 (81.4)	25 (83.3)	13 (41.9)	75 (87.2)	62 (83.8)
Treatment Emergent Adverse Events[b]	70 (81.4)	25 (83.3)	13 (41.9)	74 (86.0)	62 (83.8)
TEAEs by Maximum severity[c]					
Mild	53 (61.6)	17 (56.7)	9 (29.0)	47 (54.7)	27 (36.5)
Moderate	15 (17.4)	8 (26.7)	3 (9.7)	24 (27.9)	28 (37.8)
Severe	2 (2.3)	0	1 (3.2)	3 (3.5)	7 (9.5)
TEAEs related to study drug	47 (54.7)	11 (36.7)	1 (3.2)	51 (59.3)	22 (29.7)
Serious TEAEs [c]	1 (1.2)	1 (3.3)	1 (3.2)	5 (5.8)	6 (8.1)
Serious TEAEs related to study drug [c]	0	0	0	0	2 (2.7)
TEAEs leading to dose interruption	0	1 (3.3)	0	0	2 (2.7)
TEAEs leading to study drug discontinuation	4 (4.7)	0	0	1 (1.2)	3 (4.1)
Adverse events leading to death	0	0	0	4 (4.7)	0

[a] Adverse event that starts or increases in severity from first study-drug dose to 6 weeks after last dose.
[b] Counted once, according to the maximum severity of the adverse event.
[c] Serious TEAEs considered related were acute endocarditis and viral pneumonia.

Common AEs in the Integrated Safety Group

Table 20 summarises TEAEs that occurred in ≥5% of all participants in the integrated safety group. The values represent the number (%) of participants who experienced a particular TEAE; a participant could have experienced more than 1 occurrence of an TEAE, but it is only counted once within a preferred term or SOC category.

Injection site TEAEs including erythema, pruritus, reaction, pain, and swelling listed in Table 20 are all components of the broader ISR category.

The 3 most commonly occurring non-ISR TEAEs experienced by patients on Rilonacept vs. Placebo in the integrated safety group were arthralgia (11.7% vs. 0%), nasopharyngitis (10.8% vs. 0%) and myalgia (9.0% vs. 0%).

Other TEAEs reported in ≥5% of patients on Rilonacept vs. Placebo included headache (8.1% vs. 0%), diarrhoea (7.2% vs. 0%), cough (6.3% vs. 0%), fatigue (6.3% vs. 0%) and non-cardiac chest pain (4.5% vs. 3.2%).

Table 20: Treatment-Emergent Adverse Events in ≥5% of Participants Overall – Integrated Safety Group

Preferred Term[d]	Placebo[a] (N=31) n (%)	Rilonacept[b] (N=111) n (%)	All Participants[c] (N=111) n (%)
Participants with Any TEAEs	13 (41.9)	98 (88.3)	99 (89.2)
Injection site erythema	0	23 (20.7)	23 (20.7)
Arthralgia	0	13 (11.7)	13 (11.7)
Nasopharyngitis	0	12 (10.8)	12 (10.8)
Myalgia	0	10 (9.0)	10 (9.0)
Headache	0	9 (8.1)	9 (8.1)
Diarrhoea	0	8 (7.2)	8 (7.2)
Injection site pruritus	0	8 (7.2)	8 (7.2)
Injection site reaction	0	8 (7.2)	8 (7.2)
Musculoskeletal chest pain	4 (12.9)	4 (3.6)	8 (7.2)
Cough	0	7 (6.3)	7 (6.3)
Fatigue	0	7 (6.3)	7 (6.3)
Injection site pain	0	6 (5.4)	6 (5.4)
Injection site swelling	0	6 (5.4)	6 (5.4)
Non-cardiac chest pain	1 (3.2)	5 (4.5)	6 (5.4)

[a] Includes Study C002 placebo arm data from randomisation until bailout, treatment discontinuation + 6 weeks, end of study, or data cutoff, whichever occurs first.
[b] Includes all data for participants in Study C001 and all data for participants within the RI and RW periods of the Study C002 excluding data summarised in the Placebo column. This also excludes the LTE period.
[c] Includes data for all participants from Study C001 and the RI/RW periods of Study C002, exclusive of the LTE period of C002.
[d] MedDRA v21.1. A participant can only be counted once within a preferred term or system organ class

Related TEAEs in the Integrated Safety Group

The incidence of common TEAEs considered at least possibly related to study treatment in the integrated safety group is presented in Table 21 for events that were reported in at least 2 participants. For most participants in the rilonacept group (61.3%) treatment-related adverse events were reported compared to 1 participant (3.2%) in the placebo group.

The most commonly reported adverse reactions experienced by participants on Rilonacept vs. Placebo in the integrated safety group were administration site conditions (35.1% vs. 3.2%); most often injection site erythema (20.7% vs. 0%) followed by injection site pruritus (7.2% vs. 0%) and injection site reaction (7.2% vs. 0%).

There was also a higher risk of infections considered related to study treatment in participants on rilonacept (9.9%) compared with placebo (0%) and musculoskeletal and connective tissue disorders (13.5% vs .0%) such as arthralgia (3.6% vs. 0%) and myalgia (4.5% vs. 0%).

Table 21: Treatment-related Adverse Events in >1 Participants– Integrated Safety Group

System Organ Class[d] Preferred Term	**Placebo**[a] **(N=31) n (%)**	**Rilonacept**[b] **(N=111) n (%)**	**All Participants**[c] **(N=111) n (%)**
Any related TEAE	***1 (3.2)***	***68 (61.3)***	***68 (61.3)***
Cardiac disorders	**0**	**3 (2.7)**	**3 (2.7)**
Pericarditis	0	2 (1.8)	2 (1.8)
Ear and Labyrinth disorders	**0**	2 (1.8)	2 (1.8)
Vertigo	0	2 (1.8)	2 (1.8)
Gastrointestinal disorders	**0**	**5 (4.5)**	**5 (4.5)**
Diarrhoea	0	5 (4.5)	5 (4.5)
General disorders and administration site conditions	**1 (3.2)**	**39 (35.1)**	**40 (36.0)**
Injection site bruising	0	4 (3.6)	4 (3.6)
Injection site erythema	0	23 (20.7)	23 (20.7)
Injection site pain	0	6 (5.4)	6 (5.4)
Injection site pruritus	0	8 (7.2)	8 (7.2)
Injection site rash	0	3 (2.7)	3 (2.7)
Injection site reaction	0	8 (7.2)	8 (7.2)
Injection site swelling	0	6 (5.4)	6 (5.4)
Injection site discolouration	0	2 (1.8)	2 (1.8)
Feeling hot	0	2 (1.8)	2 (1.8)
Infections and infestations	**0**	**11 (9.9)**	**11 (9.9)**
Nasopharyngitis	0	3 (2.7)	3 (2.7)
Sinusitis	0	3 (2.7)	3 (2.7)
Subcutaneous abscess	0	2 (1.8)	2 (1.8)
Investigations[e]	**0**	**15 (13.5)**	**15 (13.5)**
Blood cholesterol increased	0	3 (2.7)	3 (2.7)
High density lipoprotein increased	0	4 (3.6)	4 (3.6)
Lipids increased	0	4 (3.6)	4 (3.6)
Hepatic enzyme increased	0	2 (1.8)	2 (1.8)
Musculoskeletal and connective tissue disorders	**0**	**15 (13.5)**	**15 (13.5)**
Arthralgia	0	4 (3.6)	4 (3.6)
Myalgia	0	5 (4.5)	5 (4.5)
Back pain	0	2 (1.8)	2 (1.8)
Joint stiffness	0	2 (1.8)	2 (1.8)
Skin and subcutaneous tissue disorders	**0**	**8 (7.2)**	**8 (7.2)**
Erythema	0	2 (1.8)	2 (1.8)
Pruritus	0	2 (1.8)	2 (1.8)

[a] Includes Study C002 placebo arm data from randomisation until bailout, treatment discontinuation + 6 weeks, end of study, or data cutoff, whichever occurs first.
[b] Includes all data for participants in Study C001 and all data for participants within the RI and RW periods of Study C002 excluding data from the placebo group. LTE period was not included.
[c] Includes data for all participants from Study C001 and Study C002 RI and RW periods, exclusive of the LTE.
[d] Only System Organ Classes (MedDRA v21.0) are presented where at least one Preferred Term was reported in >2 participants.
[e] non-fasting tests

3.3.7.3. Serious adverse event/deaths/other significant events

No deaths occurred in the recurrent pericarditis clinical development program (Study C001 and C002).

Overall, 7/111 (6.3%) participants in the integrated safety group (C001 study and RI + RW periods of C002 study) experienced a serious TEAE, 6 patients (5.4%) in the Rilonacept group and one patient in the placebo group (3.2%) (Table 22).

2 participants were in Study C001, and 5 participants were in Study C002 (4 who received rilonacept and 1 who received placebo). The participant narratives detailing the SAEs are located within the CSRs.

In Study C001, one participant experienced an SAE of non-cardiac chest pain assessed as moderate in severity and unlikely related to study drug; no action with study drug was taken (C001 CSR). The onset of the non-cardiac chest pain event occurred 2 hours after receiving the first dose of rilonacept and was subsequently diagnosed as atypical chest pain due to recent shoulder surgery. The outcome of this event was reported as recovered at Study Day 5.

One participant in Study C001 experienced an SAE of subcutaneous abscess on Study Day 28 that was assessed by the investigator as severe and possibly related to study drug; the study drug was withdrawn. This participant started study drug while on prednisone 10 mg/day. The participant was hospitalised, and the event was managed through medical and surgical interventions. The SAE resolved without sequelae approximately 2 weeks later. The SAE resolved with medical management; however, the study drug was discontinued, while the concomitant use of prednisone 10 mg daily was continued. In this participant, there was no haematological evidence of immunosuppression, as this participant had a normal white blood cell count of 9.3×10^9/L upon hospital admission for surgical drainage, compared to a count of 11.6×10^9/L the previous month. Although, a causal relationship with study drug was attributed, the concurrent use of steroids could be considered as a contributing factor to the SAE.

Of the 5 SAEs observed in any treatment arm during the RI/RW periods of the C002 study, one participant each (0.9%) receiving rilonacept in Study C002 experienced an SAE of ileus, pyrexia, squamous cell carcinoma, and cerebrovascular accident. Events of ileus and pyrexia occurred during the RW period and were assessed as mild and not related to study drug. Events of squamous cell carcinoma (RW period) and cerebrovascular accident (RI period) were classified as moderate in severity and assessed by the investigator as not related or unlikely related to study drug, respectively. No action was taken with the study drug as a result of these SAEs. While receiving placebo, one of 31 participants (3.2%) experienced an SAE of mild cardiac flutter. No modification to study drug dose was made, and the event resolved after several days.

Table 22: Serious Treatment-Emergent Adverse Events – Integrated Safety Group

System Organ Class[d] Preferred Term	Placebo[a] (N=31) n (%)	Rilonacept[b] (N=111) n (%)	All Participants[c] (N=111) n (%)
Participants with Any Serious TEAE	1 (3.2)	6 (5.4)	7 (6.3)
Cardiac disorders	1 (3.2)	0	1 (0.9)
Cardiac flutter	1 (3.2)	0	1 (0.9)
Gastrointestinal disorders	0	1 (0.9)	1 (0.9)
Ileus	0	1 (0.9)	1 (0.9)
General disorders and administration site conditions	0	2 (1.8)	2 (1.8)
Non-cardiac chest pain	0	1 (0.9)	1 (0.9)
Pyrexia	0	1 (0.9)	1 (0.9)
Infections and infestations	0	1 (0.9)	1 (0.9)
Subcutaneous abscess	0	1 (0.9)	1 (0.9)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	1 (0.9)	1 (0.9)
Squamous cell carcinoma	0	1 (0.9)	1 (0.9)
Nervous system disorders	0	1 (0.9)	1 (0.9)
Cerebrovascular accident	0	1 (0.9)	1 (0.9)

[a] Includes Study C002 placebo arm data from randomisation until bailout, treatment discontinuation + 6 weeks, end of study, or data cutoff, whichever occurs first.
[b] Includes all data for participants in Study C001 and all data for participants within RI and RW periods of the Study C002 excluding data from Placebo group. LTE period is not included.
[c] Includes data for all participants from StudyC001 and Study C002 RI and RW periods, exclusive of the LTE.
[d] MedDRA v21.0. A participant can only be counted once within a preferred term or system organ class.
TEAE = treatment-emergent adverse event

Serious TEAEs during the long-term extension (LTE) period of Study C002 are shown in Table 23.

Table 23: Serious TEAEs by System Organ Class and Preferred Term (LTE Analysis Set)

	LTE Period KPL-914 (N = 74)	
System Organ Class [a] **Preferred Term**	**Treatment Emergent** [b] **n (%)**	**On Observation** [c] **n (%)**
Participants with Any Serious AE	**6 (8.1)**	**0**
Cardiac disorders	**3 (4.1)**	**0**
Acute myocardial infarction	1 (1.4)	0
Aortic valve disease	1 (1.4)	0
Aortic valve incompetence	1 (1.4)	0
Left ventricular failure	1 (1.4)	0
Pericarditis	1 (1.4)	0
Hepatobiliary disorders	**1 (1.4)**	**0**
Bile duct stone	1 (1.4)	0

	LTE Period KPL-914 (N = 74)	
System Organ Class [a] Preferred Term	**Treatment Emergent [b] n (%)**	**On Observation [c] n (%)**
Infections and infestations	**3 (4.1)**	**0**
Acute endocarditis	1 (1.4)	0
Corona virus infection	1 (1.4)	0
Pneumonia	1 (1.4)	0
Pneumonia viral	1 (1.4)	0
Injury, poisoning and procedural complications	**1 (1.4)**	**0**
Hip fracture	1 (1.4)	0
Nervous system disorders	**1 (1.4)**	**0**
Transient ischaemic attack	1 (1.4)	0
Product issues	**1 (1.4)**	**0**
Device malfunction	1 (1.4)	0
Respiratory, thoracic and mediastinal disorders	**1 (1.4)**	**0**
Pneumothorax	1 (1.4)	0

AE = adverse event; LTE = long-term extension

[a] MedDRA v21.0. A participant could only be counted once within a preferred term or system organ class.

[b] Defined as AEs that started after randomisation withdrawal period and on or before the last dose of study drug in LTE period + 6 weeks.

[c] Defined as AEs that started after the last dose of study drug in LTE period + 6 weeks.

Of the treatment-emergent SAEs, only the subcutaneous abscess in the Study C001 and the acute endocarditis and the viral pneumonia during the long-term extension (LTE) period of Study C002 (Table 23) were considered possibly related to study drug.

3.3.7.4. Laboratory findings

Laboratory findings

No clinically meaningful adverse changes in haematology and chemistry laboratory values were observed in the integrated safety group over the course of the C001 and C002 studies.

Use of rilonacept was associated with a slight increase in mean total cholesterol, mean LDL cholesterol and triglycerides. The level of increase did not require treatment. Physicians should monitor the fasting lipid profiles of their patients (e.g. after 2 to 3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

Vital Signs

As summarised in the respective clinical study reports (CSRs), changes in pulse rate, respiratory rate, and body temperature were not clinically meaningful in both RP studies (Study C001 and C002).

A non-serious TEAE of blood pressure increased was experienced by 2 participants (1.8%) in the rilonacept group in the integrated safety group (C001, RI and RW periods of C002, exclusive of the LTE).

Additionally, in Study C002, one participant experienced an event of mild hypertension assessed as possibly related to study drug that occurred in the setting of an acute systemic allergic reaction. This

event occurred during the RI period in Study C002, and the study drug was ultimately withdrawn due to the hypersensitivity reaction (C002).

In the LTE period of C002, changes in blood pressure, pulse rate, respiratory rate, and body temperature from baseline to Month 18 were not clinically meaningful (C002 LTE).

Electrocardiograms
Within the C001 study, most abnormal findings occurred in study Part 1 during screening and baseline evaluations, but these were generally resolved by the interval evaluation visit and remained resolved through the study extension period. No clinically significant post-baseline findings were noted by local readers. Based on central read, no widespread ST-elevations or PR depressions, which are typical for pericarditis changes, were noted by central readers.

In Study C002 (RI and RW periods, exclusive of the LTE), one participant experienced a clinically significant abnormal finding not consistent with pericarditis at both RI Week 12 and RW Week 24; the finding was described as a left bundle branch block due to a pacemaker sinus tachycardia, T-wave abnormality, and prolonged QT, all present at baseline and unchanged throughout the study.

In the LTE period of C002, there were no clinically relevant changes in ECG results.

3.3.7.5. In vitro biomarker test for patient selection for safety

N/A

3.3.7.6. Safety in special populations

Paediatric population (under 12 years)
Safety and efficacy of rilonacept in children under 12 years with recurrent pericarditis have not been established; therefore, it is not recommended in this paediatric age group.

Paediatric population (aged 12 to 17 years weighing 10 kg or more):
In the phase 3 study RHAPSODY, 7 patients aged 12 to 17 years were treated with rilonacept subcutaneously with a starting 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) once weekly. These patients were treated with rilonacept for a median time of 28 months. There were no apparent differences in efficacy, safety or tolerability across age groups.

Elderly (65 years or older)
In the recurrent pericarditis program, 8 of 111 patients were aged 65 and older. The efficacy and safety profile in this age group was similar to that of the younger adult population and no new safety signals were observed.

Renal impairment
Results of a single-dose study in patients with end-stage renal disease receiving haemodialysis indicate that the rate of elimination of rilonacept was not decreased. Renal elimination of rilonacept is therefore considered to be a minor pathway for clearance. No dose adjustment is needed in patients with renal impairment.

Hepatic impairment
Limited pharmacokinetic data are available in patients with hepatic impairment. As with other large proteins, elimination of rilonacept is expected to be via proteolytic catabolism and target mediated clearance. Consequently, hepatic impairment is not expected to affect the pharmacokinetics of rilonacept in a clinically significant way.

3.3.7.7. Immunological events

Immunogenicity

As with all therapeutic proteins, rilonacept has the potential for inducing immune reactions.

Within the integrated safety analysis of the RP studies C001 and RI/RW periods of C002 (exclusive of LTE period), 40/111 participants (36.0%) were anti-drug antibody (ADA)-positive at any assessment, while 71/111participants (64.0%) were ADA-negative at every assessment.

Among the 26/86 participants (30.2%) in Study C002 who were ADA-positive at any time during the study, 6 (7.0%) had neutralising antibodies (NAb) to rilonacept. At the end of randomised treatment, 5 participants remained positive for ADA and 1 participant remained positive for NAb.

In the C001 study and the RI and RW periods of the C002 study (exclusive of the LTE period), a total of 22/40 ADA-positive participants (55.0%) experienced a drug-related TEAE within 24-hours of treatment administration, compared to 31/71 participants (43.7%) who were ADA-negative at every assessment. A total of 17/40 ADA-positive participants (42.5%) experienced injection site reactions compared to 24/71 participants (33.8%) who were ADA-negative at every assessment.

The Applicant concluded that there was no significant correlation of antibody status with safety results and the impact of immunogenicity on the B/R balance of rilonacept treatment is considered low.

Anti-drug antibody (ADA) data for the long-term extension (LTE) period of the RHAPSODY Phase 3 study were not available at the time of this filing and should be provided by the Applicant.

Systemic hypersensitivity reactions

Hypersensitivity reactions represent a potential risk with protein therapeutics in general as immune processes can overreact. ADRs of drug hypersensitivity and hypersensitivity were reported for a single participant in the RP safety population including LTE treatment. The events were mild or moderate in intensity and resolved after discontinuation or rilonacept.

- One participant experienced in Study C002 a range of TEAEs that occurred in the greater context of a systemic allergic reaction. These events included hypersensitivity, feeling abnormal, tachycardia, erythema, chills, hypertension, angioedema, feeling hot, and drug hypersensitivity. The events ranged from mild to moderate in severity and were assessed as possibly related by the investigator. The events occurred on the day of the first dose injection in the RI period, and rilonacept treatment was discontinued.

3.3.7.8. Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been performed.

Concomitant administration of Arcalyst with any TNF inhibitor is not recommended (see section 4.4 and 4.5 of SmPC), as the combination of another IL-1 blocker in combination with TNF inhibitors is associated with an increased risk of serious infections and neutropenia.

Based upon the potential for pharmacodynamic interactions, concomitant administration of Arcalyst and other medicinal products that block IL-1 or its receptors is not recommended.

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 normalised. 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 plasma concentration should be performed, and the individual dose of the medicinal product may need to be adjusted.

No data are available on either the effectiveness of live vaccination or the risks of secondary transmission of infection by live vaccines in patients receiving Arcalyst. Therefore, live vaccines should be avoided during treatment with Arcalyst. Since Arcalyst may interfere with normal immune response to new antigens, vaccines may not be effective in patients receiving Arcalyst.

Patients should receive all recommended vaccinations prior to treatment with Arcalyst, including pneumococcal vaccine and inactivated influenza vaccine, as IL-1 blockade may interfere with immune response to infections.

3.3.7.9. Discontinuation due to adverse events

Five subjects (5/111; 4.5%) in the integrated safety group (C001 study and RI +RW periods of C002 study) experienced TEAEs leading to study drug discontinuation, all of which occurred in participants receiving rilonacept; the TEAEs leading to discontinuation were assessed by the investigator as related to study drug in 4 of these 5 subjects. Potentially related TEAEs leading to discontinuation were subcutaneous abscess, erythema, alopecia, a range of TEAEs that occurred in the greater context of a systemic allergic reaction in one subject. One additional subject (0.9%) experienced a TEAE of myalgia that led to interruption of treatment.

3.3.8. Post marketing experience

The total post-marketing exposure for rilonacept (US product) in the recurrent pericarditis (RP) indication is 2509 patients and 2135 patient-years up to March 2024.

Overall, the safety profile of rilonacept observed in post-marketing surveillance is similar to what has been observed in the clinical development programme and is adequately reflected by the Table: Adverse drug reactions in section 4.8 of the SmPC.

3.3.9. Discussion on clinical safety

<u>Exposure</u>
In the two completed studies (the Phase 2 study C001 and the RHAPSODY Phase 3 study C002) for the recurrent pericarditis target indication a total of 111 patients have received at least 1 dose of rilonacept: 25 patients in the Phase 2 study (C001) and 86 patients in the RHAPSODY Phase 3 study.
Of these 86 patients, 74 transitioned into the long-term extension period, and 69 (93.2%) patients completed the long-term extension (LTE) period of the RHAPSODY Phase 3 study (up to 2 years).

Forty-four (44) participants completed the LTE period in Study C002, but did not complete the full 2-year LTE period. Of the 49 participants overall, who discontinued treatment in LTE period early, 3 discontinued because of TEAEs (acute endocarditis, COVID pneumonia, fatigue), 2 for pregnancy, 2 participant decision, and 42 participants reported "other" reasons. The Applicant should specify and discuss the possible safety issues, what were the "Other" reasons among all those who completed earlier the LTE period and among those who did not complete the full 2-year LTE period. (**OC**)

The Applicant should provide the exposure data as requested (in AR): Patient exposure (cut off) **(OC).**

<u>AEs, TEAEs, SAEs, deaths</u>

Rilonacept was generally well tolerated in the recurrent pericarditis (RP) clinical development programme. There were no deaths or life-threatening TEAEs. The safety profile was consistent with the

US ARCALYST prescribing information. No new safety findings were identified compared to the initially approved cryopyrin-associated periodic syndrome (CAPS) indication.

It is difficult to evaluate the spectrum of AEs occurring in the RP study population due to the lack of an adequate control group. The study C002 was Placebo-controlled only during the RW period until pericarditis recurrence. During the RW period, subjects in the rilonacept group received a mean total dose of 3920.0 mg rilonacept, and subjects in the placebo group received a total mean dose of 3173.6 mg rilonacept after bailout.

The exposure data are provided, where the median treatment duration with placebo was only 6.71 weeks (2-40.1 weeks). Compared to the exposure to rilonacept (all study periods), the exposure to placebo was significantly shorter, lasting only during the RW period until the bailout, making it difficult to draw a comparison.

Due to the lack of the well-comparable placebo group the safety data for RP indication should be discussed in light of the historical data from studies of previous indication of CAPS in EU. **(OC)**

Treatment-emergent adverse events (TEAEs) are defined as AEs that start or increase in severity on or after the date of first dose and before 6 weeks after the last dose of study drug. The safety data are not well comparable between the placebo and study drug groups in the study C002. The Applicant should explain, how the TEAEs in placebo group were assessed until 6 weeks after the RI period (because all the participants had received rilonacept in RI period), more precisely at the beginning of RW period, and what was the average treatment time in these groups (placebo and rilonacept) within the respective groups in RW period. **(OC)**

The Applicant should provide data on time-to-onset (TTO) for all TEAEs in placebo group **(OC).**

Important identified treatment-related adverse events of rilonacept included injection site reactions (ISRs) (erythema, swelling, pain, pruritus and rash at the site of administration) and a higher rate of infections (upper respiratory tract infections such as nasopharyngitis) probably due to the immunosuppressant mechanism of action of rilonacept (Interleukin-1 α/β inhibitor). The long-term safety (especially malignancies, complications of immunosuppression) should remain under monitoring as missing information in the RMP (RP patient registry).

The Applicant should provide the data on how much ISRs could have been related to self-administrations out of all administrations, and discuss, which risk minimisation measures could mitigate the ADRs possibly related to self-administration errors. **(OC)**

The impact of chronic immunosuppression of treatment with rilonacept on the development of malignancies is unknown. The Applicant is asked to justify the limited controlled long-term safety data for the recurrent pericarditis target indication. **(OC)**

As with all therapeutic proteins, rilonacept has the potential for inducing immune reactions.

Hypersensitivity reactions were reported for a single participant in the clinical RP development programme. The events were mild or moderate in intensity and resolved after discontinuation of rilonacept. Risk mitigation wording is included in section 4.4 of the SmPC.

The Applicant proposes to include PT "vertigo" to PI, stating that procedural dizziness is covered by vertigo. Procedural dizziness is likely a transient, non-specific sensation related to postural changes, stress, or mild systemic effects during or after a medical procedure. Dizziness is coded under general terms for balance disturbances. Procedural vertigo suggests a specific mechanism related to the vestibular system, such as positioning during the procedure or drug effects directly impacting vestibular function. Vertigo is specifically coded to reflect inner ear or vestibular involvement.

The Applicant is asked to discuss which of the above-mentioned PTs is suitable and if dizziness was caused by procedure or investigational drug and relevance of inclusion as ADR in PI. **(OC)**

The Applicant proposes to include PT "subcutaneous abscess" to PI based on one case from study C001. Abscess did not occur at the site of injection. The patient was treated concomitantly with corticosteroid which is known risk factor of infections. As infections are AESI for rilonacept, the Applicant is asked to consider using broader term "Skin and soft tissue infections" (OC)

The Applicant proposes to include PT "bacterial vaginosis" to PI. As infections are AESI for rilonacept, the Applicant is asked to consider using broader term "Reproductive tract infections" **(OC)**

Malignancy is considered an AESI, because immunosuppressants may increase the risk of malignancies. One participant experienced moderate squamous cell carcinoma on the wrist during the RW period which was surgically excised. This case was assessed as not related to study drug. There were no malignancies reported during the LTE period. Although the squamous cell carcinoma is a common type of skin cancer, it can appear suddenly and could be associated with immunosuppressive medications. The Applicant should provide the more thorough description of the malignancy case in one participant, and discus possible causes and why the squamous cell carcinoma causality with the administration of the study drug was excluded by the Investigator **(OC).**

The long-term safety (especially malignancies, complications of immunosuppression) should remain under monitoring as missing information in the RMP. The Applicant is asked to discuss the feasibility of the RP patient registry **(OC).**

Eosinophilia and neutropenia are listed ADRs in the proposed product information for rilonacept with the frequencies uncommon. The Applicant should justify the ground of inclusion of these ADRs and frequencies. **(OC)**

Liver function test increased (hepatic enzyme increased, alanine aminotransferase increased) has proposed to the PI with the frequencies of common. Incidence per 100 subject years was provided only for ALT>5xULN, AST>5xULN (rate 0), Total Bilirubin>2xULN (rate 5,1). The Applicant should provide the assessment of how these frequencies were found. Please refer to the question regarding the issues of comparison with placebo group. **(OC)**

Within the integrated safety analysis of the RP studies C001 and RI/RW periods of C002 (exclusive of LTE period), 40/111 participants (36.0%) were anti-drug antibody (ADA)-positive at any assessment, while 71/111participants (64.0%) were ADA-negative at every assessment.

As no significant correlation was observed between anti-drug antibody status and safety results in the clinical study population, the impact on the benefit-risk (B/R) balance was considered low by the Applicant. Anti-drug antibody data for the long-term extension (LTE) period of the RHAPSODY Phase 3 study were not available at the time of this filing and should be provided by the Applicant.

Regarding the use of rilonacept in the paediatric population, only 7 patients aged 12 years to 17 years were treated with rilonacept in the pivotal RHAPSODY Phase 3 study for a median duration of 15 weeks. The Applicant is asked to explain why the limited efficacy and safety data are considered sufficient to grant the recurrent pericarditis indication in paediatric patients aged 12 to 17 years. **(MO)**

The experience in elderly patients is also limited. In the recurrent pericarditis program, 8 of 111 patients were aged 65 years and older. The efficacy and safety profile in this age group appeared similar to that of the younger adult population and no new safety signals were observed.

Results of a single-dose study in patients with end-stage renal disease indicate that the rate of elimination of rilonacept was not decreased. Therefore, renal elimination of rilonacept is considered to be a minor pathway for clearance. No dose adjustment is needed in patients with renal impairment.

Limited pharmacokinetic data are also available in patients with hepatic impairment. As with other large proteins, elimination of rilonacept is expected to be via proteolytic catabolism. Consequently, hepatic impairment is not expected to affect the pharmacokinetics of rilonacept in a clinically significant way and dose adjustment is not needed.

In the recurrent pericarditis development program, use of rilonacept was associated with an increase in non-fasting total cholesterol and triglycerides. The level of increase did not require treatment. Physicians should monitor the fasting lipid profiles of their patients (e.g. after 2 to 3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

In addition, there are some qualifying questions for some PT-s in SPC (to use broader terms of infections) and justify the frequencies of laboratory findings (eosinophilia, neutropenia, liver function test increased). The Applicant is asked to assess the causality and justification for inclusion of PT "alopecia" in PI.

Post marketing experience

The Applicant has described one case of alopecia in the study C002, and based on this case has added this PT of alopecia to the ADRs with the frequency of uncommon. De-challenge result/outcome is unknown for this case, concomitant medication and the level of severity of the reported case are also not known. The patient started treatment on 03 Feb 2020 and alopecia began on an unspecified date in March 2020 , which is a fast onset. Assessor considers the data insufficient to support the addition of PT "alopecia" to PI at this timepoint. There is no disproportionate reporting of alopecia in VigiLyze database (IC 025 -0.6). The Applicant is asked to provide a review of all reported cases of alopecia (independent of indication) to assess the causality and justification for inclusion of PT "alopecia" in PI. The Applicant is asked to provide the mechanism by which the study drug may cause hair loss and provide more detailed description of this case. **(OC)**

Summary

The Applicant is asked to provide a review of all reported cases of alopecia (independent of indication) to assess the causality and justification for inclusion of PT "alopecia" in PI. The Applicant is asked to provide the mechanism by which the study drug may cause hair loss and provide more detailed description of this case. (OC)

The major safety concerns are related to the limited controlled long-term safety data from the two clinical studies for the recurrent pericarditis target indication and whether the paediatric indication can be granted based on the 7 patients aged 12 to 17 year of the RHAPSODY phase 3 study. **(MO)** However, it is acknowledged that recurrent pericarditis is an orphan disease (orphan drug designation was granted in the US in 2020 and in the EU in 2021) and that rilonacept has been approved in the US since 2008 for various therapeutic indications and since March 2021 also for the treatment and risk reduction of recurrent pericarditis both in adults and children 12 years and older.

3.3.10. Conclusions on clinical safety

Main criticism are the limited controlled long-term safety data from the two clinical studies on the recurrent pericarditis target indication and whether the paediatric indication can be granted for rilonacept based on the 7 paediatric patients aged 12 to 17 years who have been treated in the pivotal Phase 3 study RHAPSODY for a median duration of 15 weeks.

3.4. Risk management plan

3.4.1. Safety Specification

3.4.1.1. Summary of safety concerns

The Applicant proposed the following summary of safety concerns in the RMP:

Table 24: Summary of safety concerns

Important identified risks	1. Infections 2. Immunogenicity
Important potential risks	1. Systemic hypersensitivity reactions 2. Malignancy 3. Foetal defects 4. Nonteratogenic effects 5. Drug interactions
Missing information	1. Pregnant and nursing women 2. Paediatric patients with RP below the age of 12 years 3. Patients with severe hepatic impairment

3.4.2. Discussion on safety specification

The Applicant has completed Parts II SI to SVII, which corresponds to the requirements for a full marketing authorisation application. The requirements for a hybrid application are different and certain modules of part II are not required in this case (i.e., modules SII, SIV, SV, SVI). The Applicant is requested to align the RMP with the requirements corresponding to the legal basis of their application (OC).

According to GVP Module V Rev.2 the RMP elements for hybrid applications are the same as for a generic product and hence the reference product. GVP Module V Rev.2 also states that for changes in the therapeutic indications the Applicant should discuss in RMP Module SVII whether this results in the addition or deletion of a safety concern. The reference product (Rilonacept Regeneron) had a RMP, and the latest version identified by the Rapporteur is version 7. It is currently not clear if the Applicant used this RMP as reference for their application as there are notable differences between the reference RMP and the proposed RMP. Considering that pharmacovigilance planning may have evolved since the reference product has been approved such differences may well be justifiable. Nonetheless, the Applicant is requested to clarify if the proposed RMP is based on the RMP of the reference product and to state the version number of the respective RMP of the reference product. Overall, Module SVII should reflect the consideration of the reference RMP more clearly (OC).

Of note, following safety concerns are included in RMP version 7 of the reference product:

Identified risks –infection, changes in lipid profile, immunogenicity.

Potential risks – risk of neoplasm, drug interactions, hypersensitivity and immune-mediated reactions (including severe injection site reactions), lack of effect during long-term use, neutropenia, cardiovascular disorders, foetal defects, off-label use (including use in NOMID/CINCA), medication errors.

Missing information - use in hepatic impairment, confirmation of dosing regimen, possible impairment of vaccine efficacy/safety risks associated with live vaccines.

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification,

- It is considered that the following issues should be addressed:

The Applicant is requested to discuss the clinical consequence of immunogenicity with regard to safety and propose a wording that better reflects the clinical consequence of this risk (OC). The Rapporteur notes that no significant correlation was observed between anti-drug antibody status and safety results in the clinical study population (see section 3.5.7). Pending the answer to questions on immunogenicity further revision of the summary of safety concerns may become necessary.

The Applicant is requested to clarify why systemic hypersensitivity reactions are classified as important potential risk and not important identified risk, considering that hypersensitivity has been observed in clinical trials (OC).

The Applicant is requested to further specify non-teratogenic effects and justify the need to list "foetal defects" and "non-teratogenic effects" as separate important potential risks and in addition to the missing information "pregnant and nursing women" as all 3 points appear to address the same safety concern. In this discussion the Applicant should consider if "use in pregnant women" may be sufficient to address the safety concern (OC).

The Applicant is requested to discuss the clinical consequence of drug interactions that acts as driver for inclusion of this risk as safety concern in the RMP and to propose a wording that better reflects the clinical consequence of this risk (OC).

The Applicant is requested to re-word the missing information into "use in <respective population>" (OC).

With regards to "use in paediatric patients with RP below the age of 12 years" the Rapporteur notes that uncertainty around alteration of bone development in paediatric patients is of concern. The Applicant is requested to discuss why this is of concern only in patients below the age of 12, considering the more general statement in the RMP, as follows: "Paediatric patients treated with rilonacept should undergo appropriate monitoring for growth." (OC). The wording "use in paediatric patients with RP below the age of 12 years", however, does not affect the population as defined in the intended in-label population and would constitute off-label use. Therefore, "use in paediatric patients with RP below the age of 12 years" should be removed from the missing information. The Applicant is requested to comment on this proposal (OC).

The Applicant stated in the RMP that no effect of hepatic impairment on the PK of rilonacept or the risk-benefit is expected. Hence, it is not clear why use in patients with severe hepatic impairment is included in the RMP. Considering that according to GVP Module V Rev.2 absence of data itself does not automatically constitute a safety concern and risk management planning should focus on situations that might differ from the known safety profile the Rapporteur proposes to remove "patients with severe hepatic impairment" from the list of safety concerns. The Applicant is requested to comment on this proposal (OC).

Pending the answers to questions on the limited efficacy and safety data in the paediatric population and the limited long-term safety data, further revision of the summary of safety concerns may become necessary.

The Applicant should revise relevant parts of the RMP, taking into consideration the points raised above (OC).

3.4.4. Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

No additional pharmacovigilance activities are planned for rilonacept.

Overall conclusions on the PhV Plan

Depending on the outcome of the CHMP decision regarding the safety concerns to be addressed in the RMP, the MAH is requested to comment on how the risks of the product should be further evaluated or how the missing information can be sought and to propose respective activities for the RMP (OC).

3.4.5. Risk minimisation measures

Routine Risk Minimisation Measures

Table 25: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk 1: Infections	Routine risk communication: *SmPC sections 4.4, 4.8.* *PL section 4.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation to discontinue treatment in case of serious infections is included in SmPC sections 4.4* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Important identified risk 2: Immunogenicity	Routine risk communication: *SmPC sections 4.8, 5.3.* *PL section 4.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Important potential risk 1: Systemic hypersensitivity reactions	Routine risk communication: *SmPC sections 4.3, 4.4, 4.8.* *PL sections 2, 4.* Routine risk minimisation activities recommending specific clinical measures to address the risk:

	Hypersensitivity to the active substance or to any of the excipients is contraindicated (SmPC Section 4.3). If a hypersensitivity reaction occurs, administration of [Tradename] should be stopped immediately and appropiate therapy initiated (SmPC Section 4.4). Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Important potential risk 2: Malignancy	Routine risk communication: *SmPC section 4.4.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Important potential risk 3: Foetal defects	Routine risk communication: *SmPC sections 4.6, 5.3.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *As per SmPC sections 4.6, [Tradename] is not recommended during pregnancy and in women of childbearing potential not using contraception.* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Important potential risk 4: Nonteratogenic effects	Routine risk communication: *SmPC sections 4.6, 5.3.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *As per SmPC sections 4.6, [Tradename] is not recommended during pregnancy and in women of childbearing potential not using contraception.* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Important potential risk 5:	Routine risk communication:

Drug-drug interactions	*SmPC sections 4.4, 4.5.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *[Tradename] is not recommended for use with TNF inhibitors (SmPC Sections 4.4, 4.5). Concomitant administration of [Tradename] and other medicinal products that block IL-1 or its receptors is not recommended (SmPC Section 4.5). Upon initiation of [Tradename] in patients being treated with CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin), therapeutic monitoring of the effect or plasma concentration should be performed, and the individual dose of the medicinal product may need to be adjusted (SmPC Section 4.5).* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Missing information 1: Pregnant and nursing women	Routine risk communication: *SmPC sections 4.6, 5.3.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *[Tradename] is not recommended during pregnancy and in women of childbearing potential not using contraception. A decision must be made as to whether to discontinue breast-feeding or to abstain from [Tradename] therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (SmPC Section 4.6).* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Missing information 2: Paediatric patients with RP below the age of 12 years	Routine risk communication: *SmPC section 4.2.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *[Tradename] is not recommended in this paediatric age group (SmPC Section 4.2).* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*
Missing information 3:	Routine risk communication:

Patients with severe hepatic impairment	*SmPC sections 4.2, 5.2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None.* Other routine risk minimisation measures beyond the Product Information: *Legal status: medical prescription*

Additional risk minimisation measures

None.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that the routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication. Nevertheless, the risks addressed in this section of the RMP should be changed depending on the amended list of safety concerns (OC).

3.4.6. Conclusion on the RMP

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of questions below is submitted.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS/Rapporteur considers the Summary acceptable.

3.5.2. Periodic Safety Update Reports submission requirements

The Applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD) (OC).

4. Benefit/risk assessment

Overall, the pivotal clinical study showed persuasive clinically relevant and compelling statistically significant effects on resolution of pericarditis episodes and reduction in pericarditis recurrences in adult patients with RP. The prerequisites and expectations as outlined in CPMP/EWP/2330/99 for the acceptability of an application based on one pivotal trial are considered fulfilled. Data from the pivotal trial KPL-914-C002 regarding resolution of pericarditis episodes, reduction in pericarditis recurrences and long-term maintenance of efficacy are supported by consistent findings in the uncontrolled phase 2 study KPL-914-C001.

Clinical data to support an indication in the paediatric population are currently not considered sufficient to justify an indication in patients aged 12 – 17 years (MO). Considering the high incidence of pericarditis recurrence of 74% in the placebo group, the population included in the RHAPSODY study was limited to patients at high risk for recurrent pericarditis despite a combination of therapies, which is not reflected in the proposed indication and should be further discussed by the Applicant. The aspects that are inadequately demonstrated are outlined in the List of Questions below.

Regulatory background

This is a hybrid application according to Article 10(3) of Directive 2001/83/EC for Rilonacept powder for solution for s.c. injection weekly in the treatment of:

"Rilonacept is indicated in adults and paediatric patients from 12 years for the treatment of idiopathic recurrent pericarditis and reduction in risk of recurrence."

Rilonacept is a therapeutic molecule designed as a soluble decoy receptor ("cytokine trap") for the blockade of inflammation caused by the cytokines interleukin-1α and interleukin-1β which are the primary pro-inflammatory cytokines implicated as a causative factor in recurrent pericarditis (RP).

Rilonacept (Rilonacept Regeneron, previously ARCALYST) received marketing authorisation under exceptional circumstances (EU/1/09/582/001) in the EU on 23 Oct 2009 for the treatment of Cryopyrinassociated periodic syndrome (CAPS), including familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome (MWS) in adults and children aged 12 years and older.

Based on a request from Regeneron Pharmaceuticals Inc., the marketing authorisation was withdrawn as of 25 Oct 2012 in EU. The withdrawal was a business/commercial decision and was not related to any concerns with the safety or efficacy of ARCALYST.

Recurrent pericarditis has been recognised as an orphan disease in the EU. On the 06 January 2021, orphan drug designation was granted by the European Commission (EU/3/20/2390) for rilonacept for the treatment of idiopathic pericarditis.

The original ownership of the Biologics License Application for Rilonacept Regeneron in the US (previously Arcalyst) was held by Regeneron Pharmaceuticals, Inc and was subsequently transferred to the Kiniksa Pharmaceuticals Limited (UK) on 19 Jan 2021.

Clinical development programme

Rilonacept was investigated in 24 completed clinical studies for various therapeutic indications. Two clinical studies (one Phase 2 study C001 and the RHAPSODY Phase 3 study C002) were performed for the recurrent pericarditis (RP) target indication.

In the two completed clinical studies for the (RP) target indication, a total of 111 patients have received at least 1 dose of rilonacept: 25 patients in the Phase 2 study and 86 patients in the RHAPSODY Phase 3 study.

Quality

The application for Rilonacept finished product containing rilonacept as active substance is currently not approvable from a quality point of view since one major objection has been identified. The MO pertains to the pharmaceutical form 'powder and solvent for solution for injection', which is inconsistent in the eCTD (e.g. between Module 1 and Module 3 documentation). In the LoQ below, the applicant is asked to confirm the intended pharmaceutical form for the application and to ensure that all the relevant eCTD documents are amended accordingly. A number of other concerns have been noted which need to be addressed by the Applicant. These deficiencies are described in detail in the assessment report and are reflected in the LoQ below.

Manufacture of the drug substance is described with sufficient detail including flow chart and process controls performed during upstream and downstream processing. Only few comments or requests for clarification are made. Drug substance manufacture is a continuation of manufacture of rilonacept by an established process initially used to produce the product Arcalyst. By comparison of the process flow and IPCs used for the former product Arcalyst and those used for this current product only very minor adaptations are noted that reflect evolution of a process over time. Therefore, no new process validation was performed. However, it is expected that process verification data of continued process verification are provided to reflect the process in its entirety up to today.

Similarly, characterisation data are those of the formerly produced DS used in Arcalyst. Characterisation is performed with a high level of depth and a large number of orthogonal methods to cover chemical, physical and biological characteristics of the DS. Since DS manufacture is a continuation of manufacture of rilonacept for the former product Arcalyst, clarification is requested on continuation of the manufacture and qualification of the reference standard and on the use of a two-tiered system for reference standards to avoid drift in quality attributes.

The DS specification and analytical methods are largely equivalent to the formerly produced DS used in Arcalyst, except for some method changes. Still, some updates to the analytical methods are requested, as not all methods are considered state-of-the-art. The atypically large amount of commercial manufacturing batch data available shows consistent manufacturing control, as well as is supporting the stability of rilonacept.

Finished product information provided on product development, process development, manufacture and process control is considered generally acceptable. Rilonacept finished product specification is largely equivalent to those for the former FP Arcalyst and is considered sufficient to control drug product quality.

The lyophilized drug product in its commercial CCS demonstrates sufficient stability over the claimed shelf-life. Respective stability data from long-term storage conditions remain within pre-defined acceptance criteria.

Concerning adventitious agents safety a few issues are raised. Only viral filtration was shown to be effective for one model virus clearance, which is not optimal. Virus validation of this step is currently not considered to adequately model the process requiring that issues related to representativeness are adequately resolved.

Non clinical

Pharmacodynamic, pharmacokinetic and toxicological properties of rilonacept have been described extensively in the previous market authorization procedure (EU/1/09/582/001). Therefore, the Applicant has not provided additional studies. The carcinogenicity potential has been reviewed with an up to date literature research.

It would be also helpful to include any post-marketing data with pregnant and lactating /breast-feeding woman.

Clinical

Pharmaceutical development (usability)

According to the SmPC, the medicinal product is intended for self-administration by the patients if the physician deems it appropriate and provides medical follow-up if necessary. Considering the reconstitution procedure required prior to administration (withdrawal of 2.3 mL of WFI solvent, injection into the vial, waiting until reconstitution finished, withdrawal of up to 2.0 mL reconstituted drug product, administration) the presentation of the product is not considered appropriate to ensure drug product quality at the time of administration especially in view of microbiological safety. Furthermore, due to the

extensive handling instructions to be done by non-professionals patient safety might be jeopardised. The EPAR for Rilonacept Regeneron (EMEA/541561/2009) does not discuss the issue in detail and does not refer to a drug utilization study. It should be further clarified whether patients with CAPS are sufficiently representative for patients with RP (12 – 17 years of age as well as adults). Data to demonstrate appropriate handling upon self-administration for the whole target group of patients are missing and should be provided.

Clinical Pharmacology

In context with the previous marketing authorization (indication for various Cryopyrin-associated periodic syndromes [CAPS]), relevant PK data were submitted from two studies with healthy subjects (Studies IL1T-RA-0401 and -0402) as well as from a study with rheumatoid arthritis patients (IL1T-RA-0004). These data are not discussed in detail in this assessment report, as they were already previously assessed.

Assessment of PK was included in the two studies conducted in patients with RP, KPL-914-C001 and KPL-914-C002. In addition, a popPK model was developed relevant for the target group of patients.

C_{trough} values were analysed for study C001 as well as for the run-in and the randomized withdrawal period of study C002. The results show that the loading dose of 320 mg is sufficient to achieve the target plasma concentration, which is the maintained by a dose of 160 mg/week without any signs of further accumulation. The results from the paediatric population in study C002, where rilonacept was dosed according to body weight, were within the range of the adult subjects. However, only 7 paediatric subjects were included, which limits the informative value of the paediatric data.

The final popPK model for rilonacept in RP patients was a one-compartment model with first-order elimination and first-order input. Body weight (normalized to a weight of 80 kg) was a significant covariate on clearance and volume with estimated exponents. The resulting impact of very low or very high body weight on exposure in adult patients with flat dosing (LD: 320 mg and MD of 160 mg) remains unclear but needs to be shown and discussed with respect to safety and efficacy.

In addition, there are some issues on the analytical methods applied and the interpretation of the data in the two clinical studies. The results from the paediatric population, where rilonacept was dosed according to body weight, were within the range of the adult subjects. However, only 7 paediatric subjects were included, which limits the informative value of the paediatric data.

Clinical

Dose selection

No dose finding studies specific for RP were conducted. The following dose is proposed:

SC loading dose of 320 mg of rilonacept for adults and 4.4. mg/kg for paediatric subjects [≥12 and <18 years old], and 12 × QW maintenance SC doses of 160 mg for adults and 2.2 mg/kg for paediatric subjects. The rilonacept dosing regimen is same as the previously approved rilonacept dosing regimen for adult and paediatric subjects with CAPS. Reference is made to EPAR (EMEA/541561/2009).

The dose was investigated in the Phase 2 proof-of-concept study (KPL-914- C001) that indicated resolution of pericarditis episodes and reduction in pericarditis recurrences. Low weight adults may have a higher exposure than adolescents or adults at higher weight. Implications on safety should be further addressed.

Based on these data the same dose was investigated in the pivotal phase 3 study (KPL-914- C001).

Overall, the approach is acceptable. Feasibility of conducting a comprehensive dose finding programme in patients with RP is limited by the number of patients available and by variability associated with

recurrent pericarditis events. Regarding non-specific safety, data available from other indications may be supportive. At the end concluding on a positive benefit risk balance of the dose based on the pivotal RHAPSODY trial may also serve to establish the proposed dose regimen.

Clinical efficacy

(for a more detailed summary of efficacy see "discussion of clinical efficacy" above and the clinical day 80 assessment report)

The clinical program was mainly based on 1 controlled pivotal phase 3 study, study KPL-914-C002 (RHAPSODY) in patients with recurrent pericarditis, consisting of three periods:

- Period 1: Single-blind Run-In (RI) period (12 Weeks). During the single-blind RI period, treatment with open-label rilonacept was administered, and subjects were tapered off background standard-of-care (SOC) therapy for pericarditis.

- Period 2: Double-blind placebo-controlled Randomised Withdrawal (RW) period (event driven - 0 to 51 weeks):

During the pivotal RW period, eligible subjects were randomized 1:1 to double-blinded administration of study drug:

The RW period lasted until 22 independently adjudicated pericarditis cases had occurred.

- Period 3: Long Term Extension Period (LTE) (up to 24 months; ongoing): All subjects in the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) and subjects who successfully completed the RI period after closure of randomisation had the option to receive up to 24 months of open-label rilonacept. The LTE is ongoing at the time of this submission.

Endpoints

The primary efficacy endpoint was time to pericarditis recurrence (CEC-confirmed), defined as the time from randomization to the date of the first pericarditis recurrence for each subject.

Pericarditis recurrence was defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis where applicable.

Key secondary (confirmatory) endpoints for the RW period were as follows:

☐ Proportion of subjects who maintained 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 pericarditis pain is defined as non-missing NRS ≤ 2.

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

The design of the pivotal study was overall suitable to investigate efficacy in a controlled design and maintenance of efficacy up to 24 months by the means of the LTE including a milestone of 18 months where patients could opt for discontinuing therapy.

Since PROs were part of the primary efficacy endpoint (11-point Pericarditis Pain Numeric Rating Scale (11-point NRS), one of the confirmatory secondary endpoints (Patient Global Impression of Pericarditis Severity (PGIPS)), a psychometric evaluation report was provided for the 11-point NRS and the PGIPS based on data from the pivotal study KPL-914-C002. Overall, the results provide reassurance on the reliability of the data generated with the PPNRS and PGIPS within study KPL-914-C002. However, it is not entirely clear from the documentation provided whether data on an external validation of PPNRS and

PGIPS are available. In addition, the NRS threshold of 4, the key threshold used in the in the pivotal trial KPL-914-C002 for decision making should be further justified.

Additional PROs (PGA-PA, SF-36, SF-6D, EQ-5D-5L and Insomnia Severity Index (ISI)) were applied as additional secondary endpoints

Conduct

No serious GCP issues were identified with the potential to affect the integrity of the study or with an impact of the conclusions on the benefit risk balance. The report from an EMA initiated routine GCP inspection is pending.

Amendment 2 by March 2020 implemented key changes to the conduct of the ongoing study and the evaluation of the primary endpoint in as such that the duration of the RW period, formerly 24 weeks, was deleted and the study became endpoint driven (22 events). Although the Applicant claims that the amendment was driven by a recommendation of the FDA, the Applicant should comment on the information available at the time of the decision to change the protocol and provide a sensitivity analysis on the primary and key secondary outcomes for patients randomized before and after Amendment 2.

Study size

Eighty-six subjects were enrolled in the study, 79 subjects completed the RI period. Of the 61 randomized subjects 59 completed the RW period.

Seventy four of 75 eligible subjects continued into the LTE.

Study population

It was a multinational study with a very low representation of patients from the EU, only 3 out of 58 centres recruited in the EU (Italy). Transferability of the data to the EU population requires further justification.

The majority of subjects (84.9%) had been diagnosed with idiopathic recurrent pericarditis at baseline; 14.0% had post-pericardiotomy syndrome, and 1.2% had Dressler syndrome.

Of the 7 patients between 12 and 17 years included in the RI period only three entered the RW period. Further information is requested on the reason for the high rate of adolescents not entering the RW period. Considering the low representation of paediatric patients with only 3 randomized, the Applicant should provide a thorough justification for including paediatric patients between 12 and 17 years into the indication. (**MO on paediatric patients**).

Considering the high incidence of pericarditis recurrence of 74% in the placebo group, the population included in the RHAPSODY study was limited to patients at high risk for recurrent pericarditis despite a combination of therapies. In the LoQ below, the Applicant is asked to discuss whether this should be reflected in the indication (**MO**).

Statistical methods

The statistical methods were overall appropriate.

Efficacy results

Primary Efficacy Endpoint, Time to Pericarditis Recurrence in the Randomized Withdrawal Period

The time to pericarditis recurrence for the rilonacept treatment arm was significantly longer than for the placebo arm, with a hazard ratio of 0.04 (95% CI: 0.01; 0.18); rilonacept reduced the risk of recurrence by 96%. Mean time to pericarditis recurrence was not estimable in the rilonacept group because there were too few recurrences. The median time to recurrence for subjects in the placebo arm was 8.6 weeks.

Considering drop outs during the run in phase the true treatment effect in the target group of patients may be somewhat lower. The treatment effect was overall consistent in subgroups analyzed with some clarifications expected. No results were presented on efficacy for paediatric patients 12 – 17 years separately, only 3 out of 7 patients included in the RI period embarked the RW period. Further justification is requested on inclusion of paediatric patients in the indication (**MO**).

Key secondary (confirmatory) efficacy endpoints

- Significantly more subjects in the rilonacept group maintained clinical response (17/21; 81.0%) at week 16 than in the placebo group (4/20; 20.0%, p = 0.0002). A similar numerically significant response was observed at Weeks 8 and 24. Consistent results were reported at weeks 8 and 24.

- Subjects receiving rilonacept experienced significantly more days with no or minimal pericarditis pain (≤2 on the NRS) during the first 16 weeks of the RW period than did subjects who received placebo. The least squares mean of days with no or minimal pericarditis pain in the first 16 weeks were 98.6% and 47.4% for subjects receiving rilonacept and placebo, respectively (p <0.0001). Consistent results were reported for weeks 8 and 24.

- At RW week 16, in a significantly higher proportion of subjects treated with rilonacept pericarditis symptoms (based on the 7-point PGI-PS) were absent or minimal (17/21, 81.0%) than in placebo-treated subjects (5/20, 25.0%; p = 0.0006). Consistent results were reported for weeks 8 and 24.

Other secondary endpoints

Run in period

Among the 79 subjects taking background pericarditis medications at baseline, 73 (92.4%) were able to discontinue background medications and achieved rilonacept monotherapy.

Among the 79 subjects who completed treatment through Week 12, 73 subjects (92.4%) achieved the protocol definition of clinical response (weekly average of daily pericarditis pain on the 11-point NRS ≤ 2.0, CRP level ≤ 0.5 mg/dL) at this time point.

Pericardial effusion, pericarditis associated ECG signs and other pericarditis manifestations as WBC counts >ULN, Fever > 38°C, and pericardial rub disappeared in almost all patients where present during the RI period.

Patient reported outcome data

Assessments of different domains affecting patients' wellbeing and pericarditis activity by using the PGA-PA, SF-36, SF-6D, EQ-5D-5L and Insomnia Severity Index (ISI) consistently indicated improvement in different domains associated with rilonacept therapy and worsening associated with recurrence of pericarditis. Only about 50% of patients with baseline RW values provided data at week 24 which requires further discussions

Long term extension

Pericarditis recurrence before month 18. Up to the 18-month Decision Milestone, the annualised incidence of pericarditis recurrence while on rilonacept treatment was 0.043 (95% CI, 0.0009, 0.125) events/patient-year. The mean (SD) number of episodes per year was 1.27 (0.562). The results up to month 18 in the LTE period indicate maintenance of clinical efficacy in almost all of the patients being available for an assessment up to 18 months. Some clarification is requested on 22 patients not available for the 18 months assessment and on the duration of treatment in 74 patients contributing to the assessment of annualized rates.

Pericarditis Recurrence after the 18-month Decision Milestone;

At month 18 patients could continue or discontinue active treatment. Amongst the 33 participants who continued rilonacept after the 18-month Decision Milestone, the annualised incidence of pericarditis recurrence while on rilonacept treatment was 0.041 (95% CI, 0.001, 0.227) events/patient-year. Of the 8 participants who suspended treatment for observation after the 18-month Decision Milestone, 6 had an Investigator-assessed recurrence (recurrence rate, 75.0%). During the post-treatment 6-week safety follow-up after cessation of study drug rilonacept, four additional Investigator-assessed pericarditis recurrences (NRS >6; CRP >1 mg/dL, meeting RHAPSODY RW period event adjudication criteria) were reported at 6 weeks.

Clarification is requested on one patient with endocarditis.

There are several issues to be addressed (OCs).

Currently, the data presented are not sufficient to conclude on a demonstrated efficacy in the paediatric population **(MO)** and it should be further discussed whether this product should only be used in patients at high risk for recurrent pericarditis (**MO**).

Clinical safety

In the two completed studies (the Phase 2 study C001 and the RHAPSODY Phase 3 study C002) for the recurrent pericarditis target indication a total of 111 patients have received at least 1 dose of rilonacept: 25 patients in the Phase 2 study (C001) and 86 patients in the RHAPSODY Phase 3 study.
Of these 86 patients, 74 transitioned into the long-term extension period, and 69 (93.2%) patients completed the long-term extension (LTE) period of the RHAPSODY Phase 3 study (up to 2 years).

Rilonacept was generally well tolerated in the recurrent pericarditis (RP) clinical development programme. There were no deaths or life-threatening TEAEs. The safety profile was consistent with the US ARCALYST prescribing information. No new safety findings were identified compared to the initially approved cryopyrin-associated periodic syndrome (CAPS) indication.

Important identified treatment-related adverse events of rilonacept included injection site reactions (erythema, swelling, pain, pruritus and rash at the site of administration) and a higher rate of infections (upper respiratory tract infections such as nasopharyngitis) probably due to the immunosuppressant mechanism of action of rilonacept (Interleukin-1 inhibitor).

The impact of chronic immunosuppression of treatment with rilonacept on the development of malignancies is unknown. The Applicant is asked to justify the limited controlled long-term safety data for the recurrent pericarditis target indication.

As with all therapeutic proteins, rilonacept has the potential for inducing immune reactions.

Hypersensitivity reactions were reported for a single participant in the clinical RP development programme. The events were mild or moderate in intensity and resolved after discontinuation of rilonacept. Risk mitigation wording is included in section 4.4 of the SmPC.

Regarding the use of rilonacept in the paediatric population, only 7 patients aged 12 years to 17 years were treated with rilonacept in the pivotal RHAPSODY Phase 3 study for a median duration of 15 weeks. The Applicant is asked to explain why the limited efficacy and safety data are considered sufficient to grant the recurrent pericarditis indication in paediatric patients aged 12 to 17 years. **(MO)**

The experience in elderly patients is also limited. No dose adjustment is needed in patients with renal impairment. Limited pharmacokinetic data are available in patients with hepatic impairment.

In the recurrent pericarditis development program, use of rilonacept was associated with an increase in non-fasting total cholesterol and triglycerides. The level of increase did not require treatment. Physicians

should monitor the fasting lipid profiles of their patients (e.g. after 2 to 3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

The major safety concerns are related to the limited controlled long-term safety data from the two clinical studies for the recurrent pericarditis target indication and whether the paediatric indication can be granted based on the 7 patients aged 12 to 17 year of the RHAPSODY phase 3 study. However, it is acknowledged that recurrent pericarditis is an orphan disease (orphan drug designation was granted in the US in 2020 and in the EU in 2021) and that rilonacept has been approved in the US since 2008 for various therapeutic indications and since March 2021 also for the treatment and risk reduction of recurrent pericarditis both in adults and children 12 years and older.

Safety summary: Main criticism are the limited controlled long-term safety data from the two clinical studies on the recurrent pericarditis target indication and whether the paediatric indication can be granted for rilonacept based on the 7 paediatric patients aged 12 to 17 years who have been treated in the pivotal Phase 3 study RHAPSODY for a median duration of 15 weeks (**MO**).

The application contains inadequate quality and clinical data. The aspects that are inadequately demonstrated are outlined in the List of Questions.

4.1. Conclusions

The overall benefit /risk balance of Rilonacept is currently negative.