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RHAPSODY: A Pivotal Phase 3 Trial to Assess Efficacy and Safety of Rilonacept, an Interleukin 1 Alpha and Interleukin 1 Beta Blocker, in Patients With Recurrent Pericarditis

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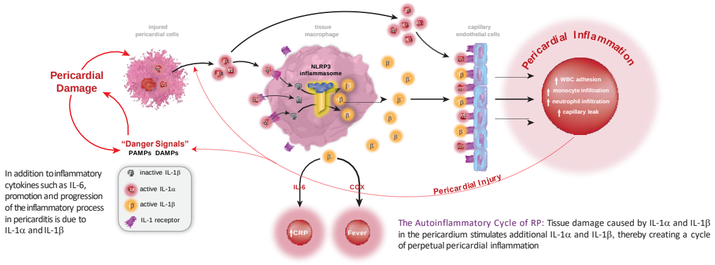
BACKGROUND

- Recurrent pericarditis (RP) is clinically defined as the recurrence of pericarditis signs and symptoms after a symptom-free period of ≥4 to 6 weeks[1]
- After an initial acute pericarditis episode, 15% to 30% of patients will experience at least 1 recurrence, of which up to 50% may experience a subsequent recurrence[1,2]
- No pharmacotherapies are formally approved by regulatory authorities in the US and much of the EU for use in RP; current guidelines recommend treatment options that may reduce inflammation and pain, including nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids (CSs)[1]
  - To avoid the long-term safety issues or dependence on CSs, and for patients who are unresponsive to conventional anti-inflammatory therapy, or cannot tolerate NSAIDs, colchicine, or CSs, other interventions are needed
- Members of the interleukin 1 (IL-1) family of cytokines are central to the pathophysiology of RP (Figure 1)[3,4]

Figure 1. Role of IL-1α and IL-1β Family in the Autoinflammatory Cycle of RP[3,4]

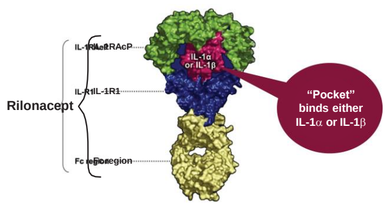


The Autoinflammatory Cycle of RP: Tissue damage caused by IL-1α and IL-1β in the pericardium stimulates additional IL-1α and IL-1β, thereby creating a cycle of perpetual pericardial inflammation

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

- Rilonacept is a dimeric fusion protein, consisting of ligand-binding domains of the extracellular portions of the human IL-1 receptor component (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked to the Fc portion of human immunoglobulin G1 (Figure 2)
- Rilonacept (Arcalyst®, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) is approved in the United States for treatment of cryopyrin-associated periodic syndromes (in patients ≥12 years), including familial cold autoinflammatory syndrome and Muckle-Wells syndrome[5]
- Rilonacept (KPL-914) is currently being investigated for RP by Kiniksa Pharmaceuticals, Ltd. (Lexington, MA)

Figure 2. Rilonacept Structure

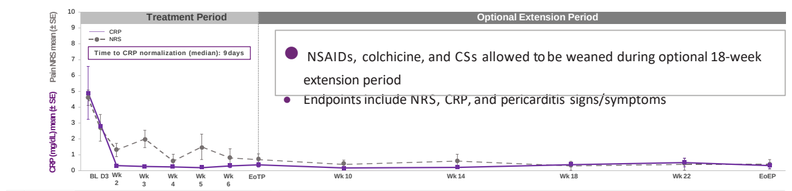


IL, interleukin; IL-1R1, IL-1 receptor subtype 1; IL-1RAcP, IL-1 receptor accessory protein.

Results From a Phase 2 Pilot Study of Rilonacept in RP

- Interim data from an open-label, Phase 2 pilot study of rilonacept in (320 mg SC loading dose, then 160 mg SC weekly maintenance) patients with RP showed[6]
  - Rapid and sustained clinically meaningful reductions in Numerical Rating Scale (NRS) pain scores and C-reactive protein (CRP) levels as early as after the first rilonacept administration (Figure 3)
  - Resolution or improvement of pericarditis manifestations and improved patient quality of life
  - Feasibility to discontinue CSs without pericarditis exacerbation

Figure 3. Rapid and Sustained Reductions in NRS Pain Scores and CRP Levels After the First Dose of Rilonacept in a Phase 2 Pilot Study (Patients Enrolled in Part 1)[a]



- NSAIDs, colchicine, and CSs allowed to be weaned during optional 18-week extension period
- Endpoints include NRS, CRP, and pericarditis signs/symptoms

BL, baseline; CRP, C-reactive protein; CSs, corticosteroids; D, day; EoEP, end of extension period; EoTP, end of treatment period; NRS, Numerical Rating Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; Wk, week.
[a]Results shown are interim results for part 1 of a 5-part Phase 2 study. Data are as of January 23, 2019.

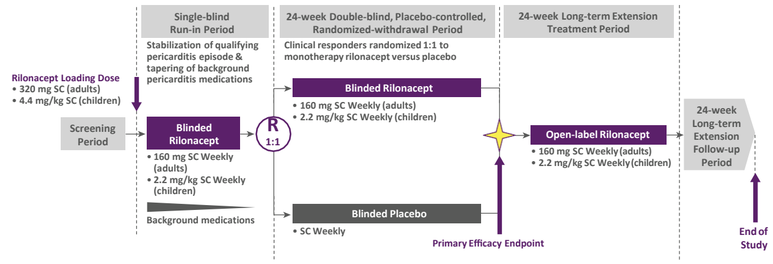
- Adverse events (AEs) in Phase 2 were consistent with the known safety profile of rilonacept; injection-site reactions were the most common AEs; all were mild and transient. Two serious treatment-emergent AEs were reported, both of which resolved (skin abscess deemed possibly related, atypical chest pain not related)
- These preliminary results from the Phase 2 pilot study informed the design of RHAPSODY (Rilonacept inHibition of interleukin 1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes stuDY) an ongoing, pivotal Phase 3 study, intended to evaluate the efficacy and safety of rilonacept treatment in patients with RP

METHODS

Study Design

- Double-blind, placebo-controlled, randomized-withdrawal trial with an open-label extension, with a planned enrollment of 56–75 patients (Figure 4)

Figure 4. RHAPSODY (Rilonacept inHibition of interleukin 1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes stuDY) Trial Design



Inclusion Criteria:
- Present at screening with at least a third pericarditis episode, defined as at least 1 day with NRS pain of ≥4 and CRP ≥1 mg/dL
- CRP value ≥1 mg/dL within the 7-day period prior to first study drug administration
- Concomitant NSAIDs and/or colchicine and/or oral CS treatment in any combination at stable doses

Primary Outcome Measure (24 weeks):
- Time to pericarditis recurrence

Secondary Outcome Measures (24 weeks):
- Proportion of patients who maintained clinical response
- Percentage of days with no or minimal pain (NRS ≤1)
- Proportion of patients with absent or minimal pericarditis symptoms
- Proportion of patients with AEs

AEs, adverse events; CRP, C-reactive protein; CS, corticosteroid; NRS, Numerical Rating Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneously.
[a]Duration of the run-in period undisclosed in order to maintain patient blinding to the start of the randomized-withdrawal period.

Patients

- Patients (≥12 y) must present with at least a third pericarditis episode (with exception of prohibited etiologies) characterized by an NRS pain score ≥4 and CRP level ≥1 mg/dL at screening
- Patients may be receiving stable doses of analgesics, NSAIDs, colchicine, and/or CSs

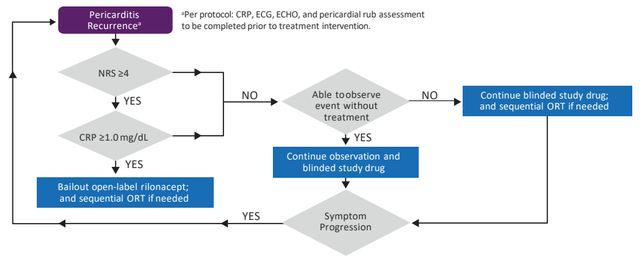
Study Visits and Treatments

- Run-in Period: After a loading dose (320 mg subcutaneously [SC] in adults and 4.4 mg/kg SC in children as 2 SC injections), all patients will receive weekly rilonacept (160 mg SC in adults and 2.2 mg/kg SC in children) during the run-in period
  - Patients will taper concomitant pericarditis medications with the goal of achieving rilonacept monotherapy by the end of the period
  - Patients who do not achieve a clinical response are discontinued from rilonacept, transitioned to standard of care pericarditis therapy, and followed through the end of the randomized-withdrawal period to better understand the natural history of RP
- Randomized-Withdrawal Period: Patients able to taper and discontinue concomitant pericarditis medications during the run-in period and achieve clinical response (mean daily NRS score ≤2.0 during the 7 days before randomization and CRP level ≤0.5 mg/dL) will be randomized 1:1 in a blinded fashion to continue rilonacept or matching placebo weekly SC injection

Monitoring Recurrence of Pericarditis

- In case of a suspected recurrence event in the randomized-withdrawal period, a diagnostic workup will be performed; all suspected events will be adjudicated by the Clinical Endpoint Committee (CEC), and only CEC-confirmed pericarditis recurrences will be used in the primary endpoint analysis
- Upon confirmation of the recurrence event, patients will be offered open-label rilonacept "bailout" (reloading with 320 mg or a corresponding pediatric dose, followed by weekly injections of 160 mg or a corresponding pediatric dose) or addition of sequential oral rescue therapy (analgesics, NSAIDs, colchicine) as bridging therapy to the open-label rilonacept bailout, based on the patient's clinical status and at the discretion of the investigator (Figure 5); patients and investigators will remain blinded to prior treatment assignment

Figure 5. Management of Suspected Pericarditis Recurrence in the Randomized-Withdrawal Period



CRP, C-reactive protein; ECG, electrocardiogram; ECHO, echocardiogram; NRS, Numerical Rating Scale; ORT, oral rescue therapy.

- Patients will continue to receive weekly study drug and the randomized-withdrawal period will continue until all patients still enrolled in the randomized-withdrawal period have achieved a minimum of 24 weeks of treatment
- Long-term Extension Treatment Period: All patients who complete the randomized-withdrawal period and attend the end-of-randomized-withdrawal visit will be given the option to enter the long-term extension period to receive up to 24 weeks of open-label rilonacept 160 mg (or 2.2 mg/kg for pediatric patients) once weekly
  - Based on enrollment assumptions and recurrence events accrual time, patients completing the long-term extension treatment period will receive rilonacept for approximately 1.2 to 3 years
- Long-term Extension Follow-up Period: The long-term extension follow-up period will follow all patients who participated in the long-term extension treatment period to assess safety and pericarditis recurrences for an additional 24 weeks while not taking study drug
  - If patients experience RP recurrence during the long-term extension follow-up period (i.e., while not taking rilonacept), they will be transitioned to conventional therapy

Efficacy Assessments

- Primary endpoint
  - Time to pericarditis recurrence (adjudicated by CEC) in the randomized-withdrawal portion of the study
  - If a recurrence does not occur, patients will be censored at the last available assessment during the randomized-withdrawal period before data cutoff
  - A sensitivity analysis will be performed based on the investigator's assessment of pericarditis recurrence; additional sensitivity analyses will be specified in the SAP
- Secondary endpoints
  - Proportion of patients maintaining a clinical response (defined as a weekly average of daily NRS pain score ≤2.0 and CRP level ≤0.5 mg/dL)
  - Percentage of days with no-to-minimal pain (NRS pain score ≤1)
  - Percentage of patients with no-to-minimal pericarditis symptoms (based on the 7-point Patient Global Impression of Pericarditis Severity scale)
- Exploratory endpoint
  - Cardiac MRI substudy is planned for a subset of patients to assess changes over time in pericardial inflammation

Safety Assessments

- AE monitoring, physical examinations, and laboratory tests
  - Severity of treatment-emergent AEs and their relationship to study drug (i.e., not related, unlikely related, possibly related, or related) will also be analyzed
  - Unexpected serious AEs will be communicated with expedited timing to investigators, institutional review boards and independent ethics committees, and health authorities
  - Because symptoms and laboratory measures of RP are related to efficacy, they will not be reported as safety events unless they are uncharacteristic of the patient's usual severity of recurrence

CONCLUSIONS

- Recurrent pericarditis imposes a significant burden on patients and is difficult to manage with existing treatment options, which themselves may introduce additional complications
  - Among patients not responding to standard treatment, including colchicine, CS are often prescribed at higher doses and for longer periods than recommended
  - As a result, serious complications have been reported, including Cushing syndrome, hypertension, osteoporosis, vertebral fractures, and glaucoma
  - Many patients have contraindications to standard therapies
- RHAPSODY is a pivotal Phase 3 trial evaluating the efficacy and safety of rilonacept in patients with RP using a double-blind, placebo-controlled, randomized-withdrawal design
- The rigorous design of the RHAPSODY trial ensures that all patients have been weaned from NSAIDs, colchicine, and/or CSs during the run-in period
  - This "enriched" patient population allows the best chance of observing a difference between continued treatment with rilonacept and switching to placebo in the randomized-withdrawal period without the confounding effects of multiple concomitant medications
  - Because all patients entering the randomized-withdrawal period have previously responded to rilonacept, the open-label rilonacept bailout allows them to return to that efficacious therapy upon recurrence of pericarditis
- This pivotal Phase 3 study was designed to yield efficacy and safety results to inform future management of this debilitating disease by disrupting the ongoing cycle of autoinflammation and pericarditis recurrence with a novel agent that inhibits both IL-1α and IL-1β

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DISCLOSURES

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