Prolonged Rilonacept Treatment in RHAPSODY Long-Term Extension Provided Persistent Reduction of Pericarditis Recurrence Risk

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BACKGROUND

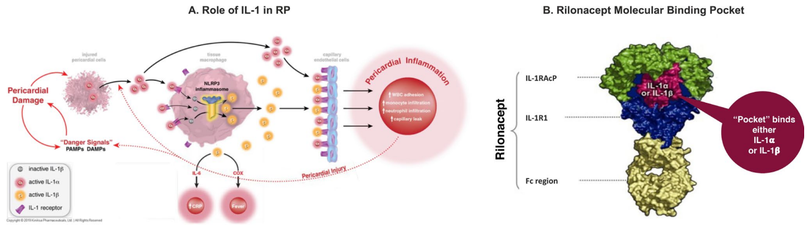
Recurrent Pericarditis (RP)

- RP is a chronic, debilitating autoinflammatory disease mediated in part by interleukin-1 (IL-1)[1,2] (**Figure 1**)
- Among patients with multiple recurrences, epidemiologic data describe a median disease duration of 2.84 years[3]
- More recently, a chart review study showed that, for patients (n = 106) presenting with an active flare (median 3 prior recurrences) and hs-CRP level > 10 mg/L (n = 92), only 31% of these patients achieved clinical remission (no longer requiring anti-inflammatory therapy) during the median 21-month observation period (IQR, 12–38 months)[4]
- Treatment for RP commonly consists of nonspecific oral therapies (e.g., NSAIDs, colchicine, or corticosteroids). However, NSAIDs and colchicine have incomplete efficacy and dose-limiting side effects, and corticosteroids have serious safety risks when used long-term[2,5,6]

Rilonacept

- Rilonacept is a once-weekly interleukin-1α (IL-1α) and interleukin-1β (IL-1β) cytokine trap that prevents engagement of IL-1 with its cell-surface receptor, thus inhibiting IL-1α and IL-1β activity (**Figure 1**)[7]
- Rilonacept is approved in the United States for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and children 12 years and older. It is also approved for cryopyrin-associated periodic syndromes (CAPS) in adults and children 12 years and older and for the maintenance of remission of deficiency of interleukin-1 receptor antagonist (DIRA) in adults and pediatric patients weighing 10 kg or more[8]

FIGURE 1. RILONACEPT MECHANISM OF ACTION



COX, cyclooxygenase; CRP, C-reactive protein; DAMP, damage-associated molecular pattern; Fc, fragment crystallizable; IL, interleukin; IL-1R1, interleukin 1 receptor component; IL-1RAcP, interleukin 1 receptor accessory protein; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; PAMP, pathogen-associated molecular pattern; RP, recurrent pericarditis; WBC, white blood cell.

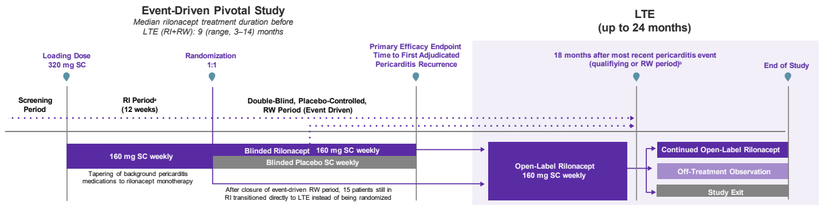
RHAPSODY[2]

- RHAPSODY was a phase 3, double-blind, placebo-controlled, event-driven, randomized-withdrawal (RW) trial of rilonacept in patients with RP, which also included a long-term extension (LTE) phase, allowing up to 24 months of additional open-label rilonacept treatment (**Figure 2**)
- Population: Patients enrolling in the pivotal study had a mean disease duration of 2.4 years and presented with an acute pericarditis recurrence (qualifying episode) despite use of NSAIDs (67%), colchicine (80%), or corticosteroids (49%)
  - Mean CRP level was 6.2 mg/dL
  - The cause of pericarditis was idiopathic in 85%, post–pericardiotomy syndrome in 14%, and Dressler syndrome in 1% of the cohort
- All suspected pericarditis recurrence events in the event-driven RW period were formally adjudicated by the Clinical Endpoint Committee (CEC)
- Results of the pivotal study
  - During the run-in period, the median (95% CI) time to pain response was 5 (4–6) days, and the median (95% CI) time to normalization of the CRP level was 7 (5–8) days. The median (95% CI) time to the prespecified treatment response was 5 (4–7) days
  - During the RW period, patients receiving rilonacept experienced a 96% reduction in the risk of recurrence (hazard ratio in a Cox proportional-hazards model, 0.04; 95% CI, 0.01–0.18; P<0.0001 by log-rank test)
    - 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 (95% CI) time to the first adjudicated recurrence in the placebo group was 8.6 (4.0–11.7) weeks
  - In the period until the event-driven RW portion of the study was closed, 2 of 30 patients (7%) in the rilonacept group experienced a pericarditis recurrence, as compared with 23 of 31 patients (74%) in the placebo group
    - The 2 recurrence events in the rilonacept group were associated with temporary interruptions of the trial-drug regimen of 1 to 3 weekly doses
  - The most common adverse events were injection-site reactions and upper respiratory tract infections

PURPOSE

- The LTE phase of RHAPSODY was designed to provide further insights into the efficacy and safety of rilonacept in patients with RP and to help inform future clinical decision-making in this disease

FIGURE 2. RHAPSODY DESIGN



[a]Duration of the RI period was concealed from patients to blind them to randomization timing.
LTE, long-term extension; RI, run-in; RW, randomized-withdrawal; SC, subcutaneous.

[b]For each LTE patient, **18 months after most recent pericarditis recurrence (qualifying or RW period), a decision was made** based on clinical status and at investigator discretion to:

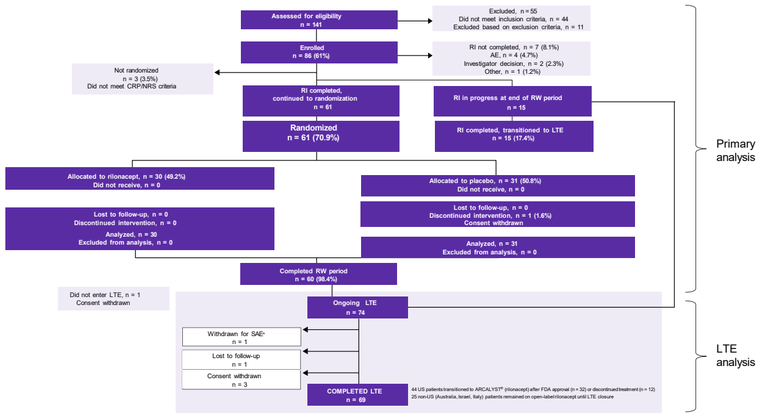
- **Continue rilonacept** on study, *OR*
- **Suspend rilonacept** treatment and remain on study for observation (rilonacept rescue for recurrence allowed) *OR*
- **Discontinue from LTE** completely (no further observation)

RESULTS

Patient Disposition

- Patients entering the LTE already had a history of 2.5 years of disease duration (mean 3.8 pericarditis recurrences) before entering RHAPSODY
- At the end of the event-driven RW study, the median duration of rilonacept therapy had reached 9 months (maximum 14 months)
- In May 2020, 74 of 75 eligible patients continued into the RHAPSODY open-label LTE (**Figure 3**)
- Baseline demographics and prior pericarditis history at run-in baseline for participants in the LTE (n = 74) are summarized in **Figure 4**
- At the 1-year anniversary of the LTE (April 2021), the median duration of continuous rilonacept treatment had reached 20 months
- All patients were followed in the LTE until geography-specific study closure
  - Total LTE—all geographies (n = 74)
    - Median rilonacept treatment duration from run-in baseline was 23 months (maximum 35 months)
  - US patients (n = 45)
    - In April 2021, the LTE was concluded in the United States, and all US patients either switched to commercial ARCALYST® (rilonacept) therapy (n = 32) or discontinued rilonacept (n = 12)
    - Median continuous rilonacept treatment duration from run-in baseline was 18 months (maximum 27 months)
  - Non-US (Italy, Israel, Australia) patients (n = 29)
    - In June 2022, the non-US LTE was concluded, and all patients discontinued rilonacept
    - Median rilonacept treatment duration from run-in baseline was 29 months (maximum 35 months)

FIGURE 3. PATIENT DISPOSITION (CONSORT DIAGRAM)



[c]Acute endocarditis.
AE, adverse event; CRP, C-reactive protein; FDA, US Food and Drug Administration; LTE, long-term extension; NRS, numerical rating scale; RI, run-in; RW, randomized-withdrawal; SAE, serious adverse event.

Efficacy Up to 18-Month Decision Point

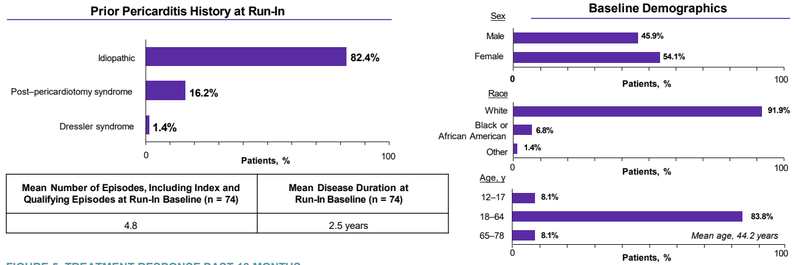
- During treatment with open-label rilonacept in the LTE (before 18-month decision point), continued rilonacept treatment resulted in continued treatment response
  - Pericarditis recurrences, inflammation signs (CRP levels), and severity of RP symptoms (Patient Global Impression of Pericarditis Severity [PGIPS]) remained low
  - At each study visit:
    - >95% of patients had CRP levels ≤1 mg/dL
    - >86% of patients reported absent or minimal pericarditis symptoms (PGIPS)
  - Only 3 investigator-assessed recurrences were reported
    - Annualized incidence: 0.04 events per patient-year

Efficacy After 18-Month Decision Point

- A total of 52 patients reached the 18-month decision point while on rilonacept (i.e., 18 months since most recent recurrence, whether qualifying episode or in the RW period)
  - 33 patients continued treatment with open-label rilonacept
  - 8 patients suspended rilonacept treatment and remained on study for observation (rilonacept rescue for recurrence was allowed)
  - 11 patients discontinued study participation
- Continued treatment with rilonacept past 18 months resulted in continued treatment response
  - There was a 98% reduction in risk of recurrence (hazard ratio, 0.02; P<0.0001[a]) (**Figure 5**)
    - Recurrence (investigator-assessed) rate was 3.0% (1/33) in the patients who continued rilonacept treatment. This recurrence occurred at 23.4 weeks into the LTE and was associated with a treatment interruption of 4 weeks
    - Recurrence (investigator-assessed) rate was 75.0% (6/8) in the patients who suspended rilonacept treatment for observation
  - The median (IQR) time to recurrence after suspending rilonacept treatment was 11.8 (3.7–not estimable [NE]) weeks
  - Reinitiation of rilonacept resulted in resolution of acute pericarditis recurrence
  - Annualized recurrence rate[b] (95% CI) was 0.18 (0.06–0.41) events per patient-year for the patients who remained on rilonacept and 2.18 (0.80–4.75) events per patient-year for the patients who interrupted rilonacept
- At the end of the LTE treatment period, patients stopped rilonacept treatment and were returned to standard of care for recurrent pericarditis. Patients were monitored in a posttreatment safety follow-up period (6 weeks post–last dose) for adverse events
  - 4 additional pericarditis recurrences occurred during the posttreatment follow-up period, at ~6 weeks post–rilonacept treatment (3 patients) and ~3 weeks post–rilonacept treatment (1 patient)

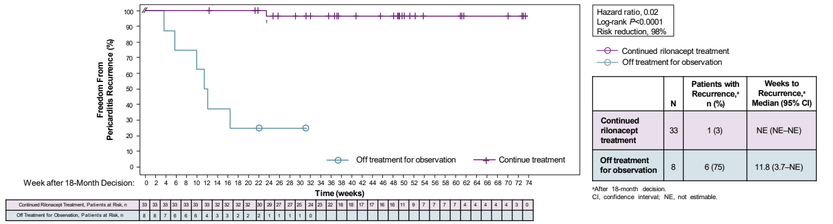
[a]Two-sided *P* value, log-rank test. [b]Number of recurrences in LTE periods for all patients/sum of patient-years in LTE periods for all patients. For patients who continued in study off treatment for observation, patient-years calculated as treatment, minimum (end-of-study date, cutoff date, first-dose date after observation -1) – LTE 18-month disposition date +1; for patients who continued treatment, patient-years calculated as minimum (end-of-study date, cutoff date) – LTE 18-month disposition date +1; 95% CI calculated using an exact method with Poisson distribution.

FIGURE 4. PATIENT COHORT (N = 74) IN RHAPSODY LONG-TERM EXTENSION



Mean Number of Episodes, Including Index and Qualifying Episodes at Run-In Baseline (n = 74)	Mean Disease Duration at Run-In Baseline (n = 74)
4.8	2.5 years

FIGURE 5. TREATMENT RESPONSE PAST 18 MONTHS



Hazard ratio, 0.02
Log-rank *P*<0.0001
Risk reduction, 98%

- Continued rilonacept treatment
- Off treatment for observation

	N	Patients with Recurrence,[a] n (%)	Weeks to Recurrence,[a] Median (95% CI)
Continued rilonacept treatment	33	1 (3)	NE (NE–NE)
Off treatment for observation	8	6 (75)	11.8 (3.7–NE)

[a]After 18-month decision.
CI, confidence interval; NE, not estimable.

[†]The patients with a recurrence at 23.4 weeks had interrupted rilonacept treatment ~4 weeks prior.

Safety (Table 1)

- During the LTE period, treatment-emergent adverse events (TEAEs) were experienced by 83.8% of patients (n = 62)
- In most patients, the maximum severity of TEAEs was mild (37.8%) or moderate (37.8%)
- 2 patients experienced serious TEAEs (acute endocarditis, viral pneumonia) considered "related" to the study drug

TABLE 1. ADVERSE EVENTS REPORTED IN RHAPSODY LONG-TERM EXTENSION

TEAE Category,[a] n (%)	LTE Period (n = 74)
Any TEAE[b]	**62 (83.8)**
TEAE by maximum severity[c]	
Mild	28 (37.8)
Moderate	28 (37.8)
Severe	6 (8.1)
TEAE related to study drug[d]	**21 (28.4)**
Patients with serious TEAEs[e]	**5 (6.8)**
Serious TEAE related to study drug	2 (2.7)
Leading to dose interruption	2 (2.7)
Leading to study drug discontinuation	3 (4.1)
Leading to death	0
Infection or infestation	31 (41.9)
TEAE of upper respiratory tract infection	12 (16.2)
TEAE of injection-site reaction	4 (5.4)

[a]Patients with multiple events were counted once in same category. [b]Adverse event that starts or increases in severity from first study-drug dose to 6 weeks after last dose. [c]Each patient represented according to maximum severity. [d]Event was related, possibly related, or missing, as assessed by investigator. *5 patients experienced serious TEAEs: 1. Pneumothorax; 2. Acute endocarditis, aortic valve disease, acute myocardial infarction, pericarditis; 3. Transient ischemic attack, coronavirus infection; 4. Pneumonia, pneumonia viral (COVID-19); 5. Left ventricular failure, hip fracture, bile duct stone, cardiac-device malfunction.
LTE, long-term extension; TEAE, treatment-emergent adverse event.

Limitations

- A relatively small number of patients participated in RHAPSODY
  - Despite the small cohort, the findings were robust and significant
- The randomized-withdrawal trial design limited the study population to patients who had a positive response to rilonacept in the run-in period
  - >90% of patients entering RHAPSODY demonstrated a treatment response (to a prespecified level) during the run-in period and were eligible for study randomization, suggesting that the study findings are relevant to many patients with RP

CONCLUSIONS

- Patients with RP have a chronic autoinflammatory disease, characterized by multiple recurrences mediated by IL-1. This disease may last several years
- In patients with symptomatic RP failing standard of care:
  - Continued rilonacept treatment during the LTE (median 18 and 29 months in the US and non-US patients, respectively) resulted in continued treatment response
  - Rilonacept reduced the risk of pericarditis by 98% beyond 18 months of treatment
    - Suspension of rilonacept treatment even after 18 months of treatment resulted in unmasking of the underlying autoinflammation process, resulting in pericarditis recurrence
    - Reinitiation of rilonacept resulted in resolution of the acute pericarditis recurrences
  - Over treatment periods of 18 months and beyond in this study, rilonacept was generally well tolerated
  - In patients with similar disease characteristics, treatment beyond 18 months may be warranted to prevent pericarditis recurrence over the long term

DISCLOSURES

Massimo Imazio reports other fees from Kiniksa Pharmaceuticals and Sobi Pharmaceuticals outside the submitted work. **Allan L. Klein** reports grants and other fees from Kiniksa Pharmaceuticals during the conduct of the study and other fees from Cardiol Therapeutics, Sobi Pharmaceuticals, and Pfizer outside the current work. **Antonio Abbate** reports other fees from Kiniksa Pharmaceuticals. **Michael Arad, Eliyazar Gaddam, Antonella Insalaco, Basil S. Lewis, Stephen J. Nicholls, Paul Sutej,** and **Yishay Wasserstrum** report no disclosures. **Antonio Brucato** reports institutional funding from Kiniksa Pharmaceuticals as an investigative site; an unrestricted research grant from Sobi Pharmaceuticals and Acarpia; and travel and accommodation for advisory committee from Sobi and Kiniksa. **Paul C. Cremer** reports grants and personal fees from Sobi Pharmaceuticals. **Martin M. LeWinter** reports grants and advisory board, consulting, and other fees from Kiniksa Pharmaceuticals outside the submitted work and consulting fees from Sobi Pharmaceuticals outside the current work. **David Lin** reports personal fees from Regeneron outside the current work. **Sushil A. Luis** reports consultant fees from Kiniksa Pharmaceuticals, Sobi Pharmaceuticals, and Medtronic. **Manoj Samant** was an employee of Kiniksa Pharmaceuticals at the time of the study. **JoAnn Clair, Indra Agarwal,** and **Sheldon Wang** are employees of Kiniksa Pharmaceuticals. **John F. Paolini** is an employee of Kiniksa Pharmaceuticals and is an inventor on patents and pending patent applications licensed to Kiniksa Pharmaceuticals covering methods of using rilonacept for treating recurrent pericarditis.

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REFERENCES

1. Klein AL, *et al. Heart.* 2021;107(6):488–496. **2.** Klein AL, et al. *N Engl J Med.* 2021;384(1):31–41. **3.** Lin D, et al. *Adv Ther.* 2021;38(10):5127–5143. **4.** Kumar AK, et al. *J Am Coll Cardiol.* 2022;79(16):1644–1645. **5.** Adler Y, et al. *Eur Heart J.* 2015;36(42):2921–2964. **6.** Brucato A, et al. *Intern Emerg Med.* 2018;13(4):475–489. **7.** Klein AL, et al. *Am Heart J.* 2020;228:81–90. **8.** ARCALYST® (rilonacept) [package insert]. London: Kiniksa Pharmaceuticals (UK), Ltd; 2021.