Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Klein AL, Imazio M, Cremer P, et al. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. N Engl J Med 2021;384:31-41. DOI: 10.1056/NEJMoa2027892

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Supplement to:

Phase 3 Trial of Interleukin-1 Trap Rilonacept in Recurrent Pericarditis

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AutoCruitment identified recurrent pericarditis patients using their web-based technology, pre-screened patients for possibly eligibility, and were compensated by Kiniksa for their work on patient recruitment.

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Authors' Roles in the Study

Trial design: JFP, AK, MI, PC, AB, FF

Protocol Authorship: JFP, AW, FF

Selection of centers: JFP

Supervision/monitoring centers: AW, JFP, AP

Selection/enrollment of patients: AK, MI, PC, AB, AA, AI, ML, BSL, DL, SAL, SJN, AW

Evaluate patients during follow-up: AK, MI, PC, AB, AA, AI, ML, BSL, DL, SAL, SJN, AW

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Store trial data: FF

Data analysis: FF, AW, JFP, AK, MI

Interpretation of results: all authors

Writing manuscript: JFP, FF, AW, AK, MI

Editing/review of manuscript: all authors

Decision to submit manuscript for publication: all authors

Supplementary Methods

Pain Numerical Rating Scale

A similar pain assessment tool was used in the earlier Phase 2 clinical trial for rilonacept,[1] but the final numerical rating scale and eDiary platform deployed for the Phase 3 study had been further refined to (1) specify that the single-item questionnaire is assessing *pericarditis* pain over the past 24 hours and not pain in general), and (2) implement a daily diary assessment schedule (in Phase 2 the assessments were done on a weekly basis at the clinical site).

The structure of the response options are individual numbers for 0 to 10, with anchors defined for both extremes (0=no pain, and 10= pain as bad as it could be). Participants select a single number that represents the severity of their average pericarditis pain over the past 24 hours using an electronic data capture device. Qualitative research with patients with recurrent pericarditis was conducted to document that recurrent pericarditis patients understand and interpret the questionnaire as intended, and quantitative analyses have been conducted to evaluate the reliability, validity, and interpretability of the score generated from this daily diary pain assessment (based on data from Phase 3).

Patient Global Impression of Pericarditis Severity

This single-item global assessment was developed for the Phase 3 clinical trial of rilonacept. Participants were instructed to complete this questionnaire at each clinic visit to report on the severity of their current pericarditis symptoms (with scores ranging from 0 to 6 and with higher scores indicating greater severity of symptoms).

Response options were the following:

0=Absent: No symptoms

1=Minimal: Can be easily ignored without effort

2=Mild: Can be ignored with effort

3=Moderate: Cannot be ignored but does not influence my daily activities

4=Moderately severe: Cannot be ignored and occasionally limits my daily activities

5=Severe: Cannot be ignored and often limits my concentration on daily activities

6=Very severe: Cannot be ignored and markedly limits my daily activities.

Patient-Reported Outcome Measures: Qualitative and Quantitative Assessment

Development and Validation of Patient-Reported Outcome Measures in Recurrent Pericarditis.

A substantial body of literature documents the validation of the use of the pain numeric rating scales in various diseases[2, 3] The pericarditis pain numeric rating scale and patient global impression of change scale are instruments that are fit for purpose in recurrent pericarditis and contribute to the primary and major secondary end points of RHAPSODY. Robust qualitative and quantitative assessments have been conducted to assess the reliability, validity, reproducibility and interpretability of each instrument. Relevant clinical outcome assessment questionnaires used to support major end points in this Phase 3 clinical trial, following both industry best practices and FDA guidance to manufacturers on the use of patient-reported outcomes were developed.[4, 5, 6]

Content validity: the 11-point numerical rating scale was developed based on qualitative research activities that identified “pain” as most important and relevant to recurrent pericarditis (based on the peer reviewed literature for both adolescents and adults, clinical experts in the field of cardiology [N=3], and hybrid concept elicitation [CE]/cognitive debriefing [CD] interviews with adult patients with recurrent pericarditis [N=10] and evaluated to confirm that respondents could

easily read, understand, and provide a meaningful response (based on the hybrid CE/CD interviews with adult patients with recurrent pericarditis [N=10]). In addition, the patient general impression of pericarditis severity scale was developed to assess global symptom severity specific to recurrent pericarditis. Interviews with ten adults with a diagnosis of recurrent pericarditis confirmed the relevance of the single-item patient general impression of pericarditis severity scale questionnaire to assess overall symptom severity associated with recurrent pericarditis, as well as the readability and comprehensibility of the questionnaire.

Measurement properties: the measurement properties of the scores generated by the 11-point numerical rating scale and patient general impression of pericarditis severity scale were examined according to the Food and Drug Administration's Patient-Reported Outcomes Guidance,[6] using the Phase 3 clinical trial data. Data generated from the participants in the Phase 3 clinical trial at run-in Baseline, run-in Week 6, randomized-withdrawal Baseline, and randomized-withdrawal Weeks 8, 16, and 24 were used to evaluate the psychometric performance of the daily and weekly 11-point numerical rating scale scores and patient general impression of pericarditis severity scale scores.

Study sample characteristics: A total of 54 adult participants and two adolescent participants from the Phase 3 clinical trial were included in the analysis population to evaluate the reliability, validity, and interpretability of scores from the 11-point numerical rating scale and the patient general impression of pericarditis severity scale; mean age of the sample was 47.1 (SD=14.6) years, most were female (n=31, 55.4%), and identified their race as White (n=52, 92.9%).

Distribution of scores: at run-in Baseline, adult and adolescent participants had mean scores of 4.65 (2.68 SD) and 3.41 (1.88 SD) on the daily 11-point numerical rating scale and patient general impression of pericarditis severity scale, respectively. Respondents used the entire range

of the response scales to respond to items based on descriptive data at run-in Baseline for the 11-point numerical rating scale and patient general impression of pericarditis severity scale, with a range of 0-10 for the daily 11-point numerical rating scale, and 0-6 for the patient general impression of pericarditis severity scale.

Test-retest reliability: reliability results indicate that 11-point numerical rating scale daily and weekly scores met standard thresholds for acceptable internal consistency for stable participants in the randomized-withdrawal period from randomized-withdrawal Baseline to Week 8. However, reliability results were inconclusive for the patient general impression of pericarditis severity scale for stable participants in the randomized-withdrawal period, but interpretable in the run-in period (between run-in Week 6 and run-in Week 12/ randomized-withdrawal Baseline). Due to small sample size and restriction of range of the stable population consisting of mostly non-severe participants, these estimates should be considered the lower bounds of reliability (i.e., the current estimates may underrepresent the strength of the reliability of the 11-point numerical rating scale and patient general impression of pericarditis severity scale).

Construct-related validity: relationships between the supporting assessments and the 11-point numerical rating scale and patient general impression of pericarditis severity scale were consistent with the a priori hypotheses (based on conceptual overlap and whether the supporting assessment was a patient- or physician-reported assessment). Results generated from known-groups analysis at all timepoints demonstrated that the 11-point numerical rating scale and patient general impression of pericarditis severity scale scores were able to distinguish between clinically distinct groups based on the Physician Global Assessment of Pericarditis Activity (PGA-PA), 36-Item Short Form health survey, version 2 (SF-36v2®) bodily pain item (Item 7), and Five-level EQ-5D Questionnaire (EQ-5D-5L) pain/discomfort item at run-in Baseline and

randomized-withdrawal Baseline, and C-reactive protein (CRP) levels at run-in Baseline only.
Sensitivity to change: the correlations between change scores on supporting assessments and on the 11-point numerical rating scale and patient general impression of pericarditis severity scale were generally as expected, demonstrating responsiveness of the 11-point numerical rating scale and patient general impression of pericarditis severity scale scores in concert with scores from the EQ-5D-5L pain/discomfort item score, EQ-5D-5L usual activities domain, SF-36v2® Physical Component Summary (PCS), SF-36v2® Mental Component Summary (MCS), and SF-6D index. Due to restricted range of change scores for participants through randomized-withdrawal Week 24, sensitivity to change results should be interpreted with caution.
Findings: the findings from the psychometric evaluation demonstrated that the 11-point numerical rating scale and patient general impression of pericarditis severity scale produced scores that are reliable (although restricted range of scores due to the study design led to results that may underestimate the reliability of the scores), valid in terms of correlations with other assessments of pain and symptom severity (i.e., the target assessments measure the constructs they are intended to measure), and can distinguish between clinically distinct groups, and are sensitive to change over time.
Interpretation of scores: interpretations of scores produced by the 11-point numerical rating scale and patient general impression of pericarditis severity scale were examined according to the Food and Drug Administration's Patient-Reported Outcomes Guidance,[6] using the Phase 3 clinical trial. Distribution-based analyses, anchor-based analyses, and empirical cumulative distribution functions were conducted/generated to evaluate changes in the 11-point numerical rating scale and patient general impression of pericarditis severity scale scores, but due to the small sample size of the clinical trial and the study design causing a restricted range of scores

during the randomized-withdrawal timepoints used for efficacy, several planned analyses for the evaluation of interpretation of score change were not conducted or not easily interpretable. Based on an evaluation of equipercentile linking for the 11-point numerical rating scale only, a score of ≥2 would indicate mild to moderate pain for daily and weekly 11-point numerical rating scale; a score ≥7 would indicate severe pain for the daily 11-point numerical rating scale score. Daily scores for the 11-point numerical rating scale were evaluated and distribution-based estimates for between group differences were one to two points, and anchor-based estimates were between two to four points change. For the patient general impression of pericarditis severity scale, distribution-based estimates were also between one to two points, and anchor-based within-person change estimated were between two to three points. Empirical cumulative distribution functions and probability density functions for the 11-point numerical rating scale and patient general impression of pericarditis severity scale were also presented to specify the change score that optimally discriminates between each group defined by the anchors. These results along with the distribution of scores over the run-in and randomized-withdrawal time points, show that change on both the 11-point numerical rating scale and patient general impression of pericarditis severity scale represent resolution of pain and pericarditis symptom severity during the clinical trial.

Conclusion: as clinical outcome assessment tools are evaluable only in their specific context of use, the qualitative and quantitative evidence supports the 11-point numerical rating scale and patient general impression of pericarditis severity scale as fit for the purpose of evaluating the Phase 3 hypotheses that rilonacept impacts patient-reported recurrent pericarditis pain and overall severity of recurrent pericarditis symptoms among patients with recurrent pericarditis. This conclusion is supported by evidence of the content validity of the 11-point numerical rating

scale and patient general impression of pericarditis severity scale (i.e., the items measure concepts that are important and relevant to patients with recurrent pericarditis and do so in ways that respondents can understand and to which they can provide meaningful responses), measurement characteristics (i.e., the instrument generate scores that are reliable, valid, and sensitive to change), and interpretability (i.e., identified changes and maintenance in scores can be distinguished as meaningful from the perspective of the patient seeking treatment).

Use of Bailout Rilonacept for Pericarditis Recurrences

Patients with a pericarditis recurrence meeting bailout criteria (at least 1 day with pericarditis pain numerical rating scale ≥4 [with values ranging from 0 to 10 and with higher scores indicating greater pain severity] and one CRP level ≥1 mg/dL [within 7 days]) could receive open-label bailout rilonacept (including a loading dose) regardless of treatment assignment and sequential oral rescue therapy (sORT: analgesics, then NSAIDs, then colchicine), if needed. If bailout criteria were not met, patients continued blinded study drug until bailout criteria were met or until the end of the randomized-withdrawal period, with sORT added per investigator's discretion.

Definition/Classification of Adverse Events

The Investigator was responsible for reporting all adverse events observed or reported during the study, regardless of relationship to study drug or clinical significance. An adverse event was defined as any untoward medical occurrence in a patient, including signs, symptoms, or disease temporally associated with the use of study drug. Adverse events also included worsening (change in frequency or intensity) of pre-existing conditions and abnormal laboratory findings

considered by the Investigator to be clinically significant. Treatment-emergent adverse events (TEAEs) were adverse events that started or increased in severity during the period between the first dose of rilonacept in the run-in period and the last visit of the randomized-withdrawal period, for patients who did not discontinue the trial regimen and who transitioned to the open-label extension. For patients who discontinued rilonacept during the run-in period or who discontinued rilonacept or placebo during the randomized-withdrawal period or at the last visit of the randomized-withdrawal period (i.e., did not continue into the long-term extension), data on adverse events continued to be collected for 6 weeks after the last dose of rilonacept or placebo. A serious adverse event was defined as resulting in death, life-threatening, requiring in-patient hospitalization, resulting in persistent or significant disability/incapacity, congenital anomaly/birth defect, or an important medical event. Intensity of adverse event was recorded as mild (easily tolerated, does not interfere with normal daily activity or require intervention), moderate (causes some interference with daily activities requiring minimal, local, or noninvasive intervention), or severe (limiting or halting daily activities; hospitalization or prolonged hospitalization). Adverse events reported during the randomized-withdrawal period are summarized in four categories: rilonacept before bailout, placebo before bailout, rilonacept including bailout, and placebo including bailout. Events during the run-in and totaled for the overall study are also reported.

Statistical Analysis

Stratification

When an analysis was to be stratified, and if a stratum had five or fewer events of interest in a log-rank test or the same response in all patients in a CMH test, the strata would be pooled. If the

same situation still existed, the analysis would be done without stratification.

Missing data

Since the analysis of the primary efficacy end point was event-driven, not all ITT patients would have been able to reach Week 16 when the data were mature for the analysis of the primary efficacy end point. The analysis of major secondary end points was based on the Week 16 ITT analysis set and included all patients who underwent randomization no less than 16 weeks before the data cutoff, including patients who discontinued treatment before Week 16. Patients who received bailout prior to Week 16 were not eligible for the secondary efficacy end point analysis. Missing data due to early discontinuation or lost to follow-up were considered as not meeting the end point criteria. Weekly average of numerical rating scale was calculated based on a 7-day increment after the first dose day. If four or more daily numerical rating scale scores were missing, weekly averages were set to missing.

Safety statistical analysis

Patients who received at least one dose of study drug were included in the safety analysis set, which was used for reporting of number and percentage of patients with treatment-emergent adverse events (TEAEs). Most frequently occurring TEAEs (≥ 5%) are provided (Table S9). For end points not adjusted for multiplicity, the widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects within subgroups or for secondary outcomes.

Supplementary Results

Primary Efficacy End Point

There were too few recurrence events in the rilonacept group during the randomized-withdrawal period to allow for the median time to first adjudicated recurrence to be calculated. The median time to first adjudicated recurrence in the placebo group was 8.6 weeks (95% CI, 4.0 to 11.7). Rilonacept led to a lower risk of pericarditis recurrence than placebo (hazard ratio, 0.04; 95% CI, 0.01 to 0.18; log-rank P<0.0001 [rounded in the manuscript to "<0.001"]).

Primary Efficacy End Point in Rilonacept Recipients

The two recurrence events in the rilonacept group were associated with temporary interruptions of the trial-drug regimen, of one to three weekly doses; one interruption was due to poor adherence to the regimen, and the other was due to an adverse event, myalgia, which resolved. In the rilonacept group, 1 of the 2 patients who had a pericarditis recurrence event received bailout rilonacept.

Primary Efficacy End Point in Placebo Recipients

The recurrence time-course in the placebo group was consistent with the expected washout pharmacokinetics of once-weekly rilonacept at steady state. Almost half of the patients in the placebo group who experienced a recurrence event did so within the first month after randomization, underscoring the tenacity of recurrent pericarditis.

Major Secondary Efficacy End Points at Week 16 of the Randomized-Withdrawal Period

Clinical response was maintained in 81% (17/21) of patients in the rilonacept group versus 20% (4/20) in the placebo group (P=0.0002 [rounded in manuscript to "<0.001"]; **Table 2**). 81%

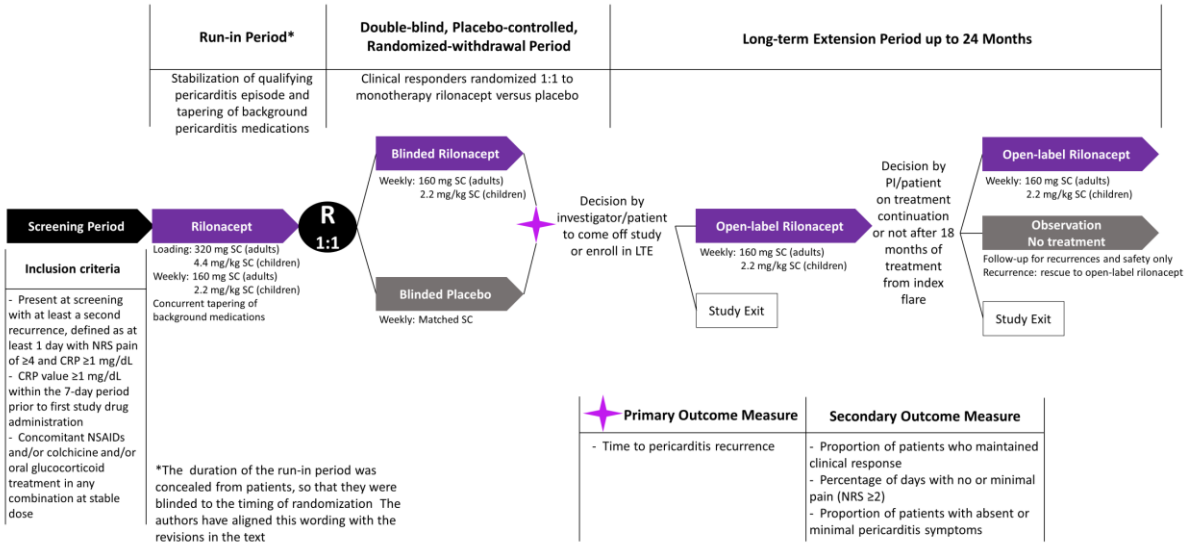
(17/21) of patients in the rilonacept group had no or minimal pericarditis symptoms on a patient-reported global impression of pericarditis severity scale versus 25% (5/20) of patients in the placebo group (P=0.0006 [rounded in manuscript to "<0.001"]). Patients in the rilonacept group also reported no or minimal pain for 97.7% (least squares mean) of randomized-withdrawal trial days through Week 16 versus 45.9% of trial days for patients in the placebo group (P<0.0001 [rounded in manuscript to "<0.001"]). In prespecified sensitivity analyses at Week 8 and Week 24, consistent results were observed (all highly statistically significant) (Tables S4 and S5).

Primary Efficacy End Point Outcome in Patients With and Without Oral Glucocorticoid Use at Baseline

The median (95% CI; N) time to the first adjudicated pericarditis recurrence event in patients with oral glucocorticoid (GC) use at baseline in patients in the rilonacept group could not be calculated, as there were too few recurrence events in these patients (12.1, NE; 13); time to the first adjudicated recurrence in the placebo group was 4.0 (2.6, 6.6; 14) weeks. In patients without oral GC use at baseline, the median time to the first adjudicated pericarditis recurrence event in patients in the rilonacept group could not be calculated (27.7, NE; 17) because there were too few recurrence events; time to the first adjudicated recurrence in patients in the placebo group was 10.7 (5.3, 19.6; 17) weeks.

Supplementary Figures

Figure S1. RHAPSODY -- Study Design.



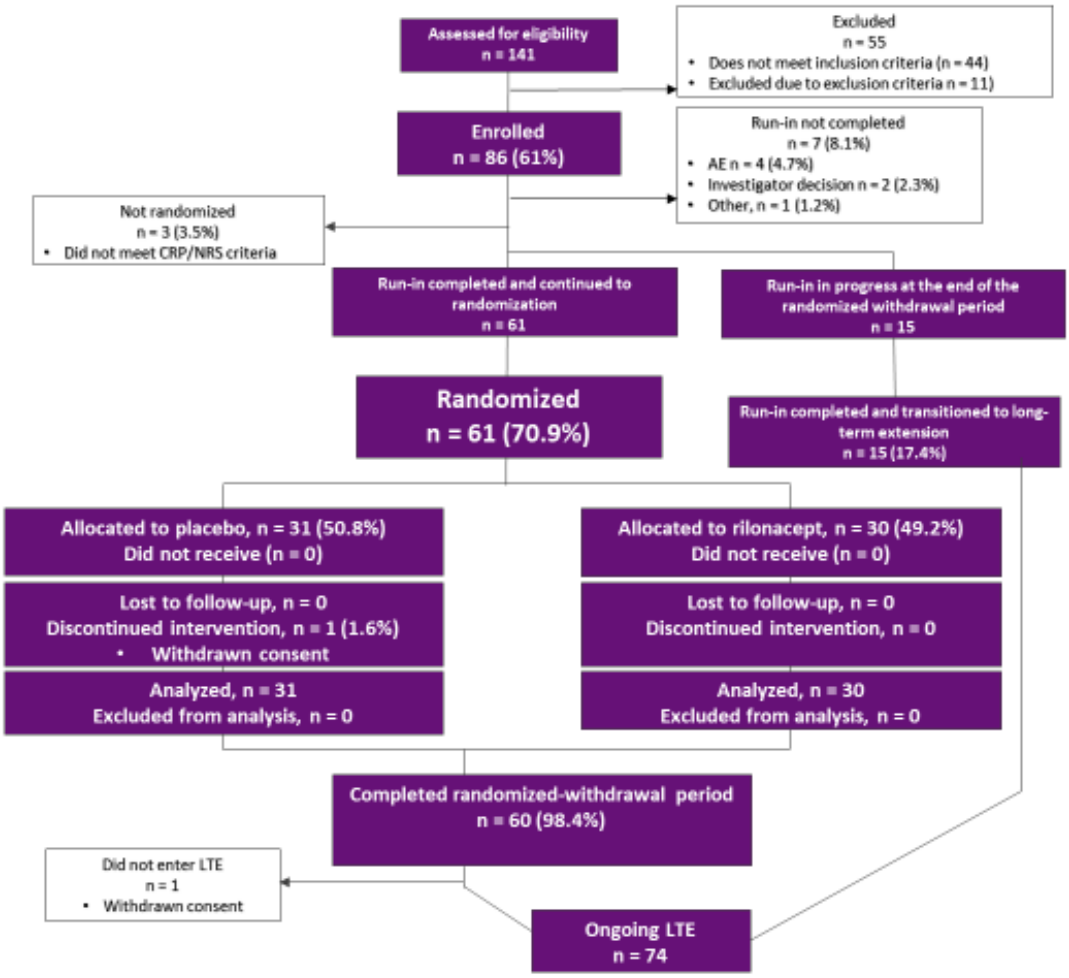
Design of the screening, run-in, randomized-withdrawal, and long-term extension periods of RHAPSODY. [7]

*The duration of the run-in period was concealed from the patients so that they would be unaware of the timing of randomization

†Index episode corresponds to the last pericarditis recurrence reported by the patient (i.e. Day 1/BL for the qualifying recurrence if no other recurrences were reported during the randomized-withdrawal period; otherwise, latest post-baseline recurrence during the randomized-withdrawal period)

AEs, adverse events; CRP, C-reactive protein; GC, glucocorticoid; LTE, long-term extension; NRS, numerical rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneously;

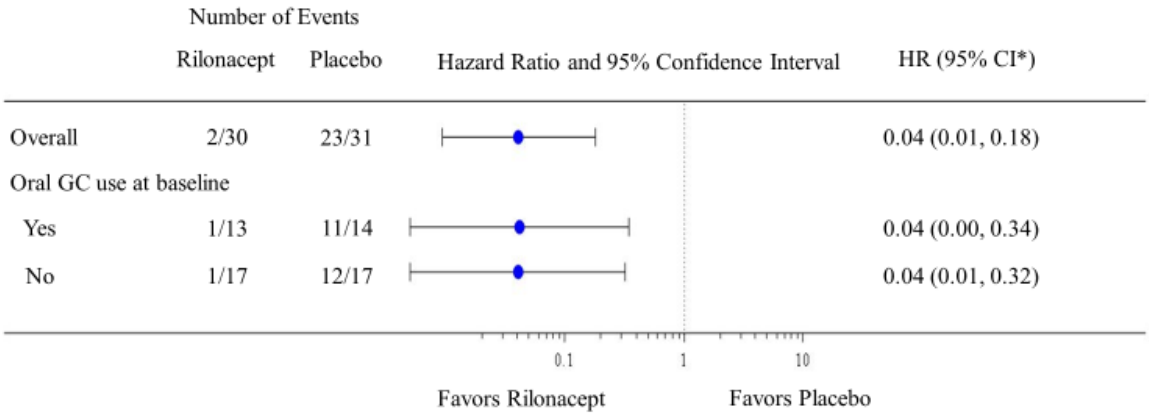
Figure S2. CONSORT Diagram



Patient disposition, including assessment, enrollment, randomization, analysis, and study period completion.

AEs, adverse events; CRP, C-reactive protein; LTE, long-term extension; NRS, numerical rating scale;

Figure S3. Forest Plot for Time to First Pericarditis Recurrence Based on CEC Adjudication



Hazard ratio and 95% CI in the overall study population and by use of oral glucocorticoids at baseline.

* The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects within subgroups or for secondary outcomes

CI, confidence interval; GC, glucocorticoid; HR, hazard ratio

Supplementary Tables

Table S1. Patient Eligibility Criteria.

Inclusion Criteria
• Provided informed written consent • Aged ≥12 yr; body weight ≥23.6 kg • Recurrent pericarditis diagnosis • ≥1 pericarditis episode prior to screening meeting ≥2 criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation/PR-segment depression, or new/worsening pericardial effusion • Presented with at least second pericarditis recurrence at screening and ≥1 day with numerical rating scale pain score ≥4 and C-reactive protein ≥1 mg/dL, within ≤7 days of each other and ≤7 days run-in baseline • If using nonsteroidal anti-inflammatory drugs and/or colchicine and/or glucocorticoids, doses are stable or not increased for ≥3 days before study drug administration • If using nonsteroidal anti-inflammatory drugs and/or colchicine and/or glucocorticoids at run-in baseline, will taper and discontinue drugs by the end of Week 10 of the Run-In period • Females: postmenopausal, incapable of pregnancy, permanently sterile, or using contraception • Sexually active males: documented vasectomy or using contraception; will not donate sperm until 3 months after last study drug administration • Up to date with all immunizations • Will adequately maintain a daily diary • Will adhere to study visit schedule and comply with other protocol requirements • Will refrain from new, major lifestyle changes that may affect pericarditis symptoms until end of randomized-withdrawal period
Exclusion Criteria
• Pericarditis secondary to tuberculosis, post-thoracic blunt trauma, myocarditis, systemic autoimmune diseases (excluding Still's disease), or neoplastic, purulent, or radiation etiologies • Pregnant, breastfeeding, or planning pregnancy/fathering child during study or ≤3 months after receiving last study drug

• History of immunosuppression, including positive human immunodeficiency virus test results

• Currently receiving glucocorticoid >60 mg/d (adults) or >0.5 mg/kg/d (pediatric patients ≥12 to <18 yr)

• History of cytotoxic drugs

• History of receiving agents that deplete B or T cells

• History of systemic immunomodulatory agents (excluding glucocorticoids) prior to run-in baseline within following time frames:

- ≤24 weeks: azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, mercaptopurine
- ≤12 weeks: TNFα inhibitors, interleukin-6 inhibitors, janus-activating kinase inhibitors, canakinumab (not discontinued for safety, excluding local injection site reactions)
- ≤6 weeks: rilonacept (not discontinued due to lack of efficacy or safety issues)
- ≤2 weeks: methotrexate
- ≤5 days: anakinra (not discontinued due to lack of efficacy or safety issues, excluding local injection site reactions)

• History of myeloproliferative disorder

• History of demyelinating disease or symptoms suggesting multiple sclerosis

• Meets tuberculosis criteria:

- History of active tuberculosis prior to screening, OR
- History of latent tuberculosis not adequately treated before screening, OR
- Signs/symptoms suggestive of active tuberculosis, OR
- Recent close contact with active tuberculosis patient, OR
- Positive/indeterminate interferon gamma release assay test results or results from another positive tuberculosis test at screening

• Posterior-anterior X-ray with evidence of malignancy/abnormality consistent with prior/active TB infection at screening or ≤12 weeks before first study drug administration

• Received live vaccine ≤12 weeks screening or expected to receive live vaccine during study or ≤12 weeks after last study drug administration

• History of positive/intermediate results for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening

• Estimated glomerular filtration rate <30 mL/min

• History of malignancy of any organ system ≤5 years screening (other than successfully treated non-metastatic cutaneous squamous cell carcinoma or basal cell carcinoma and/or localized carcinoma in situ of cervix)

• Known/suspected current active infection or history of chronic/recurrent infectious disease

• Serious infection history, admitted to hospital for infection, treated with oral antibiotics ≤2 weeks run-in baseline, or treated with intravenous (IV) antibiotics for infection ≤8 weeks run-in baseline; if patients were treated with antibiotics with no evidence of infection, they were not excluded

• History of organ transplant

• Laboratory test results meeting any of the following criteria:

- Hemoglobin level <10.0 g/dL
- WBC count $<3.0 \times 10^3/\mu L$
- Neutrophil count $<1.5 \times 10^3/\mu L$
- Platelet count $<100 \times 10^3/\mu L$
- Total bilirubin level >1.5 × upper limit of normal unless results consistent with those for Gilbert's syndrome
- Aspartate aminotransferase or alanine aminotransferase values >2 × upper limit of normal

• Investigator-determined history of alcoholism or drug/chemical abuse ≤2 years screening

• Known hypersensitivity to rilonacept or any excipients

• Received investigational drug ≤30 days (or 5 terminal half-lives) before screening or planning to use an investigational drug (other than that administered during this study) or investigational device at any time during study

• Presence of other medical condition that could adversely affect patient's participation or interfere with study evaluations

• Not likely to be compliant with study protocol

• Should not participate in this study

Table S2. Patient Not Meeting Eligibility Criteria at Screening

Exclusion Criteria	**Number of Patients Meeting Exclusion Criterion**
Meets tuberculosis criteria: History of active tuberculosis prior to screening, OR History of latent tuberculosis not adequately treated before screening, OR Signs/symptoms suggestive of active tuberculosis, OR Recent close contact with active tuberculosis patient, OR Positive/indeterminate interferon gamma release assay test results or results from another positive tuberculosis test at screening	2
History of positive/intermediate results for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening	3
Lab result: Aspartate aminotransferase or alanine aminotransferase values >2 × upper limit of normal	1
Serious infection history, admitted to hospital for infection, treated with oral antibiotics ≤2 weeks run-in baseline, or treated with intravenous (IV) antibiotics for infection ≤8 weeks run-in baseline	1
Lab result: Hemoglobin level <10.0 g/dL	1
History of systemic immunomodulatory agents (excluding glucocorticoids) prior to run-in baseline within following time frames	1

Has a diagnosis of pericarditis, including tuberculosis; neoplastic, purulent, radiation etiologies; post-thoracic blunt trauma; myocarditis; or systemic autoimmune with exception of Still disease	1
Not likely to be compliant with study protocol	1
Inclusion Criteria	**Number of Patients Not Meeting Inclusion Criterion**
Presents with at least the second recurrence of pericarditis during screening, and within 7 days prior to and including RI baseline has CRP level ≥1.0 mg/dL*	35
Presents with at least the second recurrence of pericarditis during screening, and within 7 days prior to and including RI baseline has at least 1 day with pericarditis pain ≥4 on the 11-point numerical rating scale *	6
≥1 pericarditis episode prior to screening meeting ≥2 criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation/PR-segment depression, or new/worsening pericardial effusion	2
Provided informed written consent	2
Will adhere to study visit schedule and comply with other protocol requirements	1
*Two patients failed to meet both: A) Presents with at least the second recurrence of pericarditis during screening, and within 7 days prior to and including RI baseline has: CRP level ≥1.0 mg/dL; and B) Presents with at least the second recurrence of pericarditis during screening, and within 7 days prior to and including RI	

baseline has at least 1 day with pericarditis pain ≥ 4 on the 11-point numerical rating scale; these two patients are included twice in the table (once in each category)

Table S3. Concordance of Clinical Events Committee Judgment versus Investigator Assessment.

	CEC: Pericarditis Recurrence No. (%)	**CEC: No Pericarditis Recurrence No. (%)**
Investigator: pericarditis recurrence	25 (96.2)	1 (3.8)
Investigator: no pericarditis recurrence	0	0

Table S4. Week 8 Sensitivity Analyses.

Sensitivity Analyses, assessed at wk 8	**Rilonacept**	**Placebo**	**Difference (95% CI)**
Persistent Clinical Response † ‡			
No. of patients meeting end point/no. of patients in analysis	21/27	8/31	
Percent of patients (95% CI) §	77.8 (57.7, 91.4)	25.8 (11.9, 44.6)	52.0 (30.0 - 74.0)
Days with no/minimal pain ¶			
No. of patients in analysis	27	31	
Least-squares mean percentage ‖	95.5 ± 7.3	55.7 ± 6.9	39.7 (25.0 - 54.4)
Absent/minimal pericarditis symptoms ‡ **			
No. of patients meeting end point/no. of patients in analysis	23/27	10/31	
Percent of patients (95% CI) §	85.2 (66.3, 95.8)	32.3 (16.7, 51.4)	52.9 (31.7 - 74.1)

† Persistent clinical response was defined as a weekly average of no more than 2.0 on the daily pericarditis pain score, as assessed on the numerical rating scale, and a C-reactive protein level of no more than 0.5 mg per deciliter while patients were receiving no other medications for pericarditis besides rilonacept. Patients were considered not to have had a response if they had a recurrence of pericarditis, used bailout rilonacept or rescue medication, discontinued rilonacept or placebo during the randomized period, or were lost to follow-up before that week.

‡ Percentages are based on the intent-to-treat analysis set, which include patients randomized at least 16 weeks before data cutoff. The exact 95% confidence interval was calculated with randomization strata pooled.

§ Differences between percentages are reported in percentage points. The 95% confidence intervals for the differences in percentages were based on a normal approximation. The P value for this analysis was analyzed with a Cochran–Mantel–Haenszel test with adjustment for oral glucocorticoid use and diagnosis of recurrent idiopathic pericarditis at baseline of the run-in period.

¶ No or minimal pain was defined as a nonmissing daily pericarditis pain score of no more than 2, as assessed on the numerical rating scale. The percentage of days with no or minimal pain during the first 16 weeks was calculated for each patient with the use of 112 days (i.e., 16 × 7 days) as the denominator. Days with missing values in the pain diary were counted as 0 days with no or minimal pain, as were days with use of an oral rescue therapy or glucocorticoid.

If bailout rilonacept was used, each administration (loading dose or not) was counted as 7 days without qualifying as no or minimal pain.

‖ The least-squares mean difference was calculated for the rilonacept group minus the placebo group. The two-sided P value for this analysis was calculated by an analysis of covariance with trial group, randomization strata, and the category for the weekly average numerical rating scale score (≤2 vs. >2) at baseline of the run-in period as covariates.

** Absent or minimal pericarditis symptoms were defined as a score of 0 or 1 on the patient's global impression of pericarditis severity rating scale (scores range from 0 to 6, with higher scores indicating greater severity of symptoms). For the patient's global impression of pericarditis severity, patients who had received bailout rilonacept or rescue medication before the time point were considered not to have had a response.

Table S5. Week 24 Sensitivity Analyses.

Sensitivity Analyses, assessed at wk 24	Rilonacept	Placebo	Difference (95% CI)
Persistent Clinical Response † ‡			
No. of patients meeting end point/no. of patients in analysis	13/17	3/15	
Percent of patients (95% CI) §	76.5 (50.1, 93.2)	20.0 (4.3, 48.1)	56.5 (27.9 - 85.0)
Days with no/minimal pain¶			
No. of patients in analysis	17	15	
Least-squares mean percentage ‖	99.9 ± 7.9	47.5 ± 7.6	52.5 (34.5 - 70.4)
Absent/minimal pericarditis symptoms ‡ **			
No. of patients meeting end point/no. of patients in analysis	15/17	3/15	
Percent of patients (95% CI) §	88.2 (63.6, 98.5)	20.0 (4.3, 48.1)	68.2 (42.9 - 93.6)

† Persistent clinical response was defined as a weekly average of no more than 2.0 on the daily pericarditis pain score, as assessed on the numerical rating scale, and a C-reactive protein level of no more than 0.5 mg per deciliter while patients were receiving no other medications for pericarditis besides rilonacept. Patients were considered not to have had a response if they had a recurrence of pericarditis, used bailout rilonacept or rescue medication, discontinued rilonacept or placebo during the randomized period, or were lost to follow-up before that week.

‡ Percentages are based on the intent-to-treat analysis set, which include patients randomized at least 16 weeks before data cutoff. The exact 95% confidence interval was calculated with randomization strata pooled.

§ Differences between percentages are reported in percentage points. The 95% confidence intervals for the differences in percentages were based on a normal approximation. The P value for this analysis was analyzed with a Cochran–Mantel–Haenszel test with adjustment for oral glucocorticoid use and diagnosis of recurrent idiopathic pericarditis at baseline of the run-in period.

¶ No or minimal pain was defined as a nonmissing daily pericarditis pain score of no more than 2, as assessed on the numerical rating scale. The percentage of days with no or minimal pain during the first 16 weeks was calculated for each patient with the use of 112 days (i.e., 16 × 7 days) as the denominator. Days with missing values in the pain diary were counted as 0 days with no or minimal pain, as were days with use of an oral rescue therapy or glucocorticoid.

If bailout rilonacept was used, each administration (loading dose or not) was counted as 7 days without qualifying as no or minimal pain.

‖ The least-squares mean difference was calculated for the rilonacept group minus the placebo group. The two-sided P value for this analysis was calculated by an analysis of covariance with trial group, randomization strata, and the category for the weekly average numerical rating scale score (≤2 vs. >2) at baseline of the run-in period as covariates.

** Absent or minimal pericarditis symptoms were defined as a score of 0 or 1 on the patient's global impression of pericarditis severity rating scale (scores range from 0 to 6, with higher scores indicating greater severity of symptoms). For the patient's global impression of pericarditis severity, patients who had received bailout rilonacept or rescue medication before the time point were considered not to have had a response.

Table S6. Data Imputation for End Points of Maintained Clinical Response and No/minimal Pericarditis Symptoms

	Secondary End Point			
	Maintained Clinical Response at Week 16		**No/minimal Pericarditis Symptoms (patient global impression of pericarditis severity) at Week 16**	
	Rilonacept	**Placebo**	**Rilonacept**	**Placebo**
N	**21**	**20**	**21**	**20**
Patients Meeting End Point	17 (81.0)	4 (20.0)	17 (81.0)	5 (25.0)
Patients Not Meeting End Point	4 (19.0)	16 (80.0)	4 (19.0)	15 (75.0)
Recurrence	0	15 (75.0)	0	15 (75.0)
Rescue medication	1 (4.8)	0	0	0
Numerical rating scale >2 or CRP >0.5 mg/dL	0	1 (5.0)	N/A	N/A
Missing data	3 (14.3)	0	3 (14.3)	0
Bailout	0	0	0	0
With Pericarditis Symptoms	N/A	N/A	1 (4.8)	0

Table S7. Data Imputation for Days with No/Minimal Pain in the First 16 Weeks of Randomized-Withdrawal

	Randomized-Withdrawal Period	
	Rilonacept	**Placebo**
N	**21**	**20**
Total Days	**2352**	**2240**
As Observed		
Total Patient Days	2177	1059[†]
Mean (SD)	103.7 (14.9)	53.0 (35.3)
Imputed[*]		
Total Patient-days	175	1181
Received Bailout[‡]	0	981
Received Rescue Medication[‡]	2	56
Missing NRS Data	173	144
Mean (SD)	8.3 (14.9)	59.1 (35.3)

*Includes days with missing values, days of using ORT or glucocorticoids, and days from bailout rilonacept used plus 6 days.

[†]Majority of imputed days (1037 out of 1181 days) for the placebo arm are a result of bailout and rescue treatment after a pericarditis recurrence, not missing data.

[‡]In the case of bailout and rescue treatment, "imputation" means either the NRS is set to 0 or the patient is set to non-responder.

Table S8. Treatment-Emergent Adverse Events Occurring in ≥5% Patients Overall

	Run-In	Randomized-Withdrawal				Overall Study
Category*, No. (%)	Rilonacept N = 86	Rilonacept Including Bailout N = 30	Placebo Including Bailout N = 31	Rilonacept Before Bailout N = 30	Placebo Before Bailout N = 31	Rilonacept or Placebo N = 86
Patients with any treatment-emergent adverse events	69 (80.2)	24 (80.0)	22 (71.0)	24 (80.0)	13 (41.9)	74 (86.0)
Injection site erythema	18 (20.9)	6 (20.0)	1 (3.2)	5 (16.7)	0	21 (24.4)
Arthralgia	8 (9.3)	1 (3.3)	2 (6.5)	1 (3.3)	0	10 (11.6)
Myalgia	9 (10.5)	1 (3.3)	0	1 (3.3)	0	10 (11.6)
Injection site pruritus	5 (5.8)	5 (16.7)	1 (3.2)	4 (13.3)	0	8 (9.3)
Nasopharyngitis	6 (7.0)	2 (6.7)	0	2 (6.7)	0	8 (9.3)
Headache	7 (8.1)	0	0	0	0	7 (8.1)
Musculoskeletal chest pain	3 (3.5)	1 (3.3)	4 (12.9)	1 (3.3)	4 (12.9)	7 (8.1)
Cough	5 (5.8)	1 (3.3)	1 (3.2)	1 (3.3)	0	6 (7.0)
Injection site swelling	5 (5.8)	1 (3.3)	0	1 (3.3)	0	6 (7.0)
Back pain	3 (3.5)	1 (3.3)	1 (3.2)	1 (3.3)	0	5 (5.8)
Diarrhea	5 (5.8)	0	0	0	0	5 (5.8)
Fatigue	2 (2.3)	2 (6.7)	1 (3.2)	2 (6.7)	0	5 (5.8)

Table S9. Injection Site Reactions

	Run-In	Randomized-Withdrawal				Overall Study
Category*, N (%)	**Rilonacept N = 86**	**Rilonacept Including Bailout N = 30**	**Placebo Including Bailout N = 31**	**Rilonacept Before Bailout N = 30**	**Placebo Before Bailout N = 31**	**Rilonacept or Placebo N = 86**
Patients with any treatment-emergent adverse event that is an injection site reaction†	28 (32.6)	6 (20.0)	2 (6.5)	5 (16.7)	0	29 (33.7)
General disorders and administration site conditions	25 (29.1)	6 (20.0)	2 (6.5)	5 (16.7)	0	26 (30.2)
Feeling hot	1 (1.2)	0	0	0	0	1 (1.2)
Injection site bruising	1 (1.2)	0	1 (3.2)	0	0	2 (2.3)
Injection site discoloration	2 (2.3)	0	0	0	0	2 (2.3)
Injection site erythema	18 (20.9)	6 (20.0)	1 (3.2)	5 (16.7)	0	21 (24.4)
Injection site inflammation	1 (1.2)	0	0	0	0	1 (1.2)
Injection site nodule	1 (1.2)	0	0	0	0	1 (1.2)
Injection site pain	4 (4.7)	0	0	0	0	4 (4.7)
Injection site pruritus	5 (5.8)	5 (16.7)	1 (3.2)	4 (13.3)	0	8 (9.3)
Injection site rash	3 (3.5)	0	0	0	0	3 (3.5)

Injection site reaction	2 (2.3)	0	0	0	0	2 (2.3)
Injection site swelling	5 (5.8)	1 (3.3)	0	1 (3.3)	0	6 (7.0)
Skin and subcutaneous tissue disorders	3 (3.5)	0	0	0	0	3 (3.5)
Erythema	1 (1.2)	0	0	0	0	1 (1.2)
Pruritus	1 (1.2)	0	0	0	0	1 (1.2)
Rash	1 (1.2)	0	0	0	0	1 (1.2)
Rash macular	1 (1.2)	0	0	0	0	1 (1.2)

*A patient can only be counted once within a preferred term or system organ class.

† For all treatment-emergent adverse events, investigators were asked to assess if the specific event constituted an injection site reaction. While the majority of injection site reactions were coded to events occurring at the injection site (e.g., injection site erythema or injection site pruritus), other events anatomically distant from the injection site may have been assessed as injection site reactions (e.g., feeling hot, rash).

Table S10. Upper Respiratory Tract Infections

	Run-In	Randomized-Withdrawal				Overall Study
Category*, N (%)	**Rilonacept N = 86**	**Rilonacept Including Bailout N = 30**	**Placebo Including Bailout N = 31**	**Rilonacept Before Bailout N = 30**	**Placebo Before Bailout N = 31**	**Rilonacept or Placebo N = 86**
Patients with any treatment-emergent adverse events of URTI	12 (14.0)	7 (23.3)	2 (6.5)	7 (23.3)	0	19 (22.1)
Nasopharyngitis	6 (7.0)	2 (6.7)	0	2 (6.7)	0	8 (9.3)
Sinusitis	1 (1.2)	3 (10.0)	0	3 (10.0)	0	4 (4.7)
Upper respiratory tract infection	2 (2.3)	1 (3.3)	1 (3.2)	1 (3.3)	0	4 (4.7)
Viral upper respiratory tract infection	2 (2.3)	1 (3.3)	0	1 (3.3)	0	3 (3.5)
Pharyngitis	1 (1.2)	0	0	0	0	1 (1.2)
Pharyngitis streptococcal	0	0	1 (3.2)	0	0	1 (1.2)
Rhinitis	1 (1.2)	0	0	0	0	1 (1.2)

*A patient can only be counted once within a preferred term.

Table S11. Nonfasting Lipids Over Time in the Run-in Period (Safety Population, N=86)*

Time Point	N	Mean (SD) Total Cholesterol (mg/dL)	Mean (SD) LDL Cholesterol (mg/dL)	Mean (SD) HDL Cholesterol (mg/dL)	Mean (SD) Triglycerides (mg/dL)
Baseline	85	174.3 (40.6)	108.3 (36.6) †	50.4 (16.6) †	120.4 (55.2) †
Week 12	80	190.4 (42.0)	116.0 (38.4)	56.3 (16.9)	135.3 (87.2)

*Lipid panels in patients who were in a nonfasting state were to be drawn at a minimum of every 6 months during the randomized-withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.

†N = 84

Table S12. Mean (SD) Nonfasting Lipids Over Time During the Randomized-Withdrawal Period*

		Rilonacept Including Bailout		Placebo Including Bailout		Rilonacept Before Bailout		Placebo Before Bailout	
	Time Point	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Total Cholesterol (mg/dL)	Baseline†	30	193.1 (40.3)	31	189.5 (39.3)	30	193.1 (40.3)	31	189.5 (39.3)
	Week 16	5	188.2 (28.0)	4	175.0 (44.6)	5	188.2 (28.0)	0	-
	Week 24	13	204.0 (30.8)	14	185.8 (26.5)	13	204.0 (30.8)	3	184.7 (32.5)
LDL Cholesterol (mg/dL)	Baseline†	30	120.9 (38.7)	31	116.4 (38.3)	30	120.9 (38.7)	31	116.4 (38.3)
	Week 24	13	124.8 (33.4)	14	106.9 (23.6)	13	124.8 (33.4)	3	111.7 (24.4)
HDL Cholesterol (mg/dL)	Baseline†	30	55.1 (16.2)	31	53.8 (14.3)	30	55.1 (16.2)	31	53.8 (14.3)
	Week 16	5	43.6 (12.8)	4	57.8 (5.3)	5	43.6 (12.8)	0	-
	Week 24	13	54.9 (14.4)	14	59.6 (14.5)	13	54.9 (14.4)	3	61.3 (18.8)
Triglycerides (mg/dL)	Baseline†	30	145.2 (84.3)	31	131.2 (101.5)	30	145.2 (84.3)	31	131.2 (101.5)
	Week 16	5	146.2 (40.0)	4	129.3 (58.6)	5	146.2 (40.0)	0	-
	Week 24	13	198.0 (105.8)	14	131.6 (74.4)	13	198.0 (105.8)	3	96.7 (34.0)

*Lipid panels in patients who were in a nonfasting state were to be drawn at a minimum of every 6 months during the randomized-withdrawal and LTE periods, or more frequently as needed, with mandated evaluations as detailed in the schedule of events.
†Baseline is the last value before the first dose of study medication in the run-in period.

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