Efficacy and safety of rilonacept for recurrent pericarditis: results from a phase II clinical trial

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ABSTRACT
Objective Recurrent pericarditis (RP) incurs significant morbidity. Rilonacept inhibits both interleukin-1 alpha (IL-1α) and IL-1β; these cytokines are thought to play a major role in RP. This phase II study evaluated rilonacept efficacy and safety in RP.

Methods This multicentre, open-label study enrolled adult patients with idiopathic or post-pericardiectomy RP, symptomatic (≥2 pericarditis recurrences) or corticosteroid (CS) dependent (≥2 recurrences prior). Patients received rilonacept 320 mg SC load/160 mg SC weekly maintenance in a 6-week base treatment period (TP) followed by an optional 18-week on-treatment extension period (EP) (option to wean background therapy).

Results Outcomes: pericarditis pain (numeric rating scale (NRS)) and inflammation (C reactive protein (CRP)) for symptomatic patients; disease activity after CS taper for CS-dependent patients. Secondary outcomes: health-related quality of life (HRQOL), pericarditis manifestations and additional medications. 25 unique patients enrolled, while 23 completed the EP (seven colchicine failures and five CS failures). In symptomatic patients, NRS and CRP decreased; response was observed after first rilonacept dose. NRS decreased from 4.5 at baseline to 0.7, and CRP decreased from 4.62 mg/dL at baseline to 0.38 mg/dL at end of TP. Median time to CRP normalisation: 9 days. Pericarditis manifestations resolved. 13 patients on CS at baseline completed the EP; 11 (84%) discontinued CS, and 2 tapered; CRP and NRS remained low without recurrence. Mean HRQOL scores improved in symptomatic patients. One serious adverse event (SAE) resulted in discontinuation of rilonacept.

Conclusions Rilonacept led to rapid and sustained improvement in pain, inflammation (CRP and pericarditis manifestations) and HRQOL. CSs were successfully tapered or discontinued; safety was consistent with known rilonacept safety profile.

Trial registration number NCT03980522.

INTRODUCTION
Recurrent pericarditis (RP) is associated with debilitating chest pain, physical limitations, decreased quality of life and emergency department visits and hospitalisations. 1

It frequently occurs following a first episode of acute pericarditis, with reappearance of pericarditis signs and symptoms after a symptom-free period of at least 4–6 weeks 2 and affects 15%–30% of patients. 1 The chance of future recurrences increases with each additional recurrence, 3 and among patients with two or more recurrences, the probability of further recurrence is 20%–40%. 4

The mainstay of current treatments includes non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids (CS). For colchicine-resistant and CS-dependent RP, other immunomodulatory treatments or surgical pericardiectomy are considered, though with limited data.

The broad immunosuppression and side effects of CS call for more targeted therapies in RP. While the mechanisms underlying RP are not fully elucidated, an autoinflammatory response characterised by inappropriate activation of the innate immune system, in particular the interleukin (IL) 1 family of cytokines, has been implicated. IL-1 is the primary proinflammatory cytokine responsible for autoimmune inflammatory disorders, including RP, 5 and therefore, blocking IL-1 activity was hypothesised to provide therapeutic benefit in RP. Anakinra, a recombinant IL-1 receptor antagonist, was previously evaluated in an investigator-initiated placebo-controlled study in a small number of CS-dependent colchicine-resistant patients with idiopathic RP, many of whom continued therapy with colchicine during the study, as well as in a registry in a ‘real world’ population. 6 7

Rilonacept, approved in the USA for the treatment of cryopyrin-associated periodic syndromes (CAPS) 8 (Arcalyst; Regeneron, Tarrytown, New York, USA), inhibits IL-1 by binding to IL-1α and IL-1β. 9 Given the autoimmune pathobiology of RP and the mechanism of action of rilonacept with its dual IL-1 blockade, we hypothesised that rilonacept would be an effective novel therapy in RP and conducted a pilot study in a broader population of RP patients to assess resolution of pericarditis symptoms, improvement in objective measures of disease, feasibility of weaning CS in CS-dependent patients and safety.

METHODS

Data sharing statement
The individual anonymized data supporting the analyses contained in the manuscript will be made available upon reasonable written request from researchers whose proposed use of the data for a specific purpose has been approved.
the dosages had been stable for ≥7 days; patients in parts 3 and 4 had concomitant medications (eg, CS) and evidence of pericardial inflammation assessed by delayed pericardial hypoenhancement on cardiac MRI. CS-dependent patients (parts 3 and 4) had to present with CS-dependent disease, with a first episode of acute pericarditis followed by at least two recurrent episodes and without active pericarditis at time of screening. CS dependency was based on investigator judgement and defined as anticipated return of signs and symptoms of pericarditis based on previous attempts at CS tapering. For all study parts, episodes of pericarditis were defined using the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases as a framework.5

At study entry, patients in all parts were allowed concomitant NSAIDs, and/or colchicine, and/or CS (in any combination) if the dosages had been stable for ≥7 days; patients in parts 3 and 4 were required to be taking CS at enrolment. All patients gave written informed consent.

Treatment and procedures
In the base Treatment Period (TP) eligible adults received a loading dose of 320 mg rilonacept (KPL-914), administered via subcutaneous (SC) injection on day 0, followed by 160 mg SC weekly for 5 additional doses; dose and administration schedules were consistent with the Food and Drug Administration (FDA)-approved schedules for rilonacept in CAPS.8 Conventional concomitant pericarditis medications (eg, NSAIDs, colchicine and/or CS) were maintained at prestudy dose levels, not to be changed unless medically indicated throughout the 6-week base TP. In the optional 18-week treatment extension period (EP), during which rilonacept weekly injections continued, investigators were given the option to wean their patients from concomitant medications as follows: for NSAIDs and colchicine to taper within 15 days of EP entry, and for CS to taper by 5 mg prednisone or equivalent each week in adults so as to withdraw within 6 weeks of EP entry.

Efficacy assessments
For active pericarditis patients (parts 1, 2 and 4), the primary efficacy endpoints were patient-reported pericarditis pain using an 11-point numeric rating scale (NRS), validated across multiple conditions with acute and chronic pain10–12 and CRP at baseline and on-treatment. For CS-dependent patients (parts 3 and 5), the primary efficacy endpoint was disease activity after tapering CS. Across all parts, secondary endpoints were improvement in pericarditis manifestations other than pain and CRP change in patients’ health-related quality of life (HRQOL) using the validated Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire (V.1.2-Global Health) to assess overall physical and mental well-being.13 Use of concomitant CS and changes in the use of other concomitant medications for pericarditis.

Detailed descriptions of assessment of cardiac MRI, pharmacokinetics and antidrug antibody (ADA) are provided in online supplemental methods.

Statistical analysis
Because of the small sample size and study design, no inferential statistical analyses or hierarchical testing were planned. For continuous variables (eg, change from baseline), summary
statistics were calculated as means (SD) and medians (range). For categorical variables, summary statistics were calculated for each part. All analyses are based on observed data.

Values are presented as means (SD), and/or medians (range) if only medians were available or if medians were different from means.

Select analyses were performed for pooled groups of parts 1, 2 and 4 (parts enrolling subjects during symptomatic episode) and parts 3 and 5 (parts enrolling subjects without active episode but CS dependent) for greater statistical precision in determining therapeutic response or safety.

All analyses were performed without imputation for missing data and were conducted using SAS V9.4.

In order to evaluate the effect of rilonacept treatment on pericarditis recurrence, data collected included the number of pericarditis episodes at enrolment (index, prior recurrences and current episode) and the number of episodes during the study (recurrences during base TP and EP combined). The annualised incidence of pericarditis episodes was assessed before and after treatment with rilonacept. Annualised incidence prior to the study was calculated by dividing the number of pericarditis episodes at enrolment (including index, recurrences and qualifying episode) by disease duration in years. Annualised incidence of pericarditis episodes during the study was calculated by dividing the number of recurrences during the study by study duration in years.

Safety assessments
Treatment-emergent adverse events (TEAEs; defined as Adverse events (AEs) reported after the first study drug administration) were recorded by investigators, including level of severity (mild, moderate or severe) and relationship to study drug (not related, unlikely related, possibly related or related). Serious TEAEs were defined as events that were life threatening or resulted in death, or required hospital admission or prolonged hospitalisation, or resulted in persistent or significant disability/incapacity, or important medical events that jeopardised patients or required an intervention to prevent a serious outcome. Safety clinical laboratory testing included local haematology, chemistry, urinalysis and central laboratory lipid panel. Physical examinations included vital signs, weight and height.

RESULTS
Patient disposition and demographics
Among 49 patients screened, 25 unique adult patients were enrolled and received rilonacept (online supplemental figure 1). No paediatric patients were enrolled. One patient participated in the study twice: this patient successfully completed the study but, approximately 11 weeks after rilonacept discontinuation, developed a pericarditis recurrence (pain NRS 7/10; CRP 23.1 mg/dL) and cardiac tamponade requiring pericardiocentesis. The patient was re-enrolled in the study as the 26th patient while study enrolment was still open and subsequently had resolution of pericarditis and an uneventful clinical course. Assessments from this patient’s first participation only are included in the analysis. All 25 patients were analysed for the primary efficacy endpoints and for safety. Of 23 patients who entered the EP, 23 (100%) completed it; one CS-dependent PPS patient (part 3) completed the base TP but declined to continue into the EP, and one symptomatic idiopathic RP patient (part 1) experienced a serious AE and discontinued the study drug after visit 4 in the base TP (discussed further).

Patient demographics were generally similar across study parts. Among patients entering the base TP, mean age was 42.8 years (range 26–62 years), 60% of patients were female and the majority of patients were white (table 1). Mean baseline NRS pain scores ranged from 4.0 to 4.7 for symptomatic patients (parts 1, 2 and 4), and mean baseline NRS pain scores were 1.2 and 2.0 for CS-dependent patients (parts 3 and 5, respectively). At study entry, the majority of patients (~80%) were taking two or more medications for their pericarditis. The mean (median; range) number of pre-enrolment pericarditis recurrences was 2.6 (2; 1–8), and the annualised incidence of pericarditis episodes (including index, recurrences, and qualifying episodes, if applicable) prior to study entry was 3.9 (2.3; 0.5–15).

EFFICACY
Efficacy was assessed using multiple endpoints examining patient-reported pericarditis pain, HRQOL and inflammatory and clinical manifestations of pericarditis.

Resolution of acute pericarditis episodes
In symptomatic patients with elevated CRP >1 mg/dL (n=13) (parts 1 and 4), reductions in average pericarditis pain were observed as soon as after the first (loading) dose of rilonacept, and these decreases were maintained throughout the study (figure 2). Reductions in pain averaged 4 points on an 11-point pain NRS (ranging from 0 to 10). Similarly, decreases in CRP were observed after the first rilonacept dose and were maintained throughout the study (figure 2). The median time to CRP normalisation was 9.0 days. Other pericarditis manifestations resolved in these patients (online supplemental results and online supplemental table 1). For the remaining symptomatic patients (part 2) who had confirmed pericardial inflammation by MRI (n=3), NRS pain reduction was also observed and the low levels of CRP at study entry were maintained.

Reduced annualised incidence of pericarditis
Across all study parts, there was a reduction in pericarditis episode frequency, as demonstrated by a decrease in mean annualised incidence from 3.9 (SD 3.66) episodes per year for all patients prior to study entry to 0.18 (SD 0.62) in part 1 and 0.0 for the remaining study parts during the study (ie, while on rilonacept treatment) (table 2). Pericarditis recurrence during the study was based on investigator’s judgement. The only on-study pericarditis recurrence occurred in one patient enrolled in part 1 who had a mild episode in the base TP of 5 days’ duration (NRS pain increase from 0 to 2 and CRP of 0.10 mg/dL), which did not require an increase of concomitant therapy nor the addition of a new medication to treat pericarditis; this patient completed the EP without further event.

Concomitant medication use
Overall, patients were able to stop or reduce the dose of at least one concomitant pericarditis medication without a recurrence (table 3). In particular, of 13 patients who completed the study who were receiving CS at baseline, 11 (84.6%) discontinued CS and the remaining 2 reduced the dose; there were no recurrences in these patients (table 4). Additional information can be found in online supplemental results.

Additional endpoints
HR-QOL, as measured by PROMIS questionnaire (V1.2-Global Health), improved in symptomatic patients with elevated CRP, and findings from the exploratory Cardiac MRI substudy (11...
Table 1  Baseline demographic and clinical characteristics

| Disease status: CRP requirement (mg/dL): | Idiopathic | PPS | Total |
|------------------------------------------|------------|-----|-------|
|                                         | Active *   | Active § | CS-dep † | Active *   | CS-dep † | All *†§ | N/A | N/A | 25 |
|                                         | >1         | ≤1   | N/A | >1         | N/A | N/A | 1   | 3   | 25 |
| Mean (median, range, SD) age, years      | 39.6 (42.5, 26–52, 10.2) | 42.7 (42.0, 28–58, 15.0) | 51.3 (50.5, 40–62, 7.8) | 34.0 | 42.0 (40.0, 36–50, 7.2) | 42.8 (44.0, 26–62, 10.5) |
| Female sex, n (%)                         | 9 (75.0)   | 3 (100.0) | 2 (33.3) | 0 | 1 (33.3) | 15 (60.0) |
| Race, n (%)                               | 10 (83.3)  | 2 (66.7)  | 6 (100.0) | 1 (100.0) | 3 (100.0) | 22 (88.0) |
| White                                     | 2 (16.7)   | 1 (33.3)  | 0 | 0 | 0 | 3 (12.0) |
| Black/African-American                    | 30.2 (29.4, 23.4–39.0, 5.4) | 40.0 (38.5, 28.7–52.7, 12.1) | 31.1 (33.1, 23.7–34.3, 4.1) | 29.3 | 24.7 (25.0, 22.5–26.6, 2.1) | 30.9 (29.3, 22.5–52.7, 6.7) |
| Mean (median, range, SD) BMI, kg/m²       | 4.6 (5.0, 2–8, 1.7) | 4.7 (4.0, 2–8, 3.1) | 1.2 (1.0, 0–2, 0.8) | 4.0 | 2.0 (1.0, 0–5, 2.7) | 3.4 (3.0, 0–8, 2.3) |
| Mean (median, range, SD) pain rating, NRS** | 6 (86.7) | 3 (100.0) | 6 (100.0) | 1 (100.0) | 2 (100.0) | 20 (80.0) |
| Mean (median, range, SD) baseline CRP, mg/dL | 4.9 (2.1, 0–19.8, 5.8) | 0.5 (0.3, 0.1–1.0, 0.4) | 0.2 (0.2, 0.1–0.4, 0.1) | 1.1 | 0.1 (0.1, 0–0.2, 0.05) | 2.5 (0.92, 0.1–19.8, 4.6) |
| Aspirin, n (%)                            | 0 | 0 | 2 (33.3) | 0 | 0 | 2 (8.0) |
| NSAIDs, n (%)                             | 6 (50.0) | 1 (33.3) | 4 (66.7) | 0 | 1 (33.3) | 12 (48.0) |
| Colchicine, n (%)                         | 8 (66.7) | 3 (100.0) | 6 (100.0) | 1 (100.0) | 2 (100.0) | 20 (80.0) |
| Corticosteroids, n (%)                    | 4 (33.3) | 2 (66.7) | 6 (100.0) | 0 | 3 (100.0) | 15 (60.0) |
| Pericarditis medication categories, n (%) | 0 | 3 (25.0) | 0 | 0 | 0 | 3 (12.0) |
| 1                                        | 2 (16.7) | 0 | 0 | 1 (100.0) | 0 | 3 (12.0) |
| 2                                        | 5 (41.7) | 3 (100.0) | 0 | 0 | 3 (100.0) | 11 (44.0) |
| ≥3                                       | 2 (16.7) | 0 | 6 (100.0) | 0 | 0 | 8 (32.0) |
| Number of previous pericarditis recurrences | 1.8 | 2.0 | 3.3 | 8.0 | 3.3 | 2.6 |

*Part 1.
†Part 2.
‡Part 3.
§Part 4.
¶Part 5.
**11-point numeric scale, ranging from zero (0, no pain) to 10 (10, pain as bad as possible).
BMI, body mass index; CRP, C reactive protein; CS-dep, corticosteroid dependent; NRS, numeric rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; PPS, postpericardiotomy syndrome.
patients) showed improvement of pericardial inflammation (online supplemental results, online supplemental table 2).

**SAFETY**

All patients experienced one or more TEAEs during the study (table 3). The majority of TEAEs (92%) were mild or moderate in severity. The most common AEs were injection site reactions (15/25 patients (60%)), nasopharyngitis, arthralgia and diarrhoea (online supplemental table 3). No systemic hypersensitivity reactions were reported during the study. All injection site reactions were assessed as ‘mild’ by the investigator, and none resulted in treatment discontinuations.

Drug-related TEAEs were reported in 17 (68%) patients; 64% were classified as general disorders or administrative site conditions. Two serious TEAEs were reported in patients enrolled in part 1, both of which resolved without sequelae. Rilonacept was discontinued in one patient on concomitant CS with a history of skin infections who developed a serious AE of an SC abscess (cultures positive for *Finegoldia magna*) on the torso that resolved with intravenous antibiotics and surgical incision/drainage; it was reported as a severe AE and was deemed possibly related to study drug by the investigator. The second patient experienced a serious AE of non-cardiac chest pain deemed unrelated to study drug by the investigator; patient continued rilonacept. Increases in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides levels were observed, as expected, in patients during treatment with rilonacept (online supplemental table 4). None of the patients initiated new lipid-lowering therapy on study. There were no major abnormalities noted in the haematology and chemistry test results during rilonacept treatment.

**DISCUSSION**

RP results in significant morbidity, and there are no FDA-approved therapies. This pilot study represents the first use of rilonacept in idiopathic or postpericardiotomy pericarditis. In patients with symptomatic RP with elevated CRP, rilonacept resulted in rapid and sustained reduction in patient-reported pericarditis pain and CRP. Second, annualised recurrences of pericarditis were lower after treatment, and HRQOL improved. Third, prednisone was successfully discontinued in 84.6% of patients receiving prednisone at baseline and was either discontinued or tapered in all CS-dependent patients. Fourth, imaging findings suggestive of pericardial inflammation, as assessed with cardiac MRI or echocardiography, also improved. Therapy was generally well tolerated with only one discontinuation due to a

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**Table 2**

Annualised incidence of pericarditis episodes prior to and during the study

| Disease status | Idiopathic | PPS |
|----------------|------------|-----|
| CRP requirement (mg/dL) | Active* | Active† | CS-dep‡ | Active§ | CS-dep¶ |
| N | 12 | 3 | 6 | 1 | 3 |
| Prior to the study** | N/A | 4.4 (2.4, 0.5–15.0, 4.68) | 2.0 (1.0, 1.0–4.0, 1.75) | 4.5 (3.4, 1.9–8.6, 2.58) | 3.7 (2.5, 1.5–7.1, 3.02) |
| During the study†† | N/A | 0 | 0 | 0 | 0 |
| Pericarditis episodes per year (mean, range, SD) | N/A | 0.18 (0.62) | 0 | 0 | 0 |

*Part 1.  †Part 2.  ‡Part 3.  §Part 4.  ¶Part 5.

**Annualised incidence of pericarditis episodes prior to the study was calculated by dividing the number of episodes (including index, prior recurrences and qualifying episode if applicable) by disease duration in years.

††Annualised incidence of pericarditis episodes during the study was calculated by dividing the number of recurrences during the study by duration of follow-up during the study in years.

*One subject in part 1 presented with increase in pericarditis chest pain from 0 to 2 for 5 days; no medication was added; at visit, CRP was 0.1 mg/dl; it was reported as a pericarditis recurrence by the investigator.

CRP, C reactive protein; CS-dep, corticosteroid dependent; PPS, postpericardiotomy syndrome;
serious AE. Antidrug (antirilonacept) antibodies were detected at at least one timepoint during the study in 14 out of 25 patients; the titres were low in the majority of these patients. Local injection site reactions were reported in 57.1% of ADA-positive patients versus 36.4% in ADA negative patients. Presence of ADAs had minimal impact on rilonacept concentrations.

Current treatment paradigms
When pericarditis is refractory to NSAIDs and colchicine, current guidelines recommend CS. Even though CS can provide rapid control of symptoms, notable side effects often occur, which are dose dependent and duration dependent. Unfortunately, short CS courses with rapid tapering may exacerbate recurrence.
and long durations of CS may be needed to control the disease. In addition, despite protracted courses with gradual tapering, patients often repeatedly recur when the CS dose is decreased below a specific level. Although alternative immunosuppressive options are sometimes used in patients who require unacceptably high long-term CS doses (azathioprine and intravenous immunoglobulins (IVIG)), data supporting their efficacy are lacking. Therefore, similar to systemic inflammatory diseases, CS-sparing therapies are needed for RP. Our initial results suggest that rilonacept has promise as a CS-sparing therapy.

While previous studies and case reports explored the potential for targeting the IL-1 receptor in RP, these studies with anakinra were limited in the number and characteristics of their patient population, as well as the use of concomitant colchicine. Additionally, there is evidence that targeting of IL-1β alone (eg, with canakinumab) provides insufficient control of the disease and has been associated with relapses. Targeting both IL-1α and IL-1β, as rilonacept does, provides proper control of the disease. Rilonacept offers a rapid treatment response, convenience of weekly dosing and evidence of improved quality of life.

Study limitations
This study was limited by the single-active-arm, open-label design. Specifically, there was no placebo control group, which may be particularly relevant in the assessment of subjective measures, such as pain scores. However, changes in objective measures such as CRP, pericardial inflammation by cardiac MRI and pericardial effusion by cardiac MRI and echocardiography support efficacy. Nonetheless, comprehensive cardiac imaging with MRI and echocardiography was not mandated in all patients, and there may be a selection bias in patients who underwent these evaluations. Moreover, investigators were encouraged to taper concomitant therapies during the EP, but this approach was not mandated. In particular, the majority of patients were not tapered off colchicine. This practice may reflect data supporting colchicine in RP and concern for recurrence in this high-risk patient population after conclusion of the study. Finally, the study cohort was heterogeneous and essentially consisted of two groups: patients with RP having an active recurrence and patients with RP who were CS dependent but without active recurrence. This heterogeneity, coupled with the small sample size, limits the strength of our conclusions.

However, the rapid resolution of the acute episode, reduction in number of recurrences even while tapering and discontinuing CS and improvement in HRQOL together indicate a true treatment effect of rilonacept rather than spontaneous resolution of the disease. Regardless, the study accomplished our primary objectives, which were to describe preliminary efficacy and safety data in a broader population of RP patients and inform the design of Rilonacept inHibition of interleukin-1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes
studY (RHAPSODY), the confirmatory double-blind, placebo-controlled randomised withdrawal phase III pivotal study, which evaluated the efficacy and safety of rilonacept treatment in patients with RI.28 29

CONCLUSION
In summary, this open-label study represents the first use of rilonacept in idiopathic or postpericardiotomy pericarditis. Rilonacept reduced pericardial pain and inflammation, improved objective features of pericarditis and enhanced quality of life. Furthermore, CSs were successfully tapered and discontinued without pericarditis recurrence which, if confirmed in phase III, could indicate the potential for rilonacept to offer a CS-sparing therapeutic option.

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Supplemental Materials

Supplemental Methods

*Exploratory Cardiac Magnetic Resonance Imaging Endpoint*

Cardiac magnetic resonance imaging (MRI) at baseline and at 6 months was optional, with the exception of Part 2, in which cardiac MRI was mandatory for eligibility assessment. Cardiac MRI was performed as previously described to assess changes in pericardial delayed hyperenhancement (DHE), as well as effusion size.\(^{(1)}\) In brief, DHE images were obtained in long and short-axis orientations ∼10 minutes after intravenous injection of Gd-diethylenetriamine penta-acetic acid (0.1-0.2 mmol/kg body weight). Qualitative assessment of pericardial DHE was as follows: none (≤ 50% circumferential DHE at basal, mid and apical ventricular levels), mild (> 50% circumferential DHE at either basal, mid, or apical ventricular levels), moderate (> 50% circumferential DHE at 2 of 3 levels), or severe (> 50% DHE at 3 of 3 levels). Cardiac MRIs were assessed in a core lab blinded to patient data. Both pericardial DHE and pericardial effusion were assessed to provide further objective measures of resolution of pericardial inflammation. For enrollment in part 2, pericardial DHE had to be moderate or severe.

*Pharmacokinetic (PK) Assessments*

Samples for pharmacokinetic analysis were collected at Screening Visit, day 0, weekly post-treatment for weeks 2 through end of base TP, then monthly during EP. Rilonacept concentrations were quantitated by enzyme-linked immunosorbent assay (ELISA [Regeneron]).
Anti-drug Antibody (ADA) Assessments

Samples for ADA analysis were analyzed at baseline, weeks 2, 3, 4, 6/end of base TP, month 2, and at EP Final Visit. ADAs were detected using a non-quantitative electrochemiluminescent (ECL) bridging immunoassay on the MSD instrument. The bridging assay procedure employs a mouse anti-Rilonacept monoclonal antibody, as positive control, and biotinylated Rilonacept and ruthenium-labeled Rilonacept as bridge components. A tiered risk assessment approach was used to screen, confirm and titer ADAs. Samples were treated with acid to dissociate drug:ADA complexes present in serum samples which allows improved detection of ADA while drug is present in the serum. Neutralizing ani-rilonacept antibodies were not assessed. Positive ADA status was defined as having at least one ADA-positive measurement post-baseline at any time point during the study.

Supplemental Results

Other Pericarditis Manifestations

At the end of the study, other pericarditis manifestations such as pericardial effusion on echocardiogram, ECG changes and pericardial rub also resolved in patients with symptomatic RP of idiopathic or PPS etiology with elevated CRP (Parts 1 and 4): pericardial effusion (6/7 patients), PR depression (2/3 patients), widespread ST elevation (2/2 patients), and pericardial rub (2/2 patients). At the end of the study, two patients were reported to have trivial/physiologic pericardial effusion, and 1 patient had isolated PR depression. (Supplemental Table 1).
Changes in Concomitant Medication Use

Overall, out of 20 patients on concomitant pericarditis medications at baseline and who completed the EP, 75% of patients (n=15) successfully stopped, and 30% of patients (n=6) reduced the dose of at least one concomitant pericarditis medication by the end of the study without experiencing a pericarditis recurrence (see Table 3 in main text).

Tapering and Discontinuation of Corticosteroids and Colchicine

Prednisone (the only CS used in the study for pericarditis) was most frequently discontinued or reduced. A total of 15 patients entered the study with ongoing CS treatment, receiving prednisone for pericarditis at the mean dose 12.7 mg/day (range 1mg-50 mg/day). Of these 15 patients, 13 completed the EP (one patient in Part 1 and one CS-dependent patient in Part 3 did not enter the EP). Of the 13 patients on CS at baseline who completed the study, 11 discontinued prednisone completely (4/5 symptomatic patients, and 7/8 CS-dependent patients) and 2 tapered the dose of CS (1/5 symptomatic patients, and 1/8 CS-dependent patients) without experiencing a recurrence of signs and symptoms of RP while maintaining low average pain and CRP levels (Supplemental Figure 2). One of the patients remaining on CS at study end had reduced from 30 to 2.5 mg/day, and the other remained on 30 mg/day (from 50 mg/day), per investigator discretion for disease management during the finite study period. Of the 4 acute symptomatic patients with elevated CRP (Parts 1 and 4) on CS at baseline, 1 patient did not enter the EP; all 3 patients who completed the study stopped their prednisone without disease recurrence while on rilonacept.

In the subset of 9 CS-dependent patients, who were not experiencing acute pericarditis episodes (Parts 3 and 5), 1 patient did not enter EP, but all 8 patients who completed the study either
tapered (1 patient) or stopped (7/8 patients) the CS (Supplemental Figure 2) while maintaining low average pain and CRP levels. Of these 9 CS-dependent patients, 2 patients from Part 3 presented with a pericardial effusion on echocardiogram at baseline. Pericardial effusion resolved in one patient and was assessed as trivial/physiologic in another patient at the end of the study.

In the subset of 6 CS-failure patients (patients experiencing an acute pericarditis episode at baseline while receiving CS and colchicine), 5 patients entered the EP; 4 of these patients discontinued CS during the EP.

Overall, the CS-sparing effect of rilonacept was consistent among patients with and without active recurrence at the time of enrollment, and no recurrences were observed (see Table 4 in main text).

Of 23 patients who completed the EP, 7 (30%) were experiencing an active episode while being treated with colchicine and not corticosteroids at baseline (colchicine-failure patients). One of these seven colchicine-failure patients discontinued colchicine use during the study.

Efficacy in Corticosteroid-Failure and Colchicine-Failure Patients

Of 15 patients who entered the study with ongoing CS treatment, 9 were CS-dependent, and 6 were experiencing an active episode at baseline while also receiving colchicine (CS-failure patients). CS-failure patients experienced rapid and sustained reductions in pericarditis pain and CRP with rilonacept treatment (Supplemental Figure 3).
The 7 patients who were experiencing an active episode at baseline while being treated with colchicine and not corticosteroids (colchicine-failure patients) experienced rapid and sustained reductions in pericarditis pain and CRP with initiation of rilonacept (Supplemental Figure 4).

Health-Related Quality of Life

A consistent pattern of increased PROMIS scores reflected improvement in HRQOL with rilonacept treatment (Supplemental Table 2). At baseline, mean Physical and Mental Global Health scores across all patients were below 50, which is the mean score for the general US population, indicating impaired QOL in symptomatic RP patients as well as CS-dependent patients without active pericarditis. In symptomatic patients of idiopathic (Parts 1 and 2) or PPS etiology (Part 4), the mean baseline Physical and Mental Global Health scores were 39.9 and 44.5, respectively, and improved to 51.3 and 50.5 at the Final Visit. In CS-dependent patients with RP (Parts 3 and 5), the mean baseline Physical and Mental Global Health scores were 43.3 and 46.5, respectively, and improved to 46.8 and 50.7, respectively, at the Final Visit. In addition, improvements in HRQOL were observed after the first 6 weeks of rilonacept treatment (Supplemental Table 2).

Exploratory Cardiac Magnetic Resonance Imaging Outcomes

Of 25 study patients, 11 had cardiac MRI at baseline and the Final Visit, including 6 patients with active idiopathic RP and 5 CS-dependent non-active RP patients (4 idiopathic, 1 PPS). Among 8 patients with baseline pericardial DHE (mild, moderate, or severe) and follow-up MRI, DHE improved or resolved in 6 patients. For the 2 patients in which pericardial DHE was not changed, 1 patient (Part 2) had moderate pericardial DHE at baseline and the Final Visit, and the
second patient (Part 5) had mild pericardial DHE at baseline and the Final Visit. One patient (Part 3) had no pericardial DHE at baseline and had mild DHE at the Final Visit. Improvements in DHE were associated with decreases or maintenance of low pain and CRP levels despite discontinuation of CS or reduction in dose.

**Patient Enrolled Twice**

The case study of the patient who was re-treated with rilonacept for RP provides an example of the persistence and severity of RP as well as the efficacy and tolerability of rilonacept upon retreatment. This patient with severe RP participated in the study twice, having been enrolled in the study a second time with a recurrence of pericarditis approximately 4.5 months after successfully completing 6 months of rilonacept in her first participation in the trial. Retreatment with rilonacept resulted in a similar clinically meaningful response with similar tolerability, suggesting that the disease improvements represent a true response to treatment rather than a spontaneous improvement due to natural history of the disease. In addition, although limited to one patient, this example provides a framework for evaluating the efficacy and safety of repetitive use of rilonacept in RP.

**PK Assessments**

A total of 25 unique patients provided 211 samples for pharmacokinetic analysis. The mean rilonacept concentration time profile demonstrated moderate to high variability (30.1-69.2\%CV) between patients across the duration of the study. Following the loading dose (320 mg), no
additional accumulation of rilonacept was observed, and the median trough concentration over the base TP and EP was approximately 30,000 ng/mL (Supplemental Figure 5).

Immunogenicity

In total, among 25 unique patients, 14 (56%) were classified as positive for ADA (anti-drug [rilonacept] antibodies), i.e., ADA detected in at least one post-baseline serum sample during the study. Two of these 14 patients had low titers (1:50) of pre-existing ADAs detected before administration of rilonacept and continued to have detectable low titers of ADAs (up to 1:150) during the remainder of the study. At Final Visit, 4 patients (17.4%) had detectable ADAs. The majority of patients (12 out of 14) with ADA positivity during the study had low titers (up to 1:150). Among the 14 patients who had ADAs detected at at least 1 post-baseline timepoint, 8 (57.1%) subjects had a TEAE of local injection site reaction. Among the 11 subjects negative for ADAs throughout the study, 4 (36.4%) subjects experienced injection site reactions. Presence of ADAs had a minimal impact on rilonacept trough concentrations (Supplemental Figure 6).

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Supplemental Figures

Supplemental Figure 1. Patient Disposition

Among 49 patients screened, 25 unique adult patients were enrolled and received rilonacept. One patient participated in the study twice, but only assessments from this patient’s first participation are included in the analysis. Of 23 patients who entered the EP, 23 (100%) completed it; one CS-dependent PPS patient (Part 3) completed the base TP but declined to continue into the EP, and one symptomatic idiopathic RP patient (Part 1) experienced a serious AE and discontinued the study drug after Visit 4 in the base TP.
*One patient participated in the study twice (N=26); however, data are reported for 25 unique patients.

CRP, C-reactive protein; CS-dep, corticosteroid dependent; EP, extension period; PPS, post-pericardiotomy syndrome; TP, treatment period.
Supplemental Figure 2. NRS scores (pain) and CRP levels in Non-active CS-dependent Patients

The subset of 9 CS-dependent patients who were not experiencing acute pericarditis episodes (Parts 3 and 5) maintained low average pain and CRP levels.

*Part 3 and Part 5 combined*

BL, baseline; CRP, C-reactive protein; CS-dep, corticosteroid dependent; D, day; EP, extension period; NRS, Numeric Rating Scale; RP, recurrent pericarditis; SE, standard error; TP, treatment period; W, week. The number of patients with CRP and pain data changes over time due to combining the visits for some patients and not all patients having assessments at all visits.
Supplemental Figure 3. NRS scores (pain) and CRP levels in CS-failure Patients

(n=6)a

The subset of 6 CS-failure patients who were experiencing an acute pericarditis episode despite treatment with corticosteroids at baseline experienced rapid and sustained reductions in pericarditis pain and CRP with initiation of rilonacept.

aPatients with an active pericarditis episode on CS at enrollment (safety population); one CS failure patient discontinued during the TP due to an SAE, and the resulting subgroup that completed the EP (EP population; n=5) had similar results.

BL, baseline; CRP, C-reactive protein; D, day; EoTP, end of treatment period; EoEP, end of extension period; EP, extension period; NRS, Numeric Rating Scale; RP, recurrent pericarditis; SE, standard error; TP, treatment period; W, week. The number of patients with CRP and pain data changes over time due to combining the visits for some patients and not all patients having assessments at all visits.
Supplemental Figure 4. NRS Scores (Pain) and CRP Levels in Colchicine-failure Patients

The subset of 7 colchicine-failure patients who were experiencing an acute pericarditis episode despite treatment at baseline with colchicine but not corticosteroids experienced rapid and sustained reductions in pericarditis pain and CRP with initiation of rilonacept.

Patients with an active pericarditis episode on colchicine and not CS at enrollment (safety population)

BL, baseline; CRP, C-reactive protein; D, day; EoTP, end of treatment period; EoEP, end of extension period; EP, extension period; NRS, Numeric Rating Scale; RP, recurrent pericarditis; SE, standard error; TP, treatment period; W, week. The number of patients with CRP and pain data changes over time due to combining the visits for some patients and not all patients having assessments at all visits.
Supplemental Figure 5. Mean rilonacept concentration time profile.

Mean rilonacept concentration time profile demonstrated moderate to high variability (30.1-69.2% CV) between patients across the duration of the study. Following the loading dose (320 mg), no additional accumulation of rilonacept was observed, and the median trough concentration over the base TP and EP was approximately 30,000 ng/mL.
Supplemental Figure 6 Mean Rilonacept Concentration Time Profile by ADA Status

Supplemental Figure 6. Mean rilonacept concentration time profile by ADA status. ADA, anti-drug antibody

Presence of ADAs had a minimal impact on rilonacept trough concentrations.
### Supplemental Tables

**Supplemental Table 1. Improvement in Pericarditis Symptomatology with Rilonacept**

| Disease status: CRP requirement (mg/dL): | n: | Idiopathic | PPS | Idiopathic and PPS |
|----------------------------------------|----|------------|-----|--------------------|
| |    | Active<sup>a</sup> >1/12 | Active<sup>b</sup> ≤1/3 | CS-dep<sup>c</sup> N/A | Active<sup>d</sup> >1/1 | CS-dep<sup>d</sup> N/A | Active<sup*e,d</sup> >1/13 |
| Baseline, n (%) | | | | | | |
| Widespread ST-segment elevation | 2/12 (16.7) | 0/3 | 0/6 | 0/1 | 0/3 | 2/13 (15.4) |
| PR-segment depression | 3/12 (25.0) | 0/3 | 0/6 | 0/1 | 0/3 | 3/13 (23.1) |
| Pericardial rub | 2/12 (16.7) | 0/3 | 0/6 | 0/1 | 0/3 | 2/13 (15.4) |
| Fever | 0/12 | 0/3 | 0/6 | 0/1 | 0/3 | 0/13 |
| Pericardial effusion on ECHO | 7/12 (58.3) | 0/3 | 2/6 (33.3) | 0/1 | 0/3 | 7/13 (53.8) |
| End of TP (Visit 7), n (%) | | | | | | |
| Widespread ST-segment elevation | 0/12 | 0/2 | 0/6 | 0/1 | 0/3 | 0/13 |
| PR-segment depression | 1/12 (8.3) | 0/2 | 0/6 | 0/1 | 0/3 | 1/13 (7.7) |
| Pericardial rub | 0/11 | 0/3 | 0/6 | 0/1 | 0/3 | 0/12 |
| Fever | 0/12 | 0/3 | 0/6 | 0/1 | 0/3 | 0/13 |
| Pericardial effusion on ECHO | 1/12 (8.3) | 0/2 | 1/6 (16.7) | 0/1 | 0/3 | 1/13 (7.7) |
| Final Visit, n (%) | | | | | | |
| Widespread ST-segment elevation | 0/11 | 0/3 | 0/5 | 0/1 | 0/3 | 0/12 |
| Condition                        | Part 1 | Part 2 | Part 3 | Part 4 | Part 5 | Final Visit |
|---------------------------------|--------|--------|--------|--------|--------|-------------|
| PR-segment depression           | 1/11 (9.1) | 0/3 | 0/5 | 0/1 | 0/3 | 1/12 (8.3) |
| Pericardial rub                 | 0/11 | 0/3 | 0/5 | 0/1 | 0/3 | 0/12 |
| Fever                           | 0/11 | 0/3 | 0/5 | 0/1 | 0/3 | 0/12 |
| Pericardial effusion on ECHO    | 1/9/11 (9.1) | 0/3 | 1/5 (20.0) | 0/1 | 0/3 | 1/12 (8.3) |

*Part 1; †Part 2; ‡Part 3; §Part 4; ‥Part 5; ‡Patient with effusion at baseline, no effusion at EoT Visit and trivial effusion (not pathological) at Final Visit

CRP, C-reactive protein; CS-dep, corticosteroid-dependent; ECHO, echocardiography; PPS, post-pericardiotomy syndrome; TP, treatment period.
### Supplemental Table 2: Improvements in PROMIS® Global Health, v1.2

|                      | Idiopathic or PPS |                 |                 |
|----------------------|-------------------|------------------|------------------|
|                      | **Active** † (n=16) | **CS-dependent** ‡ (n=9) |
| Global Physical Health, n, mean (Median, Range, SD) |                  |                  |
| Baseline             | 16, 39.94 (41.05, 23.50-54.10, 8.941) | 7, 43.3 (42.30, 37.40-54.10, 5.311) |
| End of TP            | 15, 51.35 (50.80, 34.90-61.90, 7.962) | 9, 45.09 (44.90, 39.80-54.10, 4.057) |
| Final Visit          | 15, 51.32 (54.10, 39.80-61.90, 6.564) | 8, 46.81 (47.70, 26.70-57.70, 9.266) |
| Global Mental Health, n, mean (Median, Range, SD) |                  |                  |
| Baseline             | 16, 44.5 (48.30, 25.10-62.50, 10.484) | 7, 46.49 (43.50, 38.80-59.00, 7.767) |
| End of TP            | 15, 50.13 (50.80, 28.40-67.60, 11.325) | 9, 47.91 (45.80, 43.50-59.00, 5.509) |
| Final Visit          | 15, 50.54 (53.30, 28.40-67.60, 10.995) | 8, 50.66 (50.80, 41.10, 59.00, 6.299) |

*PROMIS® - Patient Reported Outcomes Measurement Information System. The higher the score, the better global health is. US national average score for Global Physical and Mental Health is 50 (SD 10); †Part 1, 2, and 4; ‡Part 3 and 5
CS-dependent, corticosteroid dependent; PPS, post-pericardiotomy syndrome; SD, standard deviation; TP, treatment period.
### Supplemental Table 3. TEAEs by System Organ Class

| Disease status: CRP requirement (mg/dL): Idiopathic | PPS | Total |
|---------------------------------------------------|-----|-------|
| **Disease status:**                               |     |       |
| CRP requirement                                   |     |       |
| (mg/dL):                                          |     |       |
| n:                                                |     |       |
| Active‡  >1                                        | 12  | 1     |
| Active‡  ≤1                                       | 3   | 1     |
| CS-dep§ N/A                                       | 6   | 1     |
| Active‡  >1                                       | 1   | 1     |
| CS-dep§ N/A                                       | 3   | 1     |
| All‡,§,†,‖,#                                      | N/A | 25    |
| Number of patients with ≥1 TEAE                  | 12  | 1     |
| General disorders and administration site conditions | 6   | 1     |
| Injection site reaction                           | 1   | 1     |
| Fatigue                                           | 0   | 0     |
| Injection site bruising                           | 1   | 1     |
| Injection site erythema                           | 1   | 1     |
| Injection site pain                               | 1   | 1     |
| Non-cardiac chest pain                            | 1   | 1     |
| Peripheral swelling                               | 0   | 0     |
| Application site bruise                           | 1   | 1     |
| Application site erythema                         | 1   | 1     |
| Chest discomfort                                  | 1   | 1     |
| Injection site joint warmth                       | 1   | 1     |
| Pyrexia                                           | 1   | 1     |
| Ulcer hemorrhage                                  | 0   | 0     |
| Musculoskeletal and connective tissue disorders   | 3   | 1     |
| Arthralgia                                        | 0   | 0     |
| Musculoskeletal pain                              | 1   | 1     |
| Limb discomfort                                   | 1   | 1     |
| Muscle twitching                                  | 1   | 1     |
| Musculoskeletal chest pain                        | 0   | 1     |
| Neck pain                                         | 0   | 1     |
| Pain in extremity                                 | 0   | 1     |
| Infections and infestations                       | 5   | 1     |
| Nasopharyngitis                                   | 3   | 0     |
| Cellulitis                                        | 2   | 0     |
| Sinusitis                                         | 0   | 1     |
| Subcutaneous abscess                              | 1   | 0     |

Number of patients with ≥1 TEAE: 12 (100.0) 3 (100.0) 6 (100.0) 1 (100.0) 3 (100.0) 25 (100.0)

General disorders and administration site conditions:

- Injection site reaction: 1 (8.3) 0 2 (33.3) 1 (100.0) 2 (66.7) 6 (24.0)
- Fatigue: 0 0 1 (16.7) 0 1 (33.3) 2 (8.0)
- Injection site bruising: 1 (8.3) 0 0 1 (100.0) 0 2 (8.0)
- Injection site erythema: 1 (8.3) 1 (33.3) 0 0 0 2 (8.0)
- Injection site pain: 1 (8.3) 0 1 (16.7) 0 0 2 (8.0)
- Non-cardiac chest pain: 1 (8.3) 0 1 (16.7) 0 0 2 (8.0)
- Peripheral swelling: 0 1 (33.3) 0 0 1 (33.3) 2 (8.0)
- Application site bruise: 1 (8.3) 0 0 0 0 1 (4.0)
- Application site erythema: 1 (8.3) 0 0 0 0 1 (4.0)
- Chest discomfort: 1 (8.3) 0 0 0 0 1 (4.0)
- Injection site joint warmth: 1 (8.3) 0 0 0 0 1 (4.0)
- Pyrexia: 1 (8.3) 0 0 0 0 1 (4.0)
- Ulcer hemorrhage: 0 0 0 1 (100.0) 0 1 (4.0)
- Musculoskeletal and connective tissue disorders: 3 (25.0) 0 4 (66.7) 1 (100.0) 2 (66.7) 10 (40.0)
- Arthralgia: 0 0 2 (33.3) 0 1 (33.3) 3 (12.0)
- Musculoskeletal pain: 1 (8.3) 0 1 (16.7) 0 0 2 (8.0)
- Limb discomfort: 1 (8.3) 0 0 0 0 1 (4.0)
- Muscle twitching: 1 (8.3) 0 0 0 0 1 (4.0)
- Musculoskeletal chest pain: 0 0 0 1 (33.3) 1 (4.0)
- Neck pain: 0 0 0 1 (100.0) 0 1 (4.0)
- Pain in extremity: 0 0 1 (16.7) 0 0 1 (4.0)
- Infections and infestations: 5 (41.7) 1 (33.3) 1 (16.7) 0 1 (33.3) 8 (32.0)
- Nasopharyngitis: 3 (25.0) 0 1 (16.7) 0 0 4 (16.0)
- Cellulitis: 2 (16.7) 0 0 0 0 2 (8.0)
- Sinusitis: 0 1 (33.3) 0 0 0 1 (4.0)
- Subcutaneous abscess: 1 (8.3) 0 0 0 0 1 (4.0)
| Diagnosis                                      | Count | percentage | Count | percentage | Count | percentage | Count | percentage |
|-----------------------------------------------|-------|------------|-------|------------|-------|------------|-------|------------|
| Upper respiratory tract infection             | 0     | 0%         | 0     | 0%         | 0     | 0%         | 0     | 0%         |
| Urinary tract infection                       | 1     | 8.3%       | 0     | 0%         | 0     | 0%         | 0     | 0%         |
| Gastrointestinal disorders                    | 6     | 50.0%      | 0     | 0%         | 0     | 0%         | 6     | 24.0%      |
| Diarrhoea                                     | 3     | 25.0%      | 0     | 0%         | 0     | 0%         | 3     | 12.0%      |
| Dyspepsia                                     | 1     | 8.3%       | 0     | 0%         | 0     | 0%         | 1     | 4.0%       |
| Haemorrhoids                                  | 1     | 8.3%       | 0     | 0%         | 0     | 0%         | 1     | 4.0%       |
| Nausea                                        | 1     | 8.3%       | 0     | 0%         | 0     | 0%         | 1     | 4.0%       |
| Toothache                                     | 1     | 8.3%       | 0     | 0%         | 0     | 0%         | 1     | 4.0%       |
| Investigations                                | 2     | 16.7%      | 3     | 50.0%      | 1     | 100.0%     | 0     | 0%         |
| Blood cholesterol increased                   | 1     | 8.3%       | 0     | 0%         | 1     | 16.7%      | 0     | 0%         |
| Blood creatine phosphokinase increased        | 1     | 8.3%       | 0     | 0%         | 0     | 0%         | 1     | 100.0%     |
| Liver function test increased                 | 2     | 16.7%      | 0     | 0%         | 0     | 0%         | 2     | 8.0%       |
| Alanine aminotransferase increased            | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| Aspartate aminotransferase increased          | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| C-reactive protein increased                  | 0     | 0%         | 0     | 0%         | 1     | 100.0%     | 0     | 0%         |
| Hepatic enzyme increased                      | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| High density lipoprotein increased            | 1     | 8.3%       | 0     | 0%         | 0     | 0%         | 1     | 4.0%       |
| Lipids increased                              | 0     | 0%         | 0     | 0%         | 1     | 100.0%     | 0     | 0%         |
| Weight increased                              | 0     | 0%         | 0     | 0%         | 1     | 100.0%     | 0     | 0%         |
| Respiratory, thoracic and mediastinal disorders| 0     | 0%         | 1     | 33.3%      | 2     | 33.3%      | 0     | 0%         |
| Cough                                         | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| Dyspnoea                                      | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| Dyspnoea at rest                              | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| Painful respiration                           | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| Productive cough                              | 0     | 0%         | 1     | 33.3%      | 0     | 0%         | 1     | 4.0%       |
| Skin and subcutaneous tissue disorders        | 0     | 0%         | 1     | 16.7%      | 1     | 100.0%     | 1     | 33.3%      |
| Erythema                                      | 0     | 0%         | 0     | 0%         | 0     | 0%         | 1     | 33.3%      |
| Rash                                          | 0     | 0%         | 1     | 16.7%      | 0     | 0%         | 1     | 4.0%       |
| Condition                                      | 0   | 1   | 0   | 1 (100.0) | 0   | 1 (4.0) |
|------------------------------------------------|-----|-----|-----|------------|-----|---------|
| Skin ulcer                                     | 0   | 0   | 0   | 1 (100.0) | 0   | 1 (4.0) |
| Cardiac disorders                              | 0   | 1   | 0   | 1 (16.7)   | 0   | 0       | 2 (8.0) |
| Angina pectoris                                | 0   | 1   | 0   | 0          | 0   | 1 (4.0) |
| Cardiac discomfort                             | 0   | 0   | 0   | 1 (16.7)   | 0   | 0       | 1 (4.0) |
| Pericarditis                                    | 0   | 0   | 0   | 1 (16.7)   | 0   | 0       | 1 (4.0) |
| Ear and labyrinth disorders                    | 2   | 0   | 0   | 0          | 0   | 1 (4.0) |
| Vertigo                                        | 1   | 0   | 0   | 0          | 0   | 1 (4.0) |
| Vertigo positional                             | 1   | 0   | 0   | 0          | 0   | 1 (4.0) |
| Nervous system disorders                       | 1   | 0   | 0   | 1 (16.7)   | 0   | 0       | 2 (8.0) |
| Headache                                       | 1   | 0   | 0   | 1 (16.7)   | 0   | 0       | 2 (8.0) |
| Eye disorders                                  | 1   | 0   | 0   | 0          | 0   | 1 (4.0) |
| Dry eye                                        | 1   | 0   | 0   | 0          | 0   | 1 (4.0) |
| Injury, poisoning and procedural complications  | 1   | 0   | 0   | 0          | 0   | 1 (4.0) |
| Post procedural discharge                      | 1   | 0   | 0   | 0          | 0   | 1 (4.0) |
| Metabolism and nutrition disorders             | 0   | 0   | 0   | 1 (100.0)  | 0   | 1 (4.0) |
| Increased appetite                             | 0   | 0   | 0   | 1 (100.0)  | 0   | 1 (4.0) |

*All investigator adverse event terms are coded using MedDRA dictionary version 20.1; †Part 1; ‡Part 2; §Part 3; ‖Part 4; #Part 5;  
Note: Patients are counted only once within each system organ class and preferred term.  
MedDRA, Medical Dictionary for Regulatory Activities; PPS, post-pericardiotomy syndrome;  
TEAEs, treatment-emergent adverse events; CS-dep, corticosteroid-dependent; CRP, C-reactive protein.
### Supplemental Table 4. Summary of Lipid Changes*

|                         | Idiopathic | PPS | Total |
|-------------------------|------------|-----|-------|
| **Disease status:**     |            |     |       |
| CRP requirement (mg/dL) |            |     |       |
| n:                      |            |     |       |
| Active >1               | 172.4 [11] |     | 185.3 [19] |
| Active ≤1              | 256.0 [1]  |     | 174.5 [2]   |
| CS-dep                 | 203.8 [5]  |     | [0]    |
|                         | [N/A] 6    |     |       |
| CS-dep                   | [N/A] 1    |     |       |
| CS-dep                   | [N/A] 3    |     |       |
| CS-dep                   | [N/A] 25   |     |       |
| **Cholesterol (mg/dL)** |            |     |       |
| Mean at baseline [n]    | 45.9 [11]  |     | 49.8 [19] |
| Mean at Final Visit [n] | 56.6 [11]  |     | 54.7 [23] |
| **HDL cholesterol (mg/dL)** |        |     |       |
| Mean at baseline [n]    | 50.0 [2]   |     | 124.0 [19] |
| Mean at Final Visit [n] | 43.7 [3]   |     | 128.7 [23] |
| **LDL cholesterol (mg/dL)** |        |     |       |
| Mean at baseline [n]    | 207.6 [11] |     | 130.2 [19] |
| Mean at Final Visit [n] | 138.2 [5]  |     | 138.2 [23] |
| **Triglycerides (mg/dL)** |         |     |       |
| Mean at baseline [n]    | 156.4 [5]  |     | 133.7 [19] |
| Mean at Final Visit [n] | 199.8 [5]  |     | 159.4 [23] |

*Lipids were measured under fasting and non-fasting conditions.

*Part 1; †Part 2; ‡Part 3; §Part 4; ‖Part 5CRP, C-reactive protein; CS-dep, corticosteroid-dependent; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TP, treatment period; PPS, post-pericardiectomy syndrome