# Rilonacept as Monotherapy for Long-Term Recurrent Pericarditis Management: Sustained Disease Control Over Three Years

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**A new integrated analysis of RHAPSODY combined RW and LTE Periods confirmed a sustained 96% reduction in pericarditis recurrence risk while on rilonacept monotherapy for up to 32 months of treatment**

## BACKGROUND

### Recurrent Pericarditis (RP)

- Recurrent pericarditis (RP) predominantly shows features consistent with IL-1-mediated autoinflammatory disease[1]
  - RP negatively impacts quality of life, and refractory disease requires years of treatment[1-3]
- The emergence of data implicating IL-1 in RP pathophysiology informed a novel approach to address the well-known concerns of prolonged corticosteroid use[4-6]
- The AIRTRIP study was the first clinical trial of IL-1 pathway inhibition in RP[7]
  - AIRTRIP demonstrated that anakinra (± concomitant colchicine), when used in idiopathic RP patients flaring despite glucocorticoids, significantly reduced the risk of recurrence versus placebo
  - ~45% of patients receiving anakinra were also still receiving concomitant colchicine during the Randomized-Withdrawal (RW) Period, as monotherapy was not obligatory
- Since the anti-inflammatory effects of both IL-1 pathway inhibitors and colchicine include modulation of the NLRP3 inflammasome, this partial mechanistic overlap raised questions about the value of combination therapy vs. the potential for therapeutic redundancy[3,4]

### RHAPSODY

- The phase 3 trial RHAPSODY demonstrated that rilonacept (IL-1α and IL-1β cytokine trap) was effective in treating RP not only as a third-line agent (after glucocorticoids) but also as a second-line agent (instead of glucocorticoids) and in reducing recurrence risk, supporting authorization by the FDA as the first and only approved treatment for RP
  - In RHAPSODY (RW Period and 2-year long-term extension [LTE]), once-weekly rilonacept reduced the risk of recurrence over long-term treatment (96% and 98%, respectively)
- This reduction in recurrence in the RW period was achieved with rilonacept used as a monotherapy
  - Rilonacept as a monotherapy provided durable and complete suppression of the IL-1 pathway, obviating the need for adjunctive colchicine in preventing pericarditis recurrences

## METHODS

### Study Design

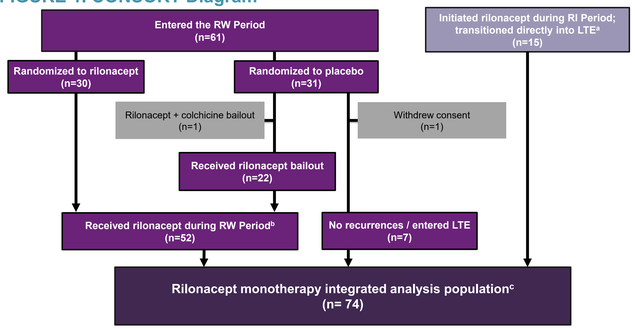
- RHAPSODY (NCT03737110) was a pivotal randomized, double-blind, placebo-controlled, event-driven trial comprised of a Run-In (RI) treatment Period, an RW Period, and an LTE
- RHAPSODY enrolled patients with an acute pericarditis recurrence despite treatment with standard therapies (NSAIDs/colchicine/oral glucocorticoids in any combination)
- Rilonacept was initiated, and patients were required to discontinue background pericarditis therapies by the end of Week 10, followed by a 2-week rilonacept monotherapy period prior to randomization
- Patients were then randomized in a 1:1 ratio to receive either rilonacept or placebo once-weekly until pericarditis recurrence or end of the event-driven RW Period. Patients with a pericarditis recurrence meeting bailout criteria could receive bailout rilonacept regardless of prior treatment assignment
- Clinically stable patients completing the RW Period (along with patients who were still in the RI period when the event-driven RW period ended and had achieved the pre-defined clinical-response criteria) were eligible to continue into the LTE and receive weekly rilonacept for up to 24 months

### Analytical Plan

- This post-hoc integrated analysis combined data from the two individual prespecified analyses of RHAPSODY (the RW and LTE Periods) in order to quantify the long-term efficacy of rilonacept monotherapy in patients with RP (**Figure 1**)
- Patients who received rilonacept in either the RW Period (either randomized to rilonacept or received bailout rilonacept if randomized to placebo) or initiated rilonacept during the LTE were included in this integrated analysis. Patients were followed until their end of treatment and were censored at the time of initiation of any concomitant therapy indicated for treatment of RP
  - This censoring ensured that outcomes were attributable exclusively to rilonacept monotherapy
- Freedom from recurrence on rilonacept monotherapy was quantified using the Kaplan-Meier (KM) method from RW start (if randomized to rilonacept) or from initiation of bailout rilonacept (e.g., if randomized to placebo) until the end of treatment
  - Only CEC-adjudicated pericarditis recurrences meeting formal RHAPSODY event adjudication criteria (i.e., pericarditis pain [patient-reported numerical rating scale [NRS] ≥4, plus C-reactive protein [CRP] level ≥1 mg/dL, and objective evidence of pericarditis [e.g., pericardial effusion, pericardial rub, or electrocardiographic changes]) were used for the endpoint of this analysis
- Safety was also evaluated over this combined integrated analysis window

## RESULTS

### FIGURE 1. CONSORT Diagram




[a]Entered LTE from RI Period after closure of the event-driven RW Period.
[b]Patient received rilonacept as monotherapy during the RW Period (either initiated during RW Period as bailout therapy or carried over from RI Period).
[c]Includes patients who received rilonacept as monotherapy during the RW Period (randomization to rilonacept, bailout rilonacept), patients who transitioned from the RI Period to the LTE and continued on rilonacept monotherapy, and patients randomized to placebo, who had no flares in the RW Period, and received rilonacept upon entering the LTE.

### Concomitant RP Medication Use in RHAPSODY RW/LTE Periods

- Before randomization, all patients discontinued background therapies (median time to monotherapy: 7.9 weeks)
- There were no additions of concomitant colchicine during the RW Period, in compliance with the study protocol
- In the LTE, colchicine was added to rilonacept in 8.1% (6/74) of patients
  - One patient received concomitant colchicine (0.6 mg BID) for 2 days due to chest pain (no CRP elevation)
  - One patient added colchicine (0.5 mg BID) prophylactically before an intentional rilonacept treatment interruption for elective cardiac surgery and experienced a recurrence during this interruption
  - Four patients received concomitant colchicine (all 0.6 mg BID) in the absence of chest pain/CRP elevation/recurrence

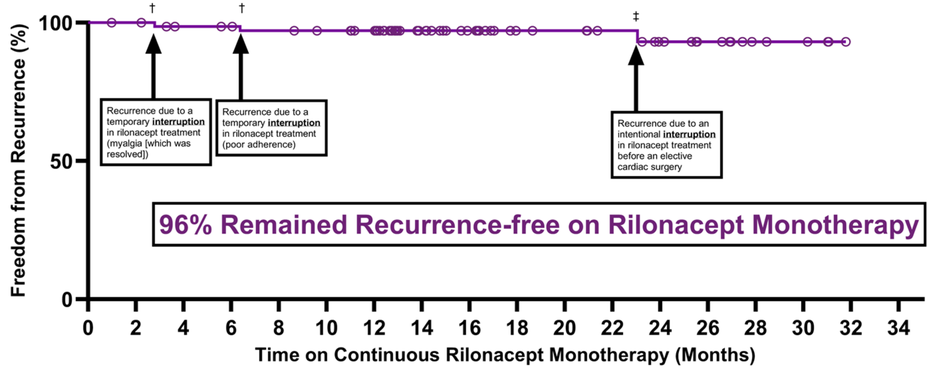
### TABLE 1. RHAPSODY RW/LTE Integrated Analysis: Demographics and Patient Characteristics*

| Characteristic | N=74 |
|---|---|
| Age, y | 43.9±15.7 |
| Age, y, distribution, no. (%) | |
| 12–17 | 6 (8.1) |
| 18–64 | 62 (83.8) |
| 65–78 | 6 (8.1) |
| Sex, no. (%) | |
| Female | 41 (55.4) |
| Race, no. (%) | |
| White | 68 (91.9) |
| Black | 5 (6.8) |
| Other | 1 (1.4) |
| Recurrent pericarditis type, no. (%) | |
| Idiopathic | 62 (83.8) |
| Post-pericardiotomy syndrome | 11 (14.9) |
| Dressler syndrome | 1 (1.4) |
| Medication used at qualifying episode of pericarditis, no. (%) | |
| NSAID | 51 (68.9) |
| Colchicine | 61 (82.4) |
| Glucocorticoids | 38 (51.4) |
| Pericarditis disease duration at RHAPSODY baseline, y | 2.5±3.2 |
| Total number of episodes of pericarditis prior to RHAPSODY** | 4.7±1.7 |
| Annualized incidence of pericarditis episodes prior to RHAPSODY | 3.9±3.9 |
| C-reactive protein level (qualifying episode), mg/dL | 6.5±7.0 |

*Plus–minus values are means ± SDs.
**Including incident and qualifying episodes.

### RHAPSODY RW/LTE Integrated Analysis: Efficacy and Safety

### Figure 2. Pericarditis Recurrence Risk Reduction While on Rilonacept as a Monotherapy (n = 74)[a,b]




[a]Patients who added colchicine (n=5 in the LTE) were censored in the KM curve at 6 days after last rilonacept dose or at colchicine initiation (whichever came first). One additional patient in the LTE added colchicine prophylactically before an intentional rilonacept treatment interruption for elective cardiac surgery and subsequently experienced a recurrence. This patient was not censored from the recurrence-free analysis at colchicine initiation in order to capture this event.
[b]Time 0 months represents RW Period start (if randomized to rilonacept or from initiation of bailout rilonacept [if patient experienced flare after being randomized to placebo]) or from start of LTE (if randomized to placebo and experienced no flares during RW [and subsequently entered into the LTE] or if transitioned directly into the LTE from the RI).
†Both recurrences in the RW were associated with temporary (1-3 doses) interruptions in rilonacept treatment (n=1, myalgia [which was resolved]; n=1, poor adherence).
‡The one recurrence in the LTE was associated with an intentional interruption of rilonacept treatment before elective cardiac surgery despite prophylactic colchicine having been added. The patient was not censored at colchicine initiation in order to capture this recurrence in this analysis. The patient restarted rilonacept after a failed attempt of NSAID/colchicine rescue and remained on rilonacept and colchicine for the remainder of the LTE with no subsequent recurrences.

### Table 2. Adverse Events

| Category, no. (%) | N=74 |
|---|---|
| Any AE | 70 (94.6) |
| AEs by maximum severity§ | |
| Mild | 27 (36.5) |
| Moderate | 30 (40.5) |
| Severe | 9 (12.2) |
| AEs related to study drug | 30 (40.5) |
| Serious AEs¶ | 10 (13.5) |
| Serious AEs related to study drug# | 2 (2.7) |
| AEs leading to dose interruption** | 3 (4.1) |
| AEs leading to study drug discontinuation†† | 3 (4.1) |
| AEs leading to death | 0 |
| Infections or infestations‡‡ | 39 (52.7) |
| Upper respiratory tract infections | 18 (24.3) |
| Injection-site reactions §§ | 12 (16.2) |
| Malignancies§§ | 1 (1.4) |

§Each patient represented according to maximum severity.
¶Ten patients experienced serious TEAEs: (1) pneumothorax; (2) acute endocarditis, aortic valve disease, acute myocardial infarction, pericarditis; (3) transient ischemic attack, coronavirus infection; (4) worsening of aortic insufficiency; (5) pneumonia, pneumonia viral (COVID-19); (6) left ventricular failure, hip fracture, bile duct stone, cardiac device malfunction; (7) palpitations after alcohol ingestion; (8) squamous-cell carcinoma; (9) pyrexia; (10) postoperative ileus.
#Events included acute endocarditis and viral pneumonia.
**Events included coronavirus infection and sinus congestion.
††Events included fatigue, acute endocarditis, and viral pneumonia.
‡‡No reported infestation adverse events.
§§All injection site reactions were mild in severity.
§§Squamous-cell carcinoma (n=1).
AE, adverse event.

## DISCUSSION

- 91.9% (n= 68/74) of patients initiating rilonacept achieved and remained on monotherapy for the duration of the study (median [range] rilonacept therapy duration was 19.5 [0.9 – 31.8] months)
- A strategy of IL-1 pathway inhibition with rilonacept as a monotherapy provided sustained pericarditis recurrence risk reduction, provided the blockade of IL-1 was consistent and continuous
  - 95.9% (n=71/74) of patients remained recurrence-free while receiving rilonacept as monotherapy (**Figure 2**)
  - The three adjudicated recurrences observed in this analysis were each associated with temporary interruptions of 1-3 doses of rilonacept
- The reduction in annualized incidence of pericarditis recurrence on rilonacept as monotherapy was consistent with previously-reported findings from the pivotal study and LTE[5]
  - In RHAPSODY, the annualized incidence of pericarditis recurrence was 0.04 events/patient-year (PY) up to the 18-month decision milestone vs. 4.4 events/PY prior to RHAPSODY
  - In this longer analysis, the annualized incidence of pericarditis recurrence was 0.03 events/PY for up to 32 months of rilonacept as monotherapy vs. 3.9 events/PY prior to RHAPSODY
- Rilonacept was well tolerated over the integrated analysis period; injection-site reactions were lower in the LTE vs. the RW Period, possibly due to accumulated tolerance or familiarity with injections

### Limitations

- Despite the limitations of sample size in this rare disease study, the efficacy findings were robust and clinically significant
- Whereas previously-adjudicated (CEC) pericarditis recurrences from the RW Period were used for this analysis, since the CEC had not adjudicated the suspected pericarditis events during the LTE portion of study, the events from the LTE portion of this analysis were derived from the original published LTE analysis, which had applied the same rigorous adjudication criteria that the CEC used to review suspected events, in order to assure consistency in endpoint quality
  - The suspected events included in this post-hoc analysis were validated recurrences since they each met strict RHAPSODY criteria of CRP ≥1 mg/dL and an NRS score ≥4

## CONCLUSIONS

- Rilonacept as a monotherapy was associated with complete abrogation of pericarditis recurrence over the three-year trial duration when used continuously without interruption
  - Pericarditis recurrences while on treatment in the RW and LTE occurred only after temporary interruptions in rilonacept therapy
- These findings support evidence-based use of rilonacept as a monotherapy in long-term RP management, minimizing need for adjunctive treatments and reducing polypharmacy
- Further investigations are warranted to address how to assess patients who are well-managed on long-term therapy for subsequent determination of total duration of treatment and timing of cessation of IL-1 pathway inhibition

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### DISCLOSURES

D. Lotan: consultant and speaker for Kiniksa; M. Imazio: advisory board for Kiniksa Pharmaceuticals; A.L. Klein: grants and consultant fees from Kiniksa Pharmaceuticals, Cardiol Therapeutics, Ventyx, and Pfizer; A. Brucato: institutional funding from Kiniksa Pharmaceuticals as an investigative site, an unrestricted research grant from Sobi, Acarpia, and Kiniksa, and travel and accommodation for advisory committee from Sobi, Kiniksa, and Monteresa; A. Abbate: Consultant and speaker for Kiniksa Pharmaceuticals, received research support from and has served as an advisor to Swedish Orphan Biovitrum, Kiniksa, and Olatec; M. Arad: no disclosures to report; P.C. Cremer: grants and consultant fees from Kiniksa Pharmaceuticals, grants and personal fees from Sobi; S.A. Luis: consultant fees from Kiniksa Pharmaceuticals, Cardiol Therapeutics, and Medtronic; S. Wang, J. Clair, J.F. Paolini: shareholders and employees of Kiniksa Pharmaceuticals; A. Curtis: employee of Kiniksa Pharmaceuticals at the time of this analysis.

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