RHAPSODY: Rilonacept, an IL-1α and IL-1β Trap, Resolves Pericarditis Episodes and Reduces Risk of Recurrence in a Phase 3 Trial of Patients with Recurrent Pericarditis

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*These authors are co-principal investigators and contributed equally to this work.

RHAPSODY: Rilonacept inHibition of interleukin-1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes stuDY
Disclosures and Acknowledgements

• Thanks to my co-principal investigator, Massimo Imazio

• Dr. Klein reports receiving a research grant from Kiniksa Pharmaceuticals, Ltd., fees for serving on the scientific advisory board from Kiniksa Pharmaceuticals, Ltd., and fees for serving on advisory boards from Swedish Orphan Biovitrum AB and Pfizer

• The authors would like to thank:
  • the patients, along with their families and caregivers, for their participation in this study
  • all investigators who contributed to the study, as well as sub-investigators, site coordinators, and all study site personnel
  • members of the Clinical Events Committee and of the Data Monitoring Committee
  • C5Research biostatistics for independent confirmation of the study results
  • Scott Mellis, Regeneron Pharmaceuticals, for his knowledge and expertise on rilonacept and IL-1 antagonism and his unwavering support of the pericarditis program
  • Kiniksa Pharmaceuticals Corp. employees who contributed to the conduct and analyses of the study

• The study was funded in full by Kiniksa Pharmaceuticals, Ltd.

• Rilonacept in Recurrent Pericarditis is for Investigational Use Only; Clinicaltrials.gov: NCT03980522
Recurrent Pericarditis (RP)
- Chronic, debilitating autoinflammatory disease often requiring months to years of treatment\(^1\)-\(^3\)
- No FDA-approved therapies
- Non-specific immunosuppressants commonly used: NSAIDs/colchicine/corticosteroids
  - Corticosteroids associated with significant morbidity\(^1\)-\(^2\)

Role of IL-1
- Interleukin 1 (IL-1) has been implicated as a key mediator of recurrent pericarditis\(^4\)-\(^8\)

Rilonacept
- Once-weekly IL-1\(\alpha\) and IL-1\(\beta\) cytokine trap

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**Inclusion Criteria:**
- Presenting with at least 2nd pericarditis recurrence; pain NRS ≥4, CRP≥1 mg/dL
- NSAIDs/Colchicine/Corticosteroids in any combination
- Multiple etiologies

**Definition of Clinical Response**
- Weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS
- CRP level ≤0.5 mg/dL
- On monotherapy study drug without a recurrence

**Primary Efficacy Endpoint**
- Time to pericarditis recurrence

**Major Secondary Efficacy Endpoints**
- Proportion of patients maintaining Clinical Response
- Percent of days with no/minimal pain (NRS ≥2)
- Proportion of patients with absent/minimal pericarditis symptoms

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**RHAPSODY**: Global, Double-blind, Placebo-controlled, Randomized Withdrawal Phase 3

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Period</td>
<td>320 mg SC Loading Dose</td>
</tr>
<tr>
<td>Run-In Period</td>
<td>12-week</td>
</tr>
<tr>
<td>Randomization</td>
<td>1:1</td>
</tr>
<tr>
<td>Double-Blind, Placebo-Controlled, Randomized-Withdrawal (RW) Period</td>
<td>Event Driven – n=22</td>
</tr>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>Time-to-First-Adjudicated Pericarditis-Recurrence</td>
</tr>
<tr>
<td>Long-Term Extension (LTE)</td>
<td>(up to 24 months)</td>
</tr>
<tr>
<td>End of Study (EOS)</td>
<td></td>
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</tbody>
</table>

**Clinical responders randomized 1:1 to monotherapy rilonacept or placebo**

**Open-Label Rilonacept**

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**Hypothesis**
- Once-weekly IL-1α/IL-1β trap rilonacept resolves active episodes and decreases recurrence risk

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1 Klein and Imazio et al. AHJ 2020
Baseline Demographics and Clinical Characteristics

Baseline Demographics (n=86)

- **Sex**
  - Male: 43%
  - Female: 57%

- **Race**
  - White: 93%
  - Black or African American: 5.8%
  - Other: 1.2%

- **Age**
  - 12-17: 8.1%
  - 18-64: 82.6%
  - 65-78: 9.3%
  - Mean age = 44.7

Prior Pericarditis History at Baseline (n=86)

- **Idiopathic**: 85%
- **Post-Pericardiotomy Syndrome**: 14%
- **Dressler’s Syndrome**: 1%

Qualifying Episode NRS & CRP (n=86)

- **NRS Score**: Mean = 6.2
- **CRP Level mg/dL**: Mean = 6.2
  - CRP ≤ 0.5 is normal

SoC Received at Qualifying Episode (n=86)

- **NSAIDs**: 67%
- **Colchicine**: 80%
- **Stereoids**: 49%
- **No Background Therapy**: 6%

Pericarditis Manifestations at Qualifying Episode (n=86)

- **Pericardial Effusion**: 38%
- **Pericardial Rub**: 15%
- **ST Elevation or PR Depression**: 19%

**Total Number of Episodes Including Index and Qualifying Episodes**

- Mean Run-in Period (n=86) = 4.7

CRP = C-reactive protein; NRS = Numerical Rating Scale; SoC = Standard of Care; NSAIDs = nonsteroidal anti-inflammatory drugs
Of 86 enrolled patients, 79 (91.9%) completed the run-in
61 patients were randomized; 31 placebo and 30 rilonacept
Event-driven trial: 15 patients transitioned from run-in to LTE after randomization stopped

*Adverse Events n = 4 (4.7%); Protocol Deviation / Withdrawn Consent / Sponsor/Investigator Decision n = 3 (3.5%)
Rilonacept Initiation Resulted in Rapid Resolution of Acute Pericarditis Episodes
Run-In Period (n=86)

Median (95% CI) Time to Pain Response: 5.0 (4.0, 6.0) days
Median (95% CI) Time to CRP Normalization\textsuperscript{b}: 7.0 (5.0, 8.0) days

\textsuperscript{a}Mean pain NRS and CRP at BL differs from those at qualifying episode: investigator could temporarily manage pericarditis episode with SOC prior to enrollment
\textsuperscript{b}CRP \leq 0.5 mg/dL

Key Points

- Pain NRS and CRP rapidly decreased after the first rilonacept dose
- All patients on corticosteroids successfully tapered and transitioned to monotherapy rilonacept during the run-in
Rilonacept Reduced the Risk of Pericarditis Recurrence
Primary Efficacy Endpoint (Randomized Withdrawal Period; n=61)

- **Hazard Ratio = 0.04**  
  Log-rank p-value < 0.0001  
  Risk Reduction = 96%

### Key Points

- **Lower Annualized Incidence of Pericarditis Recurrences while on treatment**
  - Study entry -- 4.42 (2.73, 0.2-24.9) episodes/year
  - RW period\(^b\) -- 0.15 (0.65, 0.0-3.4) episodes/year
- **No patient receiving open-label bailout rilonacept experienced a recurrence during the remainder of the RW**

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<table>
<thead>
<tr>
<th></th>
<th>Number of Patients with Recurrence(^a) n (%)</th>
<th>Number of Weeks to Recurrence(^a) Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilonacept</td>
<td>2 (6.7)</td>
<td>NE (NE, NE)</td>
</tr>
<tr>
<td>Placebo</td>
<td>23 (74.2)</td>
<td>8.6 (4.0, 11.7)</td>
</tr>
</tbody>
</table>

\(^a\)First adjudicated pericarditis recurrence  
NE, not estimable

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\(^{a}\)Mean (median, range); \(^{b}\)Patients randomized to rilonacept
Patients Receiving Rilonacept Maintained Improvements in Symptoms and Disease Severity

Major Secondary Efficacy Endpoints (Randomized Withdrawal Week 16)

Proportion of Patients Who Maintained Clinical Response at Week 16

- **KPL-914**: 81%
- **Placebo**: 20%

Data at Weeks 8 and 24 were consistent (Week 8, p < 0.0001; Week 24, p = 0.0022)

Definition of Clinical Response
- Weekly average daily pericarditis pain: ≤2.0 (11-point NRS)
- CRP level ≤0.5 mg/dL
- On monotherapy of study drug without a recurrence

Proportion of Patients with Absent/Minimal Pericarditis Symptoms based on the 6-point PGIPS at Week 16

- **KPL-914**: 81%
- **Placebo**: 25%

Data at Weeks 8 and 24 were consistent (Week 8, p < 0.0001; Week 24, p = 0.0002)

PGIPS:
- Patient Global Impression of Pericarditis Severity

Percent of Days with No or Minimal Pain in First 16 Weeks

- **KPL-914**: 98%
- **Placebo**: 46%

Data at Weeks 8 and 24 were consistent (Week 8, p < 0.0001; Week 24, p < 0.0001)

**Note:**
- No or minimal pain is defined as non-missing daily NRS ≤ 2. The percentage of days with no or minimal pain in the first 24, 16, and 8 weeks is calculated for each subject using 24x7, 16x7, 8x7, respectively, as the denominator. Missing values in pain diary will be counted as 0 day with no or minimal pain. On days of using ORT or corticosteroid, count as 0 day with no or minimal pain. If bailout rilonacept was used, each administration (loading dose or not) will be counted as 7 days without qualifying no or minimal pain.
- P-values for Week 8 and Week 24 are nominal and not adjusted for multiplicity.
# Rilonacept Was Well-tolerated With No Drug-related Serious Adverse Events

<table>
<thead>
<tr>
<th>Category of Treatment-Emergent Adverse Events (TEAEs)², n (%)</th>
<th>Run-In</th>
<th>Randomized Withdrawal</th>
<th>Overall Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rilonacept (N = 86)</td>
<td>Rilonacept Before Bailout (N = 30)</td>
<td>Placebo Before Bailout (N = 31)</td>
</tr>
<tr>
<td>Any TEAE³</td>
<td>69 (80.2)</td>
<td>24 (80.0)</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>TEAE by maximum severity⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>52 (60.5)</td>
<td>16 (53.3)</td>
<td>9 (29.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 (17.4)</td>
<td>8 (26.7)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (2.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug related TEAE⁵</td>
<td>46 (53.5)</td>
<td>10 (33.3)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>1 (1.2)</td>
<td>1 (3.3)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Drug related serious adverse event</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs leading to dose interruption</td>
<td>0</td>
<td>1 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs leading to study drug discontinuation</td>
<td>4 (4.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs of infection or infestation</td>
<td>14 (16.3)</td>
<td>12 (40.0)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>TEAEs of upper respiratory tract infection</td>
<td>12 (14.0)</td>
<td>7 (23.3)</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs of injection-site reaction</td>
<td>28 (32.6)</td>
<td>5 (16.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

⁴ Patients with multiple events were counted once in the same category. ⁵ TEAEs: AEs that start or increase in severity; from first study drug dose to 6 weeks after last dose; ⁶ Each patient represented according to the maximum severity; ⁷ These events were related, possibly related, or missing, as assessed by investigator

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### Key Points

- Injection site reactions and upper respiratory tract infections were the most common adverse events
- Adverse events were consistent with the US FDA–approved rilonacept label for CAPS³

Conclusion: Rilonacept Resolved Acute Episodes and Reduced Risk of Pericarditis Recurrence

In patients with symptomatic recurrent pericarditis failing SoC, rilonacept (once-weekly IL-1α and IL-1β trap):

- **Resolution of Acute Episode**
  - Recurrent pericarditis episodes resolved with addition of rilonacept
  - Rapid (after first dose) and sustained reductions in pain NRS and CRP
  - Resolution of pericarditis manifestations\(^a\)

- **Reduced Risk of Recurrence\(^b\)**
  - Monotherapy rilonacept reduced the risk of pericarditis recurrence by 96%
  - Primary Efficacy Endpoint: HR 0.04; p<0.0001
  - The only events in rilonacept arm (n=2) occurred during temporary drug interruptions of 1 and 3 weeks
  - No recurrences during remainder of RW period in patients who received bailout rilonacept

- **Corticosteroid-Sparing**
  - Rilonacept supported steroid tapering/discontinuation and obviated initiation in colchicine resistant patients
  - 49% of patients were on corticosteroids at baseline; 80% of patients were on colchicine at qualifying episode
  - Primary efficacy endpoint was consistent independent of CS use at baseline

- **Improved Quality of Life**
  - Improvements in symptomatology maintained throughout the study while on treatment
  - 81% of patients on rilonacept reported no/minimal pericarditis symptoms at RW Wk 16 versus 25% for placebo (p = 0.0006)
  - 98% of trial days with none/minimal pain versus 45.9% for placebo (LS mean; p < 0.0001)
  - Consistent results at randomized withdrawal Week 24

\(^a\)Where present at baseline

\(^b\)While on treatment