ORIGINAL ARTICLE

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

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## ABSTRACT

### BACKGROUND

Interleukin-1 has been implicated as a mediator of recurrent pericarditis. The efficacy and safety of rilonacept, an interleukin-1$\alpha$ and interleukin-1$\beta$ cytokine trap, were studied previously in a phase 2 trial involving patients with recurrent pericarditis.

### METHODS

We conducted a phase 3 multicenter, double-blind, event-driven, randomized-withdrawal trial of rilonacept in patients with acute symptoms of recurrent pericarditis (as assessed on a patient-reported scale) and systemic inflammation (as shown by an elevated C-reactive protein [CRP] level). Patients presenting with pericarditis recurrence while receiving standard therapy were enrolled in a 12-week run-in period, during which rilonacept was initiated and background medications were discontinued. Patients who had a clinical response (i.e., met prespecified response criteria) were randomly assigned in a 1:1 ratio to receive continued rilonacept monotherapy or placebo, administered subcutaneously once weekly. The primary efficacy end point, assessed with a Cox proportional-hazards model, was the time to the first pericarditis recurrence. Safety was also assessed.

### RESULTS

A total of 86 patients with pericarditis pain and an elevated CRP level were enrolled in the run-in period. During the run-in period, the median time to resolution or near-resolution of pain was 5 days, and the median time to normalization of the CRP level was 7 days. A total of 61 patients underwent randomization. During the randomized-withdrawal period, there were too few recurrence events in the rilonacept group to allow for the median time to the first adjudicated recurrence to be calculated; the median time to the first adjudicated recurrence in the placebo group was 8.6 weeks (95% confidence interval [CI], 4.0 to 11.7; hazard ratio in a Cox proportional-hazards model, 0.04; 95% CI, 0.01 to 0.18; P<0.001 by the log-rank test). During this period, 2 of 30 patients (7%) in the rilonacept group had a pericarditis recurrence, as compared with 23 of 31 patients (74%) in the placebo group. In the run-in period, 4 patients had adverse events leading to the discontinuation of rilonacept therapy. The most common adverse events with rilonacept were injection-site reactions and upper respiratory tract infections.

### CONCLUSIONS

Among patients with recurrent pericarditis, rilonacept led to rapid resolution of recurrent pericarditis episodes and to a significantly lower risk of pericarditis recurrence than placebo. (Funded by Kiniksa Pharmaceuticals; RHAPSODY ClinicalTrials.gov number, NCT03737110.)

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Recurrent pericarditis is a disease characterized by chronic and debilitating pericardial inflammation, with wide-ranging effects on physical function, well-being, and productivity, in addition to considerable demands on health care resources.[1-7] Approximately 15 to 30% of patients who have an initial pericarditis episode will have a recurrence despite treatment with colchicine.[2,3] Among the limited therapeutic options available, glucocorticoids are of particular concern because of nonspecific immunosuppression and because of the risk of serious adverse events associated with long-term use.[1,2]

Interleukin-1 has been implicated in the pathophysiology of recurrent pericarditis[8-13] and is a viable target for intervention in patients who have evidence of systemic inflammation (e.g., elevated C-reactive protein [CRP] levels). The potential of interleukin-1 inhibition was evaluated in a trial of the recombinant interleukin-1–receptor antagonist anakinra in a small number of patients with colchicine-resistant idiopathic recurrent pericarditis who had previously had pericarditis recurrence after the withdrawal of glucocorticoids; many of the patients continued using colchicine during that trial.[14] A subsequent phase 2 trial of rilonacept, an interleukin-1$\alpha$ and interleukin-1$\beta$ cytokine trap,[15,16] provided early evidence of resolution of pericardial inflammation.[13,17] We designed the phase 3 trial RHAPSODY (Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: a Pivotal Symptomatology and Outcomes Study) to test the primary hypothesis that rilonacept would lead to a lower risk of pericarditis recurrence than placebo.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

We conducted this multicenter, double-blind, placebo-controlled, randomized-withdrawal trial of rilonacept in Australia, Israel, Italy, and the United States. Full details of the trial design have been published previously.[18] The trial was funded by Kiniksa Pharmaceuticals. The protocol, which is available with the full text of this article at NEJM.org, was designed by the first four authors and by the sixth and last authors (employees of Kiniksa Pharmaceuticals) and was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and all relevant regulations. The protocol was approved by the relevant institutional review boards or independent ethics committees for all participating centers. The sponsor directed all aspects of the trial, held the data, and performed the statistical analyses. The academic research organization C5Research provided independent confirmation of the trial analyses. The first two authors and the sixth and last two authors (employees of Kiniksa Pharmaceuticals) vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

### POPULATION OF PATIENTS

Adult and adolescent patients (≥12 years of age) with recurrent pericarditis were eligible to participate if they presented with acute signs and symptoms of pericarditis during at least a second recurrence (having met the 2015 European Society of Cardiology criteria for pericarditis[2] at least once), despite treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or oral glucocorticoids in any combination. A pain score of at least 4 on a numerical rating scale (with values ranging from 0 to 10 and with higher scores indicating greater pain severity) and a CRP level of at least 1 mg per deciliter within 7 days before the first administration of trial treatment (rilonacept) were required for enrollment. The numerical rating scale is described in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org, and complete eligibility criteria are listed in Table S1 in the Supplementary Appendix.

### TRIAL PROCEDURES

The trial comprised four periods, which began for each patient with a screening period of 4 weeks' duration (or less) to establish trial eligibility, followed by a 12-week run-in period (Fig. S1). During the run-in period, all the patients received rilonacept, administered subcutaneously as a loading dose of 320 mg (or 4.4 mg per kilogram of body weight in patients <18 years of age), followed by weekly maintenance doses of 160 mg (or 2.2 mg per kilogram in patients <18 years of age). The 12-week run-in period included a 1-week stabilization period, a 9-week period to wean from background therapy for pericarditis, and a 2-week period of rilonacept monotherapy. The

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

Patients who met prespecified clinical-response criteria (CRP level of ≤0.5 mg per deciliter and a weekly mean daily numerical rating scale score of ≤2 [no or minimal pain] while they were receiving rilonacept monotherapy and did not have a recurrence) at the end of the run-in period were eligible to enter the randomized-withdrawal period. Eligible patients were randomly assigned in a 1:1 ratio to receive either continued rilonacept or matching placebo, administered weekly. The randomization schedule was generated with the use of SAS software, version 9.4 (SAS Institute), and administered by means of an interactive Web-response system. Randomization was stratified according to oral glucocorticoid use at baseline of the run-in period (yes or no) and according to diagnosis of idiopathic pericarditis (yes or no). The patients, investigators, clinical and administrative staff, and the sponsor were unaware of the randomized group assignments.

Trial closure (i.e., the end of the randomized-withdrawal period) was triggered, as prespecified, by the accrual of 22 adjudicated first postrandomization recurrence events of pericarditis (primary efficacy end point). Trial closure entailed the cessation of new randomizations and the transition of eligible patients who were in the run-in and randomized-withdrawal periods to the long-term extension period, during which eligible patients were offered up to 24 months of open-label rilonacept.[18]

#### EFFICACY ASSESSMENTS

The analysis of the primary efficacy end point included only recurrence events that had been confirmed by the independent clinical-events committee, whose members were unaware of the trial-group assignments. A recurrence event was defined as the return of pericarditis pain and an increase in the CRP level, as well as supportive objective evidence of pericarditis (e.g., pericardial effusion, pericardial rub, or electrocardiographic changes). Bailout rilonacept was used as rescue medication for qualifying recurrence events (numerical rating scale score of ≥4 and CRP level of ≥1 mg per deciliter), as described in the Supplementary Methods section.

The major secondary efficacy end points included the percentage of patients who had a persistent clinical response at the week-16 assessment, the percentage of days with no or minimal pericarditis pain (numerical rating scale score ≤2) through week 16, and the percentage of patients with absent or minimal pericarditis symptoms (score of 0 or 1), according to the patient's global impression of pericarditis severity rating scale (scores range from 0 to 6, with higher scores indicating greater severity of symptoms), at the week-16 assessment. This scale is described in the Supplementary Methods section.

Secondary efficacy end points that were assessed during the run-in period included the time to pain response (rolling mean numerical rating scale score of ≤2 on 3 consecutive days), the time to normalization of the CRP level (to ≤0.5 mg per deciliter), the time to prespecified treatment response (time to pain response and normalization of the CRP level within 7 days before or after the pain response), and the time by which the patients discontinued standard therapy and were receiving rilonacept monotherapy.

#### SAFETY ASSESSMENTS

Safety assessments included adverse events, physical examinations, and laboratory tests. For patients who did not discontinue the trial regimen and who transitioned to the open-label extension period, the adverse events reported here are those that occurred between the first dose of rilonacept in the run-in period and the last visit during the randomized-withdrawal period. For patients who discontinued rilonacept during the run-in period or who discontinued rilonacept or placebo during the randomized-withdrawal period or at the end of the randomized-withdrawal period (i.e., did not continue into the long-term extension period), data on adverse events continued to be collected for 6 weeks after the last dose of rilonacept or placebo. Safety data were reviewed by the data monitoring committee. Details are provided in the Supplementary Methods section.

#### STATISTICAL ANALYSIS

We calculated that for the trial to have 90% power to evaluate the primary efficacy end point, 22 recurrence events would be needed in order to detect a significant difference in the time to pericarditis recurrence, assuming a hazard ratio

of 0.244 for rilonacept as compared with placebo and a one-sided alpha level of 0.025 (two-sided alpha level, 0.05). The analysis for the primary efficacy end point was performed in the intention-to-treat population (all the patients who underwent randomization). Patients without pericarditis recurrence had their data censored at the last assessment by the end of the randomized-withdrawal period. A log-rank test that was stratified according to oral glucocorticoid use at baseline of the run-in period was used to analyze the time to recurrence. The hazard ratio (rilonacept vs. placebo) and 95% confidence interval for the primary efficacy end point were obtained from a Cox proportional-hazards model, with trial group as a covariate and with stratification according to oral glucocorticoid use at baseline of the run-in period.

All three major secondary efficacy end points were assessed in the patients who had undergone randomization at least 16 weeks before the data-cutoff date. For the major secondary efficacy end points, a Cochran–Mantel–Haenszel test, with adjustment for the randomization stratification factors, was used for binary variables; an analysis of covariance with trial group, randomization stratum, and pain score at baseline of the run-in period (numerical rating scale score, ≤2 vs. >2) as covariates was performed for continuous variables.

A gatekeeping multiplicity-adjustment procedure in combination with the Hochberg procedure was applied for prespecified stepwise testing of the primary end point and the major secondary end points. If the one-sided P value for the primary end point was no more than 0.025 (two-sided P value of ≤0.05), the first major secondary end point (the percentage of patients who had a persistent clinical response at week 16) would be tested at the same alpha level. If both the primary end point and the first major secondary end point were significant, then the second and third major secondary end points would be tested at an overall one-sided alpha level of 0.025 (two-sided alpha level of 0.050). Details of the statistical methods are provided in the Supplementary Appendix.

## RESULTS

### PATIENTS

A total of 141 patients were assessed for eligibility, and 86 patients were enrolled in the trial (Fig. S2). Enrollment began on January 9, 2019, and concluded on January 17, 2020. Reasons for the exclusion of patients who did not meet eligibility criteria are provided in Table S2. The mean age of the enrolled patients was 44.7 years, and 57% of the patients were female. The predominant underlying cause of pericarditis was idiopathic (in 85% of the patients), with 15% of the patients having post–cardiac-injury pericarditis. Approximately half the patients were taking glucocorticoids at the time of the qualifying pericarditis episode.

Of the 86 enrolled patients, 61 patients had completed the run-in period and had undergone randomization before enrollment was stopped because of the accrual of the prespecified number of adjudicated primary efficacy end-point events. A total of 3 patients did not undergo randomization because they did not meet the prespecified clinical-response criteria, and 7 did not complete the run-in period because of adverse events (in 4), a decision by the investigator (in 2), or another reason (in 1). The additional 15 patients who were still in the run-in period were allowed to complete the run-in period but did not undergo randomization; they transitioned directly to the long-term extension period.

The demographic and clinical characteristics of the patients at baseline were balanced between the two randomized trial groups (Table 1). The median duration of rilonacept treatment, including the run-in period, was 9 months (range, 3 to 14). The mean (±SD) adherence to the trial regimen (the number of actual administrations divided by the number of planned administrations) was 98.7±4.6% throughout the entire trial (run-in and randomized-withdrawal periods).

### RUN-IN PERIOD

In the 86 patients who participated in the run-in period, rapid (after the first dose of rilonacept) and sustained reductions in the mean pain score on the numerical rating scale and the mean CRP level showed resolution of the enrollment-qualifying acute pericarditis episode (Fig. 1). The median time to pain response was 5 days (95% confidence interval [CI], 4 to 6), and the median time to normalization of the CRP level was 7 days (95% CI, 5 to 8). The median time to the prespecified treatment response was 5 days (95% CI, 4 to 7).

Manifestations of pericarditis (pericardial effusion, pericardial rub, or electrocardiographic

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Run-In Period | Randomized-Withdrawal Period | |
|---|---|---|---|
| | Rilonacept (N=86) | Rilonacept (N=30) | Placebo (N=31) |
| Age | | | |
| Mean — yr | 44.7±16.1 | 48.0±15.7 | 44.8±14.5 |
| Distribution — no. (%) | | | |
| 12–17 yr | 7 (8) | 1 (3) | 2 (6) |
| 18–64 yr | 71 (83) | 24 (80) | 27 (87) |
| 65–78 yr | 8 (9) | 5 (17) | 2 (6) |
| Female sex — no. (%) | 49 (57) | 16 (53) | 16 (52) |
| Race — no. (%)† | | | |
| White | 80 (93) | 28 (93) | 28 (90) |
| Black | 5 (6) | 1 (3) | 3 (10) |
| Other | 1 (1) | 1 (3) | 0 |
| Cause of pericarditis — no. (%) | | | |
| Idiopathic | 73 (85) | 26 (87) | 26 (84) |
| Post-pericardiotomy syndrome | 12 (14) | 3 (10) | 5 (16) |
| Dressler syndrome‡ | 1 (1) | 1 (3) | 0 |
| Medication used in the qualifying episode of pericarditis — no. (%) | | | |
| NSAID | 58 (67) | 20 (67) | 19 (61) |
| Colchicine | 69 (80) | 27 (90) | 26 (84) |
| Glucocorticoid§ | 42 (49) | 14 (47) | 14 (45) |
| Duration of previous treatment with glucocorticoids — wk¶ | 19.9±36.3 | 17.4±40.0 | 15.1±28.7 |
| Total no. of episodes of pericarditis, including index and qualifying episodes | 4.7±1.7 | 5.1±2.0 | 4.8±1.5 |
| Duration of disease — yr | 2.4±3.1 | 3.1±4.4 | 1.9±2.1 |
| No. of recurrent episodes per yr | 4.4±4.9 | 4.4±5.2 | 4.3±2.9 |
| Pain score for the qualifying episode, according to the numerical rating scale‖ | 6.2±1.8 | 6.4±1.7 | 6.3±1.9 |
| C-reactive protein level for the qualifying episode — mg/dl | 6.2±6.7 | 6.6±7.3 | 6.0±5.1 |
| Manifestations of pericarditis in the qualifying episode — no. (%) | | | |
| Pericardial effusion** | 33 (38) | 10 (33) | 11 (35) |
| Pericardial rub | 13 (15) | 6 (20) | 3 (10) |
| ST-segment elevation or PR depression | 16 (19) | 5 (17) | 6 (19) |

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NSAID denotes nonsteroidal antiinflammatory drug.

† Race was reported by the patient.

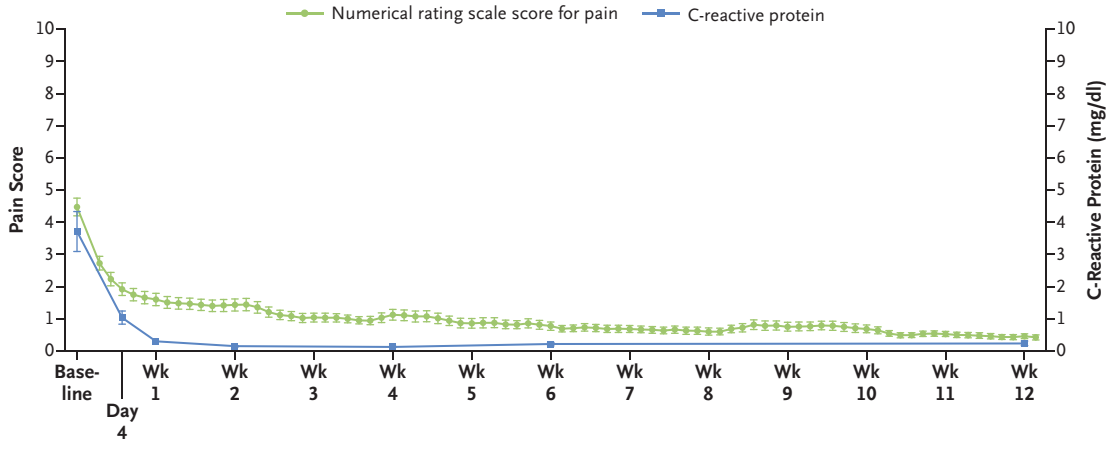
‡ The cause of the Dressler syndrome was catheter ablation for atrial fibrillation.

§ The medications at the baseline (initiation of treatment) visit differ from those being taken at the time that the qualifying episode of pericarditis was documented. To allow for the completion of screening procedures, the investigator was permitted to treat each patient with standard-of-care medications temporarily during the interval between presentation with the qualifying episode and the baseline visit or trial enrollment. Glucocorticoid use at baseline of the run-in period was reported in 41 patients (48%) overall, in 13 patients (43%) who were randomly assigned to receive rilonacept, and in 14 patients (45%) who were randomly assigned to receive placebo. Oral glucocorticoid use at baseline of the run-in period was used for stratification and subgroup analysis.

¶ The duration of glucocorticoid use was for the most recent episode of pericarditis. For the run-in period, 41 patients were using glucocorticoids before baseline. For the randomized-withdrawal period, 13 patients in the rilonacept group and 14 in the placebo group used glucocorticoids before baseline.

‖ Scores on the numerical rating scale for pain range from 0 to 10, with higher scores indicating greater pain severity.

** Pericardial effusion was defined as new or worsening pericardial effusion, independent of the imaging method.




| | Base-line | Day 4 | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 6 | Wk 7 | Wk 8 | Wk 9 | Wk 10 | Wk 11 | Wk 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No. of Patients** | 86 | 86 | 85 | 85 | 85 | 85 | 85 | 85 | 84 | 84 | 84 | 83 | 82 | 79 |
| **Pain Score** | | | | | | | | | | | | | | |
| No. of patients | 84 | | 84 | 84 | 83 | 83 | 84 | 83 | 83 | 82 | 81 | 82 | 82 | 78 |
| Mean value | 4.50 | | 1.60 | 1.43 | 1.04 | 1.13 | 0.86 | 0.78 | 0.68 | 0.61 | 0.76 | 0.69 | 0.53 | 0.46 |
| **C-Reactive Protein** | | | | | | | | | | | | | | |
| No. of patients | 85 | 79 | 82 | 81 | | 79 | | 82 | | | | | | 81 |
| Mean value | 3.70 | 1.00 | 0.30 | 0.15 | | 0.13 | | 0.22 | | | | | | 0.24 |

**Figure 1. Mean Numerical Rating Scale Scores for Pain and C-Reactive Protein Levels over the 12-Week Run-In Period.**

Numerical rating scale scores for pain and C-reactive protein (CRP) levels as assessed by a central laboratory were recorded during the run-in period, during which all the patients received rilonacept. The mean pain numerical rating scale score and mean CRP level at the baseline visit differ from those recorded for the qualifying pericarditis episode; to allow for the completion of screening procedures, the investigator was permitted to treat each patient with standard-of-care medications temporarily during the interval between presentation with the qualifying episode and the baseline visit or trial enrollment. A 3-day rolling mean was calculated on the basis of nonmissing values over each successive 3-day interval. In accordance with the protocol, pain was assessed daily with the use of a numerical rating scale (with scores ranging from 0 to 10 and with higher scores indicating greater pain severity). CRP was measured at baseline, on day 4, and at weeks 1, 2, 4, 6, and 12. At week 12, a total of 81 patients had assessments of the CRP level, but 2 of these patients had discontinued treatment before week 12; therefore, only 79 patients were considered to still be participating in the run-in period. I bars indicate the standard error.

changes), when they were present at baseline, resolved by the time of randomization, except in one patient (who was assigned to the rilonacept group); this patient had a pericardial friction rub, which resolved by the end of the randomized-withdrawal period. The median time to rilonacept monotherapy was 7.9 weeks (95% CI, 7.0 to 8.1); all the patients who had been taking glucocorticoids discontinued them and transitioned to receive rilonacept monotherapy during the run-in period.

### RANDOMIZED-WITHDRAWAL PERIOD

When the randomized-withdrawal period closed on May 29, 2020, a total of 25 primary efficacy end-point events had accrued (3 events occurred during the period of time required to complete the closure of the trial). During the randomized-withdrawal period, there were too few recurrence events in the rilonacept group to allow for the median time to the first adjudicated recurrence to be calculated; the median time to the 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; $P<0.001$ by the log-rank test) (Fig. 2 and Table 2). During this period, in the intention-to-treat population, 2 of 30 patients (7%) in the rilonacept group had a pericarditis recurrence event, as compared with 23 of 31 patients (74%) in the placebo group.

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

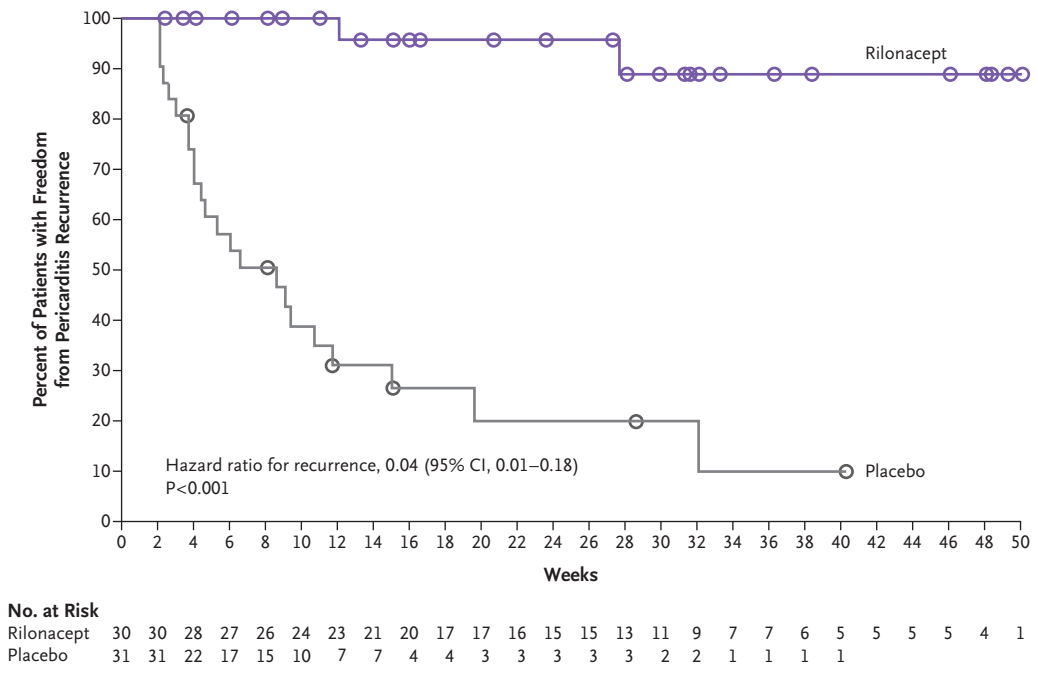



**Figure 2. Time to the First Adjudicated Pericarditis Recurrence.**

Curves for the time to the first adjudicated pericarditis recurrence in the randomized-withdrawal period are shown. Circles indicate the time of data censoring for reasons other than a primary efficacy end-point event (e.g., a visit at the end of the randomized-withdrawal period). Overall, 2 patients (7%) in the rilonacept group and 23 (74%) in the placebo group had pericarditis recurrence. The median time to recurrence could not be estimated in the rilonacept group and was 8.6 weeks (95% CI, 4.0 to 11.7) in the placebo group.

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 pericarditis recurrence events received bailout rilonacept. In the placebo group, all 23 patients who had pericarditis recurrence received bailout rilonacept. No patient who received bailout rilonacept had pericarditis recurrence during the remainder of the randomized-withdrawal period.

The findings with regard to the primary efficacy end point were consistent regardless of baseline glucocorticoid use (Fig. S3 and the Supplementary Results section). The concordance between the investigator and clinical-event-committee assessments of recurrence events was 96.2% (Table S3).

All three major secondary efficacy end points (assessed at week 16 of the randomized-withdrawal period) showed a benefit of rilonacept monotherapy in providing a sustained clinical response and reducing the symptoms of pericarditis (Table 2). Results of sensitivity analyses at week 8 and week 24 were consistent with those at week 16, and analyses to address missing data were also performed (Tables S4 through S7).

### SAFETY

For patients who did not discontinue the trial regimen and who transitioned to the open-label extension period, the adverse events reported here are those that occurred 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 period. For patients who discontinued rilonacept during the run-in period (10 patients) or discontinued rilonacept or placebo during the randomized-withdrawal period (1 patient) or at the end of the randomized-withdrawal period (1 patient), data on adverse events continued to be collected for 6 weeks after the last dose of the trial regimen.

Five serious adverse events occurred during

**Table 2. Trial End Points, Assessed in the Randomized-Withdrawal Period.**

| End Point | Rilonacept (N=30) | Placebo (N=31) | Hazard Ratio or Difference (95% CI) | P Value |
|---|---|---|---|---|
| **Primary efficacy end point** | | | | |
| Median time to pericarditis recurrence (95% CI) — wk* | NE | 8.6 (4.0–11.7) | 0.04 (0.01–0.18) | <0.001 |
| **Major secondary end points, assessed at 16 wk** | | | | |
| Persistent clinical response†‡ | | | | |
| No. of patients who met the end point/no. of patients in the analysis | 17/21 | 4/20 | | |
| Percent of patients (95% CI)§ | 81 (58–95) | 20 (6–44) | 61 (37–85) | <0.001 |
| Days with no or minimal pain¶ | | | | |
| No. of patients in analysis | 21 | 20 | | |
| Least-squares mean percentage‖ | 97.7±7.5 | 45.9±7.2 | 51.8 (35.3–68.4) | <0.001 |
| Absent or minimal pericarditis symptoms‡** | | | | |
| No. of patients who met the end point/no. of patients in the analysis | 17/21 | 5/20 | | |
| Percent of patients (95% CI)§ | 81 (58–95) | 25 (9–49) | 56 (31–81) | <0.001 |

* The Kaplan–Meier method was used to estimate the freedom from pericarditis recurrence for each trial group. The primary efficacy analysis included all the patients who had undergone randomization. The median time to recurrence could not be estimated (NE) in the rilonacept group. The hazard ratio and 95% confidence interval for rilonacept as compared with placebo were based on a Cox proportional-hazards model with trial group as a covariate and with stratification according to oral glucocorticoid use at baseline of the run-in period. The two-sided P value for the primary analysis is from the log-rank test, with stratification according to oral glucocorticoid use at baseline of the run-in period.

† Persistent clinical response was defined as a weekly mean 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 taking no other medications for pericarditis (see the protocol). Patients were considered not to have had a response if they had pericarditis recurrence, used bailout rilonacept or rescue medication (see the protocol), discontinued rilonacept or placebo during the randomized-withdrawal period, or were lost to follow-up before week 16.

‡ Percentages are based on the intention-to-treat analysis set, which included patients who had undergone randomization at least 16 weeks before the data-cutoff date. 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 during which "no or minimal pain" could not be noted.

‖ 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 mean 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). With regard to 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.

the trial. One serious adverse event (stroke due to carotid-artery dissection) occurred during the run-in period, and four serious adverse events occurred during the randomized-withdrawal period; these included palpitations after alcohol ingestion (in the placebo group), squamous-cell carcinoma (in the rilonacept group), and pyrexia and postoperative ileus (in 1 patient each; both after rilonacept bailout in the placebo group). Overall, the investigators reported adverse events in 74 of the 86 enrolled patients (86%) (Table 3 and Table S8). Four patients had adverse events leading to the discontinuation of rilonacept therapy; these events, all of which occurred during the run-in period, included alopecia, extrinsic allergic alveolitis, erythema, and systemic allergic reaction (hypersensitivity). There were no deaths during the trial.

**Table 3. Adverse Events.***

| Event | Run-In Period | Randomized-Withdrawal Period | | | | Total (N=86) |
|---|---|---|---|---|---|---|
| | Rilonacept (N=86) | Rilonacept, Including Bailout (N=30) | Placebo, Including Bailout (N=31) | Rilonacept, before Bailout (N=30) | Placebo, before Bailout (N=31) | |
| | *number of patients with event (percent)* | | | | | |
| Any adverse event | 69 (80) | 24 (80) | 22 (71) | 24 (80) | 13 (42) | 74 (86) |
| Adverse events according to maximum severity† | | | | | | |
| Mild | 52 (60) | 16 (53) | 17 (55) | 16 (53) | 9 (29) | 47 (55) |
| Moderate | 15 (17) | 8 (27) | 5 (16) | 8 (27) | 4 (13) | 25 (29) |
| Severe | 2 (2) | 0 | 0 | 0 | 0 | 2 (2) |
| Serious adverse event | 1 (1) | 1 (3) | 3 (10) | 1 (3) | 1 (3) | 5 (6) |
| Adverse event leading to death | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse event leading to dose interruption | 0 | 1 (3) | 0 | 1 (3) | 0 | 1 (1) |
| Adverse event leading to discontinuation of rilonacept or placebo | 4 (5) | 0 | 0 | 0 | 0 | 4 (5) |
| Cancer‡ | 0 | 1 (3) | 0 | 1 (3) | 0 | 1 (1) |
| Injection-site reaction | 28 (33) | 6 (20) | 2 (6) | 5 (17) | 0 | 29 (34) |
| Infection or infestation | 14 (16) | 12 (40) | 7 (23) | 12 (40) | 3 (10) | 29 (34) |
| Upper respiratory tract infection | 12 (14) | 7 (23) | 2 (6) | 7 (23) | 0 | 19 (22) |

* For patients who did not discontinue the trial regimen and who transitioned to the open-label extension period, the adverse events reported here are those that occurred between the first dose of rilonacept in the run-in period and the last visit during the randomized-withdrawal period. For patients who discontinued rilonacept during the run-in period (10 patients) or who discontinued rilonacept or placebo during the randomized-withdrawal period (1 patient) or at the end of the randomized-withdrawal period (1 patient) (i.e., did not continue into the long-term extension period), data on adverse events continued to be collected for 6 weeks after the last dose of rilonacept or placebo. Patients with multiple events were counted once in each appropriate category.

† Each patient was counted once, according to the maximum severity of the adverse event.

‡ Cancer was an event of special interest. Basal-cell carcinoma of the skin was excluded.

Injection-site reactions and upper respiratory tract infections were the most common adverse events. During the run-in and randomized-withdrawal periods, injection-site reactions (all of mild or moderate severity) occurred in 29 patients (34%), all of whom were rilonacept recipients. Upper respiratory tract infection was reported in 7 patients (23%) who received rilonacept before bailout and in no patients who received placebo before bailout. All the upper respiratory tract infections were mild or moderate in severity.

At week 24, the mean low-density lipoprotein cholesterol level, assessed in patients who were in a nonfasting state, was higher with rilonacept before bailout than with placebo before bailout (124.8±33.4 mg per deciliter [3.25±0.85 mmol per liter] vs. 111.7±24.4 mg per deciliter [2.90±0.65 mmol per liter]); the mean triglyceride level, assessed in patients who were in a nonfasting state, was also higher with rilonacept before bailout (198.0±105.8 mg per deciliter [2.24±1.20 mmol per liter] vs. 96.7±34.0 mg per deciliter [1.10±0.40 mmol per liter]). Details of the injection-site reactions, upper respiratory tract infections, and lipid variables are provided in Tables S9 through S12.

## DISCUSSION

RHAPSODY showed that treatment with rilonacept, an interleukin-1$\alpha$ and interleukin-1$\beta$ cytokine trap, led to a lower risk of pericarditis recurrence than placebo. Rilonacept therapy also led to rapid resolution of pericarditis episodes and successful weaning from glucocorticoids. The trial results were consistent regardless of previ-

ous glucocorticoid use. Injection-site reactions and upper respiratory tract infections were the most common adverse events. In addition, higher lipid levels, as assessed in patients who were in a nonfasting state, were observed with rilonacept than with placebo, as has been reported elsewhere.[13,19]

The management of recurrent pericarditis with targeted monotherapy such as rilonacept could offer an alternative therapeutic option for patients. The results of this trial suggest that patients treated with rilonacept may be able to discontinue colchicine and glucocorticoids. The rate of tapering of standard-of-care therapies after the initiation of rilonacept was more rapid than that in usual practice; the median time by which the patients discontinued standard therapy and were receiving rilonacept monotherapy was 7.9 weeks. No patient in the randomized-withdrawal period had a reintroduction of glucocorticoid therapy, and no pericarditis recurrences were reported during the randomized-withdrawal period in patients receiving bailout rilonacept.

The resolution of acute episodes and the prevention of subsequent episodes during rilonacept monotherapy support the hypotheses that interleukin-1 is an important mediator of recurrent pericarditis in patients who have evidence of systemic inflammation, as characterized by elevated CRP levels, and that targeted inhibition of the interleukin-1 pathway is sufficient for the treatment and prevention of pericarditis episodes. Preformed interleukin-1$\alpha$ is released by damaged or inflamed pericardial cells and may contribute to the propagation and maintenance of inflammation by means of activation of the nucleotide oligomerization domain (Nod)–like receptor protein 3 (NLRP3) inflammasome, which then augments the inflammatory response by producing interleukin-1$\beta$ in a cascade amplification system. The nonredundant roles of interleukin-1$\alpha$ and interleukin-1$\beta$ in inflammation underscore the importance of a treatment that targets both cytokines.[20,21] The generalizability of the results of a previous small trial was limited by the selective recruitment of patients who had previously been observed to have had a pericarditis recurrence after the withdrawal of glucocorticoids, many of whom also continued concomitant use of colchicine, an inflammasome inhibitor, during the randomized-withdrawal period of the trial.[14] The role of interleukin-1 antagonism in patients with pericarditis without elevated inflammation markers remains to be tested.

Our trial has limitations, including the relatively small number of enrolled patients; however, the effect size was large and significant. The randomized-withdrawal trial design restricts the findings to patients who had already had a response to therapy. However, 77 of the 86 patients who entered the run-in period had the prespecified treatment response that was considered to be necessary in order for them to undergo randomization, which suggests that the findings may be applicable to many patients with recurrent pericarditis. The median duration of exposure to rilonacept was 9 months, with about half the patients being followed through 24 weeks after the 12-week run-in period of this event-driven trial. The long-term extension period is ongoing.

In this randomized-withdrawal trial, the interleukin-1$\alpha$ and interleukin-1$\beta$ cytokine trap rilonacept was studied in patients with recurrent pericarditis. During run-in therapy with rilonacept, most patients had a rapid clinical response and could be weaned from other therapy, including glucocorticoids. During the subsequent randomized-withdrawal period, adjudicated recurrences of pericarditis were significantly less frequent in patients treated with rilonacept than in those who received placebo.

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a shareholder in Kiniksa Pharmaceuticals and being an inventor on a pending patent application (PCT/US2018/052985; U.S. patent application number, 16/143,391; and corresponding national stage applications) covering methods of using rilonacept for treating recurrent pericarditis, licensed to Kiniksa Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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## APPENDIX

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