

Rilonacept in Recurrent Pericarditis: First Efficacy and Safety Data From an Ongoing Phase 2 Pilot Clinical Trial

Allan Klein¹, David Lin², Paul Cremer¹, Saifullah Nasir³, Sharon Crugnale⁴,
Larisa Collins⁴, Fang Fang⁴, Anna Beutler⁴, John F. Paolini⁴

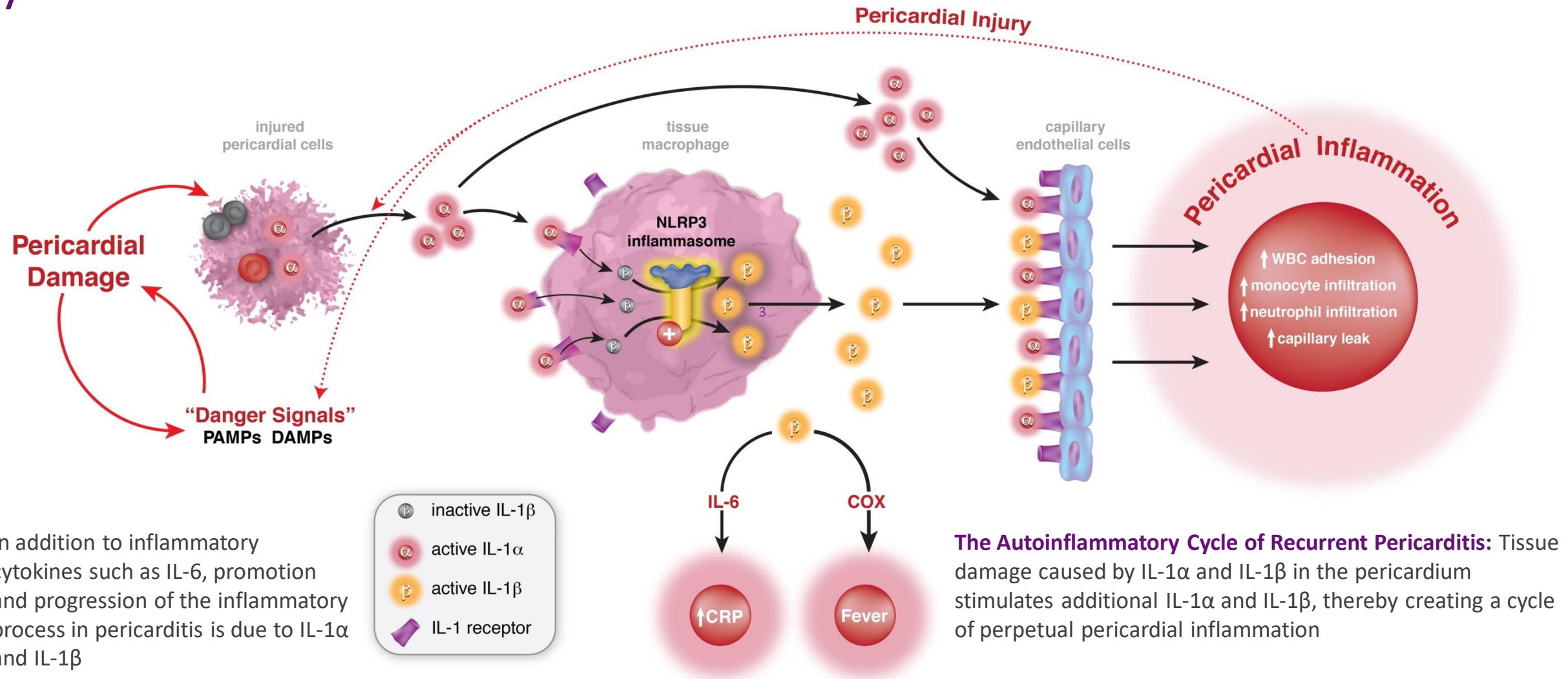
*¹Cleveland Clinic, Cleveland, Ohio, USA; ²Minneapolis Heart Institute, Minneapolis, Minnesota, USA;
³Affinity Clinical Research Institute, Oak Brook, Illinois, USA; ⁴Kiniksa Pharmaceuticals Corp., Lexington,
Massachusetts, USA*

Presented at the 68th Annual Scientific Session of the American College of Cardiology
March 16-18, 2019, New Orleans, LA
Poster No.: 052

Background

- Recurrent pericarditis (RP) is characterized by the recurrence of pericarditis signs and symptoms after a symptom-free period of ≥ 4 to 6 weeks¹
- RP affects 20% to 30% of patients with acute pericarditis and can be debilitating owing to pain and physical limitations²
- There are no approved therapies for RP; current treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids (CS)³
- Interleukin-1 (IL-1) is a cytokine central to the pathophysiology of recurrent pericarditis (**Figure 1**)

Figure 1. Role of IL-1 α and IL-1 β in the Autoinflammatory Cycle of Recurrent Pericarditis^{4,5}

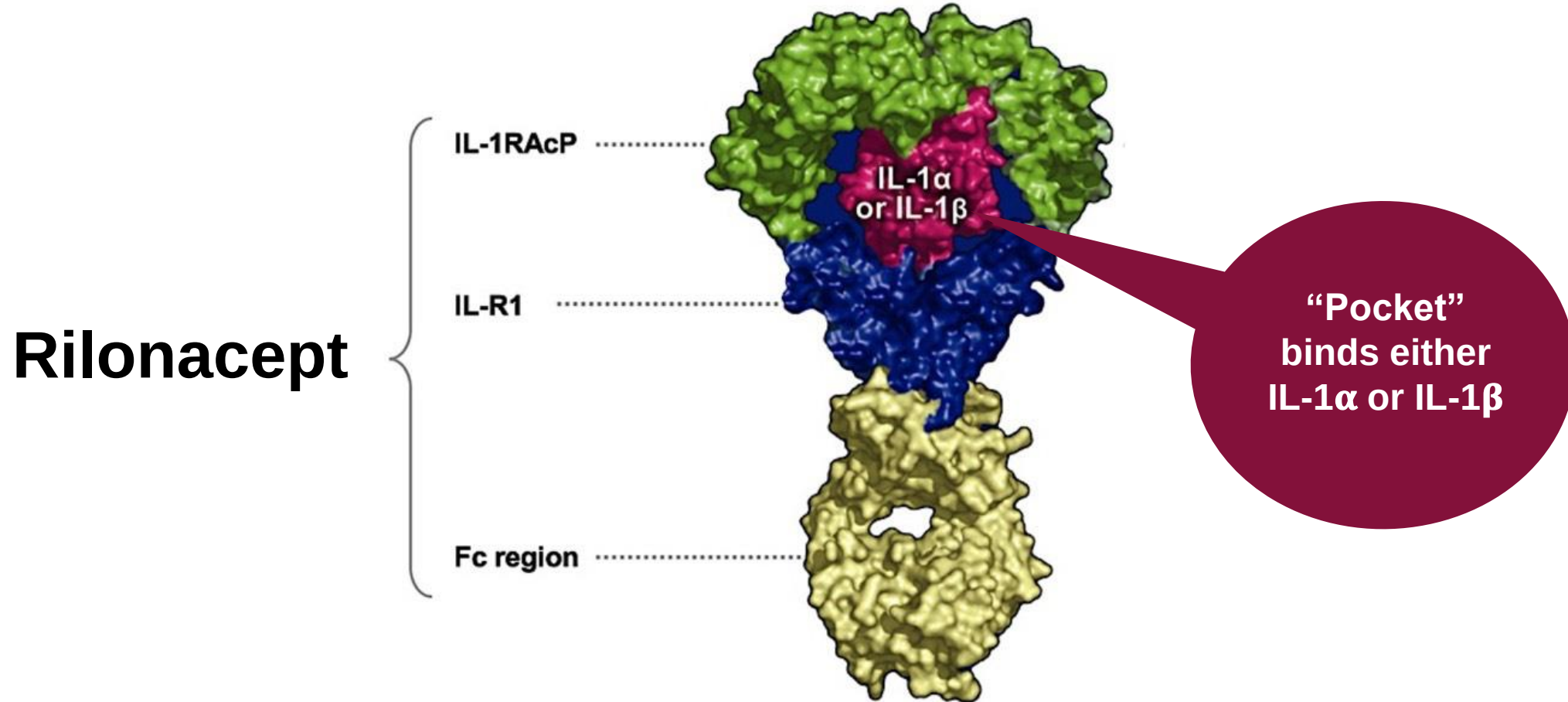


CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; IL, interleukin; PAMPs, pathogen-associated molecular patterns; WBC, white blood cell.

Background (continued)

- Rilonacept is a dimeric fusion protein consisting of ligand-binding domains of the extracellular portions of the human IL-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked to the Fc portion of human IgG1 (Figure 2)
- Arcalyst[®] (rilonacept, Regeneron, Tarrytown, NY) is approved in the US for treatment of Cryopyrin-Associated Periodic Syndrome, including Familial Cold Autoinflammatory Syndrome, and Muckle-Wells Syndrome and is administered as weekly subcutaneous (SC) injections
- Rilonacept is currently being investigated for RP by Kiniksa Pharmaceuticals, Ltd. (Lexington, MA)
- Study purpose: to measure inter- and intra-patient variability in pain numeric rating scale (NRS) and C-reactive protein (CRP) levels and to understand measures of improvement of RP

Figure 2. Rilonacept Mechanism of Action



IL, interleukin; IL-1RAcP, IL-1 receptor accessory protein; IL-1RI, IL-1 receptor subtype 1.

Methods

Study Design

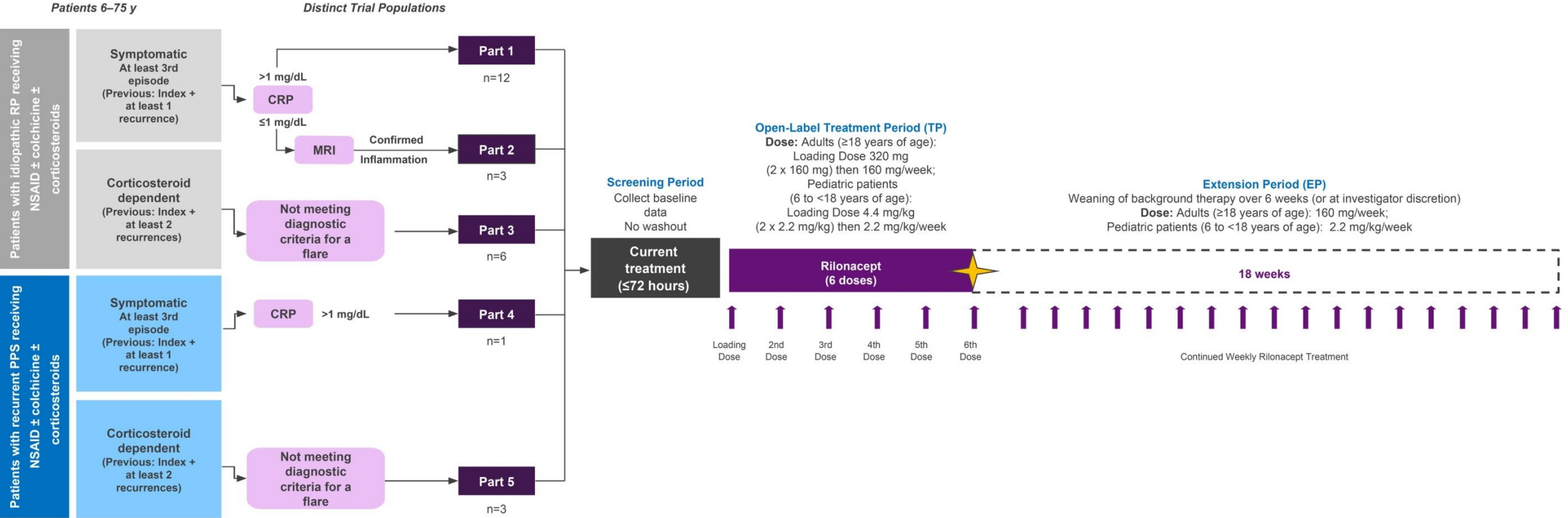
- Open-label, single-active-arm, 5-part pilot study explored clinical and biochemical endpoints of pericarditis symptomatology and collected inter- and intra-patient variability data for baseline and on-treatment parameters (Figure 3)
- Eligible patients were adult patients (18 to 75 y) or pediatric patients (≥ 6 to < 18 y) with recurrent pericarditis due to idiopathic or post-pericardiotomy syndrome etiology, presenting with at least a third pericarditis episode or with at least 3 prior episodes if not flaring but CS dependent at the time of enrollment
- Patients in all parts of the study may have been taking concomitant NSAIDs, and/or colchicine, and/or CS treatment (in any combination) if the dosages were stable for ≥ 7 days; patients in Parts 3 and 5 must have been taking CS at enrollment
 - No changes in concomitant medications were allowed during the 6-week open-label treatment period (TP)

Methods

Treatment and Procedures

- In the TP:
 - Adults (≥ 18 y) received a loading dose of 320 mg (2×160 mg) rilonacept, administered via SC injection on day 0, followed by 160 mg SC weekly for 5 additional doses
 - Children (≥ 6 to < 18 y) received a loading dose of 4.4 mg/kg (2×2.2 mg/kg) rilonacept, administered via SC injection on day 0, then 2.2 mg/kg SC weekly for 5 additional doses
- In the optional 18-week extension period (EP), during which rilonacept weekly injections continued, patients were encouraged to wean from concomitant medications according to the following recommended schedule:
 - NSAIDs and colchicine: tapered and withdrawn within 15 days of EP entry
 - CS: taper by 5 mg and 0.2 mg/kg each week in adults and children, respectively; discontinue within 6 weeks of EP entry

Figure 3. Trial Design



CRP, C-reactive protein; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PPS, post-pericardiotomy syndrome; RP, recurrent pericarditis.

Methods (continued)

Efficacy Assessments

- For continuous variables (e.g., change from baseline), summary statistics were calculated as mean and median; for categorical variables, frequency and percentage were calculated
- Primary endpoints
 - Parts 1, 2, and 4: inter- and intra-patient variability estimates for pain NRS and CRP levels at baseline and on treatment
 - Part 3 and 5: disease activity after CS taper in patients with CS-dependent disease
- Secondary endpoints
 - Improvement in pericarditis symptomatology
 - Change in patients' quality of life using validated Patient-Reported Outcomes Measurement Information System (PROMIS) Questionnaire (v1.2) to assess overall physical and mental well-being⁶
 - Use of concomitant CS (prednisone)
 - Changes in the use of other concomitant medications for pericarditis

Methods (continued)

Safety Assessments

- Adverse events (AEs) were recorded with the level of severity (i.e., mild, moderate, or severe) and relationship to study drug based on investigators' judgement (i.e., not related, unlikely related, possibly related, or related)

Results*: Patients

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Part 1	Part 2	Part 3	Part 4	Part 5	Total
Number of patients	12	3	6	1	3	25
Mean (SD) age, y	39.6 (10.2)	42.7 (15.0)	51.3 (7.8)	34.0	42.0 (7.2)	42.8 (10.5)
Female sex, n (%)	9 (75.0)	3 (100.0)	2 (33.3)	0	1 (33.3)	15 (60.0)
Race, n (%)						
White	10 (83.3)	2 (66.7)	6 (100.0)	1 (100.0)	3 (100.0)	22 (88.0)
Black/African American	2 (16.7)	1 (33.3)	0	0	0	3 (12.0)
Mean (SD) BMI, kg/m ²	30.2 (5.4)	40.0 (12.1)	31.1 (4.1)	29.3	24.7 (2.1)	30.9 (6.7)
Mean (SD) pain rating, NRS ^a	4.6 (1.7)	4.3 (2.5)	1.2 (0.8)	4.0	2.0 (2.7)	3.4 (2.2)
Mean (SD) baseline CRP, mg/dL	4.9 (5.8)	2.8 ^b (4.0)	0.2 (0.1)	1.1	0.1 (0.04)	2.8 (3.3)
Pericarditis medications, n (%)						
Aspirin	0	0	2 (33.3)	1 (100.0)	0	3 (12.0)
NSAIDs	6 (50.0)	1 (33.3)	3 (50.0)	0	1 (33.3)	11 (44.0)
Colchicine	8 (66.7)	3 (100.0)	6 (100.0)	1 (100.0)	2 (66.7)	20 (80.0)
Corticosteroids	4 (33.3)	2 (66.7)	6 (100.0)	0	3 (100.0)	15 (60.0)

BMI, body mass index; CRP, C-reactive protein; CS, corticosteroid; NRS, numeric rating scale; NSAID, nonsteroidal anti-inflammatory drug.

*As of January 23, 2019. See Supplementary Figure 1 for CONSORT details.

^a11-point numeric scale, ranging from zero (0, no pain) to ten (10, pain as bad as possible).

^bCRP levels of patients enrolled in Part 2 were ≤1 mg/dL at screening; an error in the study database resulted in a mean number of 2.8 mg/dL and will be corrected at time of final data analysis.

Table 1. Baseline Demographic and Clinical Characteristics (*cont'd*)

Characteristic	Part 1	Part 2	Part 3	Part 4	Part 5	Total
Pericarditis medication categories, n (%)						
0	3 (25.0)	0	0	0	0	3 (12.0)
1	2 (16.7)	0	0	0	0	2 (8.0)
2	5 (41.7)	3 (100.0)	1 (16.7)	1 (100.0)	3 (100.0)	13 (52.0)
≥3	2 (16.7)	0	5 (83.3)	0	0	7 (28.0)
Number of previous pericarditis recurrences						
Mean	2.7	3.0	3.2	9.0	3.7	3.2

Results: Efficacy

Part 1 (symptomatic idiopathic RP with CRP >1 mg/dL)

- A reduction in both inflammation and reported pain were noted after the first dose followed by a persistent clinical response throughout the 6-week open-label TP
 - Mean patient-reported pericardial pain on the 11-point pain NRS decreased from 4.6 at baseline to 0.8 at 6 weeks. Mean CRP decreased from 4.9 mg/dL at baseline to 0.3 mg/dL at 6 weeks; median time to CRP normalization was 9 days (**Figure 4**)
 - Pericarditis manifestations resolved, including 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 TP (see **Supplementary Table 1**)
- 7 patients who completed 24 weeks exhibited a continued clinical response to rilonacept
 - Mean patient-reported pericardial pain on the 11-point pain NRS further decreased to 0.4, and mean CRP was 0.3 mg/dL at 24 weeks
 - Pericardial effusion and PR depression resolved during the EP

Results: Efficacy (continued)

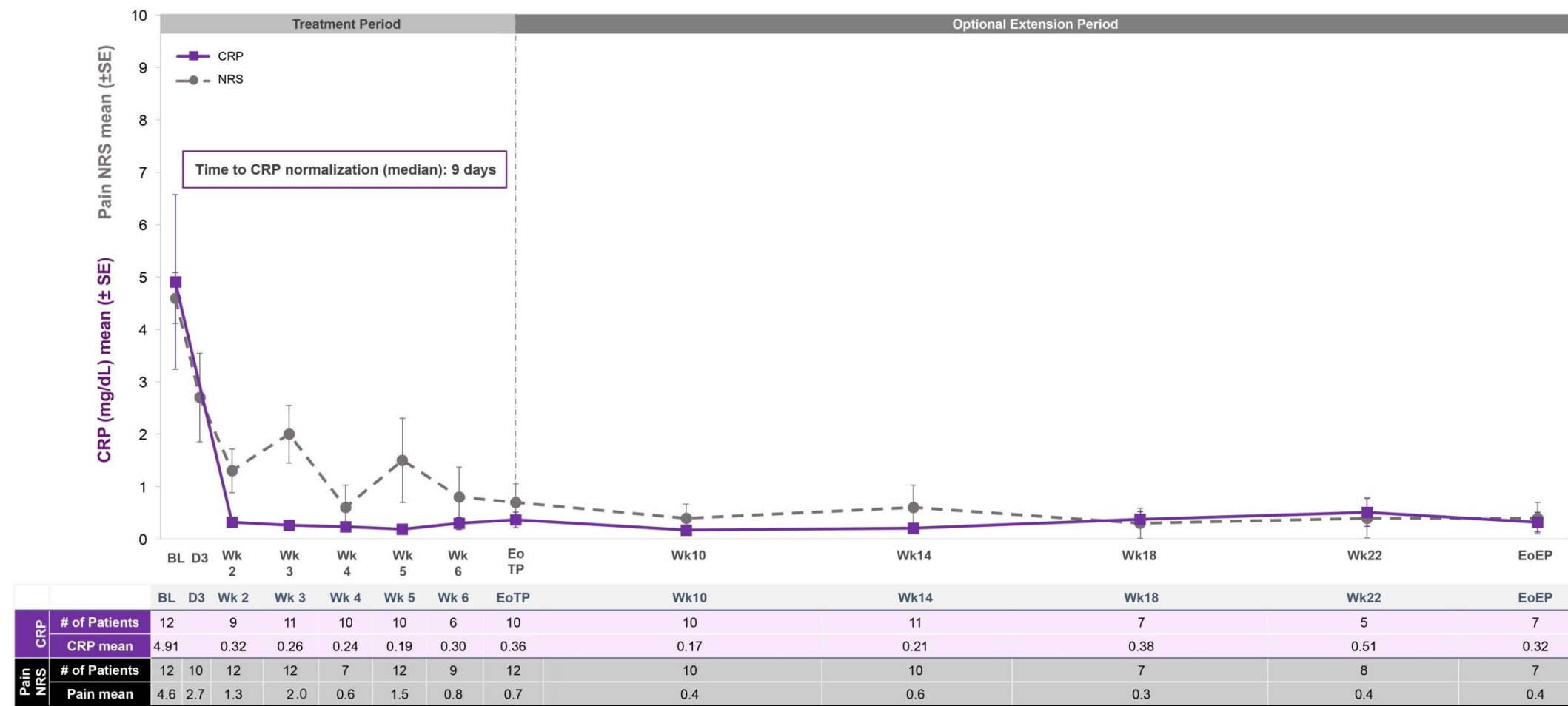
Parts 2 and 4 (symptomatic idiopathic RP with CRP ≤ 1 mg/dL and MRI inflammation; symptomatic PPS RP with CRP > 1 mg/dL)

- The 3 patients enrolled in Part 2 and the 1 patient enrolled in Part 4 completed the 6-week TP and showed a reduction in both CRP and pain
- Additionally, 2 of the patients enrolled in Part 2 completed 24 weeks of treatment and showed a persistent clinical response to rilonacept (see **Supplementary Figure 2**)

Parts 3 and 5 (asymptomatic CS-dependent idiopathic RP and PPS RP)

- Among the 6 patients enrolled in Part 3 and the 3 patients enrolled in Part 5 who completed the 6-week TP, pain scores and CRP levels remained low
- Additionally, 2 of the patients enrolled in Part 3 completed 24 weeks of treatment. For these patients, pain scores and CRP levels remained low while CS were tapered and discontinued (see **Supplementary Figure 2**)

Figure 4. Rapid and Sustained Reductions in NRS Scores (Pain) and CRP Levels After the First Dose (Part 1)



CRP, C-reactive protein; NRS, numeric rating scale; BL, baseline; D, day; Wk, week; EoTP, end of treatment period; EoEP, end of extension period.

Results: QOL

Quality of Life

- Increased PROMIS scores reflect improvement in quality of life with rilonacept treatment (**Table 2**)
 - At baseline, mean scores across Parts 1 to 5 were below 50, which is the mean score for the general US population⁶
 - During rilonacept treatment, increases in Global Physical Health and Global Mental Health were observed, with mean scores for both instruments increasing to above 50 for patients in Parts 1 and 2 at the end of the TP (visit 7) and at the end of the EP
 - Increases in scores were also observed in patients in Part 3, with no or minimal changes in Parts 4 and 5

Table 2. Rilonacept Improved Quality of Life as Assessed by PROMIS Questionnaire

Domain	Part 1 (n=12)	Part 2 (n=3)	Part 3 (n=6)	Part 4 (n=1)	Part 5 (n=3)
Global Physical Health, mean (SD)					
Baseline	41.3 (8.6)	36.2 (12.1)	43.7 (6.5)	34.9	42.3 (0.0)
End of TP (visit 7)	51.0 (8.1)	57.7 (0.0)	45.2 (4.8)	42.3	44.0 (1.5)
Final visit	50.5 (7.2)	58.0 (5.5)	42.2 (21.9)	N/A	N/A
Global Mental Health, mean (SD)					
Baseline	46.8 (9.5)	41.4 (14.2)	47.7 (9.2)	31.3	43.5 (0.0)
End of TP (visit 7)	50.9 (10.6)	56.2 (4.0)	49.3 (6.2)	28.4	45.1 (2.8)
Final visit	51.6 (10.6)	63.3 (6.1)	48.6 (10.5)	N/A	N/A

PROMIS, Patient-Reported Outcomes Measurement Information System; TP, treatment period.
N/A: not available; corresponding data collection is ongoing.

Results: Concomitant Medications

Changes in Concomitant Corticosteroids for RP During the Study

- 15/25 patients received CS at baseline; of these 15 patients, 5 completed the EP and tapered and subsequently discontinued CS:
 - 1 patient discontinued CS early during the TP and remained off CS throughout the study
 - 4 additional patients discontinued CS in the EP (2 in Part 1 and 2 in Part 3)
 - Refer to the Supplemental material for additional details on other concomitant pericarditis medications

Results: Case Study: Treatment — Retreatment with Rilonacept

- One Part 1 patient, who completed the 6-week base TP and the 18-week EP (symptom-free, normalized CRP), experienced recurrence of pericarditis symptoms requiring addition of celecoxib approximately 8 weeks after completing rilonacept treatment.
- The patient subsequently experienced a frank recurrence of pericarditis with tamponade physiology and re-enrolled into the study, resulting in rapid reductions in CRP and pericardial pain after re-initiation of rilonacept treatment.
- Rilonacept was well tolerated. Refer to the Supplemental material for additional case details.

Results: Safety

- Overview of AEs (**Table 3**)
 - The majority of AEs were mild
- There were 2 serious treatment-emergent AEs reported in Part 1, both of which resolved
 - 1 patient with skin abscess deemed possibly related to study drug discontinued rilonacept treatment
 - 1 patient with atypical chest pain not related to study drug continued rilonacept treatment
- AEs observed with rilonacept treatment on top of background pericarditis therapies are consistent with the known safety profile of rilonacept
- The most common AEs were observed in the general disorders and administration site conditions (injection site reactions), infections and infestations, and musculoskeletal and connective tissue disorders classes (**Table 4**) (see **Supplementary Tables 2 and 3**)

Table 3. Overview of Adverse Events

	Part 1 (n=12)	Total (N=25)
Patients with ≥1 AE, n (%)	12 (100.0)	23 (92.0)
Patients with ≥1 TEAE, n (%)	12 (100.0)	23 (92.0)
Patients with ≥1 treatment-related TEAE, n (%)	9 (75.0)	17 (68.0)
Patients with ≥1 serious TEAE, n (%)	2 (16.7)	2 (8.0)
Patients with ≥1 treatment-related serious TEAE, n (%)	1 (8.3)	1 (4.0)
Patients with ≥1 TEAE leading to treatment discontinuation, n (%)	1 (8.3)	1 (4.0)
Patients with ≥1 TEAE leading to death, n (%)	0	0
Patients with TEAEs by severity, n (%)		
Mild	9 (75.0)	18 (72.0)
Moderate	2 (16.7)	4 (16.0)
Severe	1 (8.3)	1 (4.0)

AE, adverse event; TEAE, treatment-emergent adverse event.

Table 4. Summary of AEs by System Organ Class

System Organ Class	Part 1 (n=12)	Total (N=25)
General disorders and administration site conditions, n (%)	6 (50.0)	15 (60.0)
Infections and infestations, n (%)	5 (41.7)	7 (28.0)
Musculoskeletal and connective tissue disorders, n (%)	3 (25.0)	7 (28.0)
Gastrointestinal disorders, n (%)	6 (50.0)	6 (24.0)
Investigations, n (%)	2 (16.7)	6 (24.0)
Respiratory, thoracic, and mediastinal disorders, n (%)	0	3 (12.0)
Ear and labyrinth disorders, n (%)	2 (16.7)	2 (8.0)
Skin and subcutaneous tissue disorders, n (%)	0	2 (8.0)
Cardiac disorders, n (%)	0	1 (4.0)
Eye disorders, n (%)	1 (8.3)	1 (4.0)
Nervous system disorders, n (%)	1 (8.3)	1 (4.0)
Unspecified, n (%)	1 (8.3)	1 (4.0)

Results: Lipid Changes During Rilonacept Treatment

- Increases in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were observed in patients treated with rilonacept (refer to Supplemental material)
- Chronic inflammation alters lipid level metabolism, resulting in decreases in HDL-C and LDL-C⁷
- Treatment of the underlying inflammatory condition leads to elevations in these lipid parameters⁷ (see **Supplementary Table 4**)

Conclusions

- Data from this ongoing open-label study of rilonacept treatment in RP show
 - Rapid and sustained clinically meaningful reductions in pain scores and CRP levels as early as after the first rilonacept administration
 - Resolution of pericarditis manifestations, including pericardial rub, ECG changes, and pericardial effusion
 - Improved quality of life measured by Global Physical and Mental Health domain scores on the PROMIS Questionnaire
 - Feasibility to discontinue CS without pericarditis exacerbation
- AEs observed to date are consistent with the known safety profile of rilonacept; injection site reactions were the most common AEs; all were mild and transient
- The study is ongoing, and patient follow-up continues
- Interpretation of efficacy and safety outcomes is limited by small number of patients in each study part and open-label study design
- **Results from this study informed the design of RHAPSODY, an ongoing, double-blind, placebo-controlled randomized withdrawal (RW) Phase 3 pivotal study with an open-label extension, intended to evaluate the efficacy and safety of rilonacept treatment in patients with recurrent pericarditis**

References

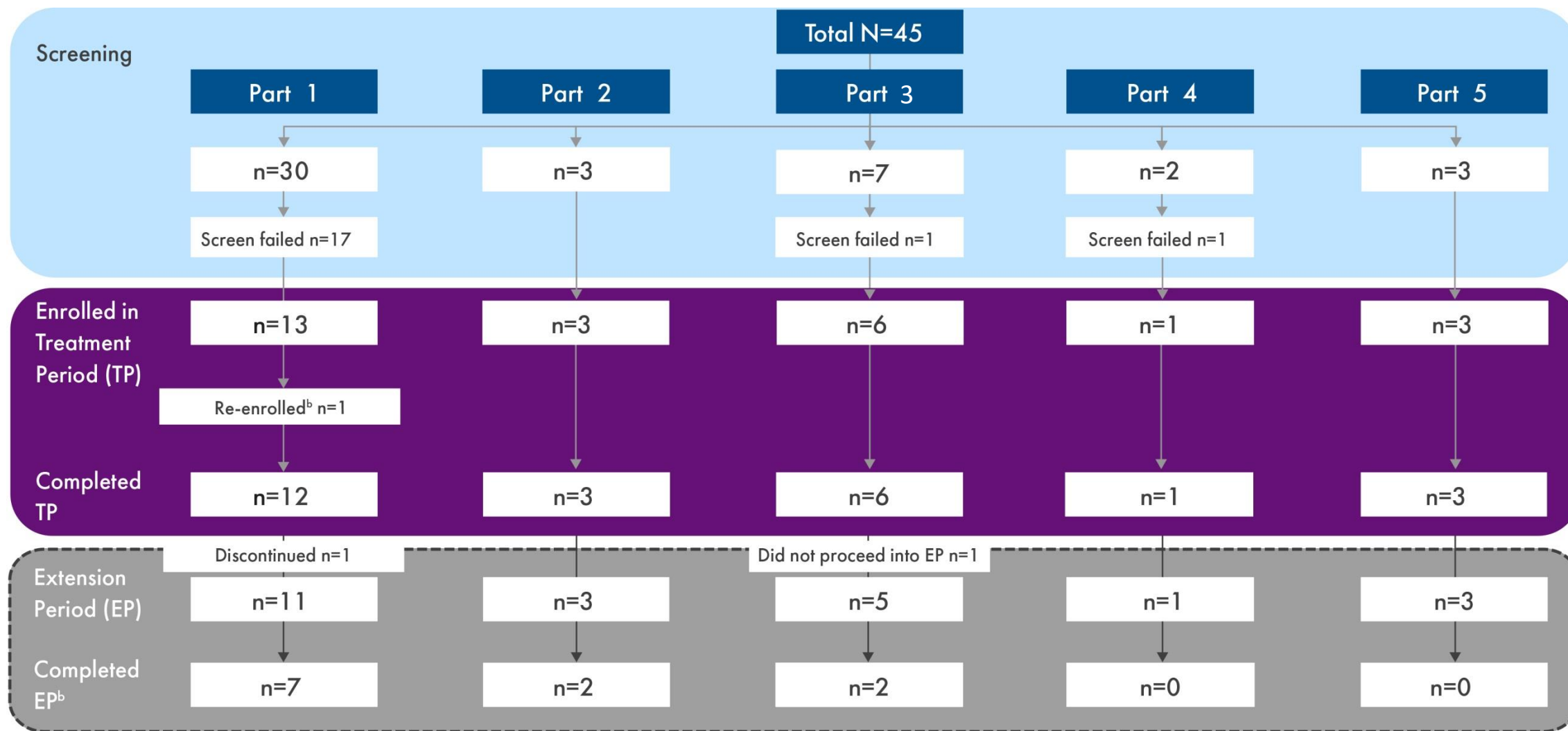
1. Adler Y, et al. *Eur Heart J*. 2015;36:2921-64.
2. Imazio M. *Rev Esp Cardiol*. 2014;67:345-8.
3. Lilly LS. *Circulation*. 2013;127:1723-6.
4. Brucato A, et al. *Int Emerg Med*. 2018;13(6):839-44.
5. Dinarello CA, et al. *Nat Rev Drug Discov*. 2012;11:633-52.
6. Hays RD, et al. *Qual Life Res*. 2009;18:873-80.
7. Feingold K, Grunfeld C. NCBI Bookshelf; January 8, 2019.

Disclosures

This study is being sponsored by Kiniksa Pharmaceuticals, Ltd.
Rilonacept is manufactured by Regeneron Pharmaceuticals, Inc.
Medical writing assistance was provided by Peloton Advantage, LLC, an OPEN Health company, funded by Kiniksa Pharmaceuticals, Ltd.

Supplemental Information

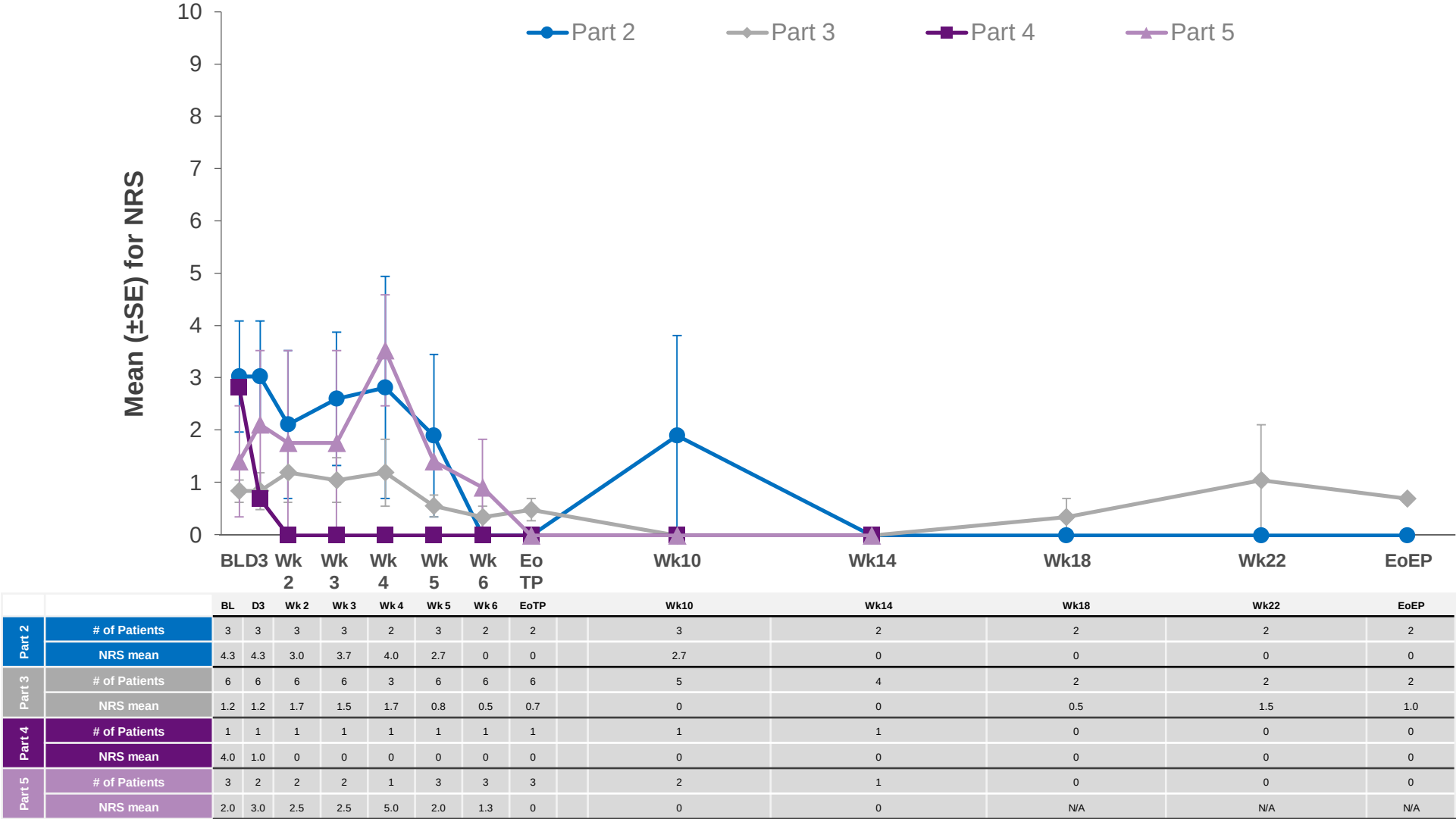
Supplementary Figure 1. Patient Disposition^a



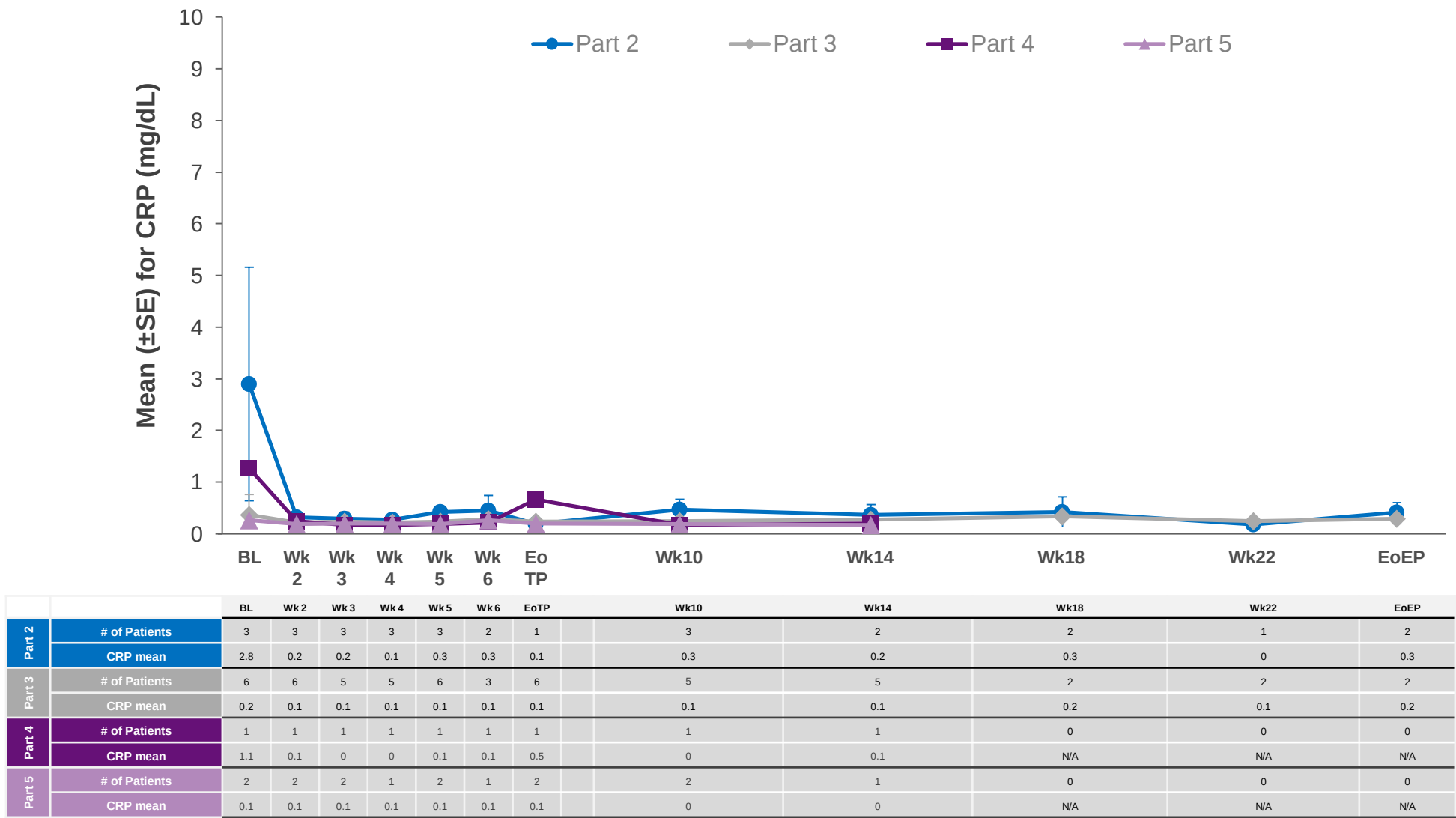
^aAs of January 23, 2019.

^bOne patient participated in the study twice (N=26); however, data are reported for 25 unique patients.

Supplementary Figure 2. Pain NRS Scores Levels in Parts 2, 3, 4, and 5



Supplementary Figure 2. CRP Levels in Parts 2, 3, 4, and 5



Supplementary Table 1. Treatment with Rilonaccept Resulted in Resolution of Pericardial Rub, ECG Changes, and Pericardial Effusion on Echocardiography

Time Point	Part 1 n/N (%)	Part 2 n/N (%)	Part 3 n/N (%)	Part 4 n/N (%)	Part 5 n/N (%)
Baseline					
Widespread ST elevation	2/12 (16.7)	0/3	0/6	0/1	0/3
PR depression	3/12 (25.0)	0/3	0/6	0/1	0/3
Pericardial rub	2/12 (16.7)	0/3	0/6	0/1	0/2
Fever	0/12	0/3	0/6	0/1	0/3
Pericardial effusion on ECHO	7/12 (58.3)	0/3	2/6 (33.3)	0/1	0/2
End of TP (visit 7)					
Widespread ST elevation	0/12	0/2	0/6	0/1	0/3
PR depression	1/12 (8.3)	0/2	0/6	0/1	0/3
Pericardial rub	0/11	0/2	0/6	0/1	0/3
Fever	0/12	0/2	0/6	0/1	0/3
Pericardial effusion on ECHO	1/12 (8.3)	0/2	1/6 (16.7)	0/1	0/3
Final visit					
Widespread ST elevation	0/7	0/2	0/2	0/0	0/0
PR depression	0/7	0/2	0/2	0/0	0/0
Pericardial rub	0/7	0/2	0/2	0/0	0/0
Fever	0/7	0/2	0/2	0/0	0/0
Pericardial effusion on ECHO	0/7	0/1	0/2	0/0	0/0

ECHO, echocardiography; TP, treatment period.

Changes in Concomitant Medications for Pericarditis During the EP (in 11 Patients Who Completed the EP):

- 4/4 patients tapered (2 in Part 1 and 2 in Part 3) and subsequently discontinued CS in the EP
- 3/3 patients discontinued NSAIDs in the EP (1 each in Parts 1, 2, and 3); 1 patient (Part 1) in the EP was prescribed an NSAID empirically after stopping CS
- 2/8 patients (1 each in Parts 1 and 2) discontinued colchicine in the EP

Supplementary Table 2. Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term ^a	Part 1 (n=12)	Part 2 (n=3)	Part 3 (n=6)	Part 4 (n=1)	Part 5 (n=3)	Total (N=25)
Number of subjects with at least 1 TEAE	12 (100.0)	3 (100.0)	4 (66.7)	1 (100.0)	3 (100.0)	23 (92.0)
Cardiac disorders	0	0	1 (16.7)	0	0	1 (4.0)
Cardiac discomfort	0	0	1 (16.7)	0	0	1 (4.0)
Pericarditis	0	0	1 (16.7)	0	0	1 (4.0)
Ear and labyrinth disorders	2 (16.7)	0	0	0	0	2 (8.0)
Vertigo	1 (8.3)	0	0	0	0	1 (4.0)
Vertigo positional	1 (8.3)	0	0	0	0	1 (4.0)
Eye disorders	1 (8.3)	0	0	0	0	1 (4.0)
Dry eye	1 (8.3)	0	0	0	0	1 (4.0)
Gastrointestinal disorders	6 (50.0)	0	0	0	0	6 (24.0)
Diarrhea	3 (25.0)	0	0	0	0	3 (12.0)
Dyspepsia	1 (8.3)	0	0	0	0	1 (4.0)
Hemorrhoids	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)
General disorders and administration site conditions	6 (50.0)	2 (66.7)	3 (50.0)	1 (100.0)	3 (100.0)	15 (60.0)
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)
Chest pain	0	0	0	0	1 (33.3)	1 (4.0)
Fatigue	0	0	1 (16.7)	0	0	1 (4.0)

Note: Patients are counted only once within each system organ class and preferred term.

^aAll adverse event terms are coded using MedDRA dictionary version 20.1.

^bPatient had 2 AEs, uncoded as of January 23, 2019: tubal ligation, and drainage at tubal ligation incision site.

Supplementary Table 2. Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term ^a	Part 1 (n=12)	Part 2 (n=3)	Part 3 (n=6)	Part 4 (n=1)	Part 5 (n=3)	Total (N=25)
General disorders and administration site conditions (cont'd)	6 (50.0)	2 (66.7)	3 (50.0)	1 (100.0)	3 (100.0)	15 (60.0)
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 joint warmth	1 (8.3)	0	0	0	0	1 (4.0)
Injection site pain	1 (8.3)	0	1 (16.7)	0	0	2 (8.0)
Injection site reaction	1 (8.3)	0	2 (33.3)	1 (100.0)	2 (66.7)	6 (24.0)
Non-cardiac chest pain	1 (8.3)	0	0	0	0	1 (4.0)
Peripheral swelling	0	1 (33.3)	0	0	1 (33.3)	2 (8.0)
Pyrexia	1 (8.3)	0	0	0	0	1 (4.0)
Infections and infestations	5 (41.7)	1 (33.3)	1 (16.7)	0	0	7 (28.0)
Cellulitis	2 (16.7)	0	0	0	0	2 (8.0)
Nasopharyngitis	2 (16.7)	0	1 (16.7)	0	0	3 (12.0)
Sinusitis	0	1 (33.3)	0	0	0	1 (4.0)
Subcutaneous abscess	1 (8.3)	0	0	0	0	1 (4.0)
Urinary tract infection	1 (8.3)	0	0	0	0	1 (4.0)
Investigations	2 (16.7)	0	3 (50.0)	1 (100.0)	0	6 (24.0)
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)
Blood cholesterol increased	1 (8.3)	0	1 (16.7)	0	0	2 (8.0)
Blood creatine phosphokinase increased	1 (8.3)	0	0	1 (100.0)	0	2 (8.0)
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)
Liver function test increased	2 (16.7)	0	0	0	0	2 (8.0)

Supplementary Table 2. Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term ^a	Part 1 (n=12)	Part 2 (n=3)	Part 3 (n=6)	Part 4 (n=1)	Part 5 (n=3)	Total (N=25)
Musculoskeletal and connective tissue disorders	3 (25.0)	0	3 (50.0)	1 (100.0)	0	7 (28.0)
Arthralgia	0	0	1 (16.7)	0	0	1 (4.0)
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 pain	1 (8.3)	0	1 (16.7)	0	0	2 (8.0)
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)
Nervous system disorders	1 (8.3)	0	0	0	0	1 (4.0)
Headache	1 (8.3)	0	0	0	0	1 (4.0)
Respiratory, thoracic, and mediastinal disorders	0	1 (33.3)	2 (33.3)	0	0	3 (12.0)
Cough	0	0	1 (16.7)	0	0	1 (4.0)
Dyspnea	0	0	2 (33.3)	0	0	2 (8.0)
Painful respiration	0	0	1 (16.7)	0	0	1 (4.0)
Productive cough	0	1 (33.3)	0	0	0	1 (4.0)
Skin and subcutaneous tissue disorders	0	0	0	1 (100.0)	1 (33.3)	2 (8.0)
Erythema	0	0	0	0	1 (33.3)	1 (4.0)
Hyperkeratosis	0	0	0	1 (100.0)	0	1 (4.0)
Unspecified	1 (8.3)	0	0	0	0	1 (4.0)
Uncoded ^b	1 (8.3)	0	0	0	0	1 (4.0)

Note: Patients are counted only once within each system organ class and preferred term.

^aAll adverse event terms are coded using MedDRA dictionary version 20.1.

^bPatient had 2 AEs, uncoded as of January 23, 2019: tubal ligation, and drainage at tubal ligation incision site.

Supplementary Table 3. Overview of Adverse Events by Study Parts

	Part 1 (n=12)	Part 2 (n=3)	Part 3 (n=6)	Part 4 (n=1)	Part 5 (n=3)	Total (N=25)
Patients with ≥1 AE, n (%)	12 (100.0)	3 (100.0)	4 (66.7)	1 (100.0)	3 (100.0)	23 (92.0)
Patients with ≥1 TEAE, n (%)	12 (100.0)	3 (100.0)	4 (66.7)	1 (100.0)	3 (100.0)	23 (92.0)
Patients with ≥1 treatment-related TEAE, n (%)	9 (75.0)	2 (66.7)	3 (50.0)	1 (100.0)	2 (66.7)	17 (68.0)
Patients with ≥1 serious TEAE, n (%)	2 (16.7)	0	0	0	0	2 (8.0)
Patients with ≥1 treatment-related serious TEAE, n (%)	1 (8.3)	0	0	0	0	1 (4.0)
Patients with ≥1 TEAE leading to treatment discontinuation, n (%)	1 (8.3)	0	0	0	0	1 (4.0)
Patients with ≥1 TEAE leading to death, n (%)	0	0	0	0	0	0
Patients with TEAEs by severity, n (%)						
Mild	9 (75.0)	3 (100.0)	2 (33.3)	1 (100.0)	3 (100.0)	18 (72.0)
Moderate	2 (16.7)	0	2 (33.3)	0	0	4 (16.0)
Severe	1 (8.3)	0	0	0	0	1 (4.0)

AE, adverse event; TEAE, treatment-emergent adverse event.

Supplementary Table 4. Summary of Lipid Changes^a

Lipid	Part 1 (n=12)	Part 2 (n=3)	Part 3 (n=6)	Part 4 (n=1)	Part 5 (n=3)	Total (N=25)
Cholesterol (mg/dL)						
Mean at baseline [n]	172.2 [10]	256.0 [1]	203.8 [5]	[0]	174.5 [2]	185.9 [18]
Mean at end of TP (visit 7) [n]	197.5 [4]	[0]	218.0 [3]	[0]	133.0 [1]	197.1 [8]
Mean at final visit [n]	206.9 [7]	265.5 [2]	243.0 [2]	[0]	[0]	224.1 [11]
HDL cholesterol (mg/dL)						
Mean at baseline [n]	45.8 [10]	64.0 [1]	55.6 [5]	[0]	50.0 [2]	50.0 [18]
Mean at end of TP (visit 7) [n]	60.3 [4]	[0]	71.3 [3]	[0]	39.0 [1]	61.8 [8]
Mean at final visit [n]	57.9 [7]	77.0 [2]	46.0 [2]	[0]	[0]	59.2 [11]
LDL cholesterol (mg/dL)						
Mean at baseline [n]	107.3 [10]	147.0 [1]	127.0 [5]	[0]	102.0 [2]	114.4 [18]
Mean at end of TP (visit 7) [n]	118.3 [4]	[0]	129.3 [3]	[0]	77.0 [1]	117.3 [8]
Mean at final visit [n]	126.4 [7]	165.0 [2]	181.5 [2]	[0]	[0]	143.5 [11]
Triglycerides (mg/dL)						
Mean at baseline [n]	119.8 [10]	130.0 [1]	156.4 [5]	[0]	172.0 [2]	136.3 [18]
Mean at end of TP (visit 7) [n]	150.3 [4]	[0]	146.3 [3]	[0]	136.0 [1]	147.0 [8]
Mean at final visit [n]	147.4 [7]	177.5 [2]	175.0 [2]	[0]	[0]	157.9 [11]

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aLipids were measured under fasting and nonfasting conditions.

Case Study: Treatment/Retreatment of RP With Rilonacept

- **Patient:** 50-year-old female with idiopathic pericarditis and 1 prior recurrence, enrolled in Part 1 during her third episode (pain NRS 6/10; CRP 8.85 mg/dL; pericardial effusion on echocardiography) while receiving colchicine 0.6 mg bid.
- **Pain and CRP Reduction During the Study:** Addition of rilonacept to colchicine background rapidly reduced pain (week 2 pain NRS 1/10; week 24 pain NRS 0/10), decreased CRP (week 2 CRP 0.66 mg/dL; week 24 CRP 0.09 mg/dL), and resolved pericardial effusion.
- **Safety:** Mild, transient injection site reactions occurred for 21 of 24 rilonacept injections.
- **After Completing the EP:** Approximately 8 weeks after rilonacept discontinuation, while continuing on colchicine 0.6 mg bid, the patient presented with pericarditis symptoms requiring addition of celecoxib 200 mg/day. Ten weeks later the patient developed frank pericarditis recurrence (pain NRS 7/10; CRP 23.1 mg/dL) and cardiac tamponade requiring pericardiocentesis. The patient was re-enrolled in the study.
- **Pain and CRP Normalized and Pericardial Effusion Resolved with Rilonacept Retreatment:** Rapid improvements in pain and CRP were observed after the first rilonacept administration (week 2 pain NRS 0/10; CRP 0.57 mg/dL). At the week 7 visit, NRS pain was 1/10, CRP was 0.09 mg/dL, and there was no evidence of pericardial effusion on echocardiography. At the last study evaluation available (1 month EP), NRS pain was 0/10 and CRP remained normal (0.08 mg/dL).
- **Safety:** Three mild, transient injection site reactions occurred out of 11 rilonacept injections; the patient also developed a mild AE of hypokalemia. Treatment was ongoing as of January 23, 2019 and the patient has received 1 month of EP rilonacept treatment.