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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BACKGROUND

Recurrent Pericarditis (RP)

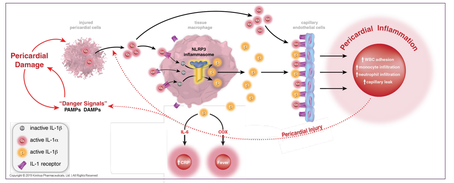
- Chronic, debilitating autoinflammatory disease often requiring months to years of treatment[1-3]
- Non-specific immunosuppressants commonly used: NSAIDs/colchicine/corticosteroids
  - Corticosteroids associated with significant morbidity[1-2]

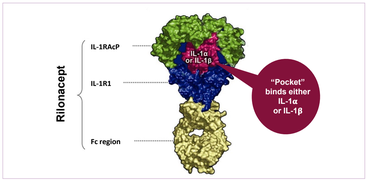
Role of IL-1

- Interleukin 1 (IL-1) has been implicated as a key mediator of recurrent pericarditis[4-8]

Rilonacept

- Once-weekly IL-1α and IL-1β cytokine trap
- Rilonacept is the first FDA-approved therapy for RP.[9]





METHODS

RHAPSODY[1]: Global, Double-blind, Placebo-controlled, Randomized Withdrawal Phase 3

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

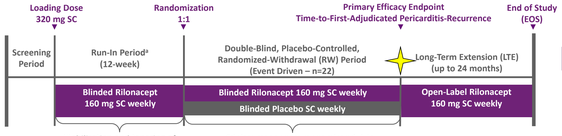
- Weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS
- CRP level ≤0.5 mg/dL
- On monotherapy study drug without a recurrence

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

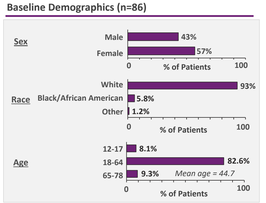


[a]The duration of the run-in period was concealed from patients, so that they were blinded to the timing of randomization

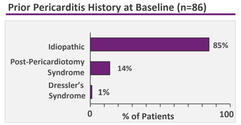
Hypothesis

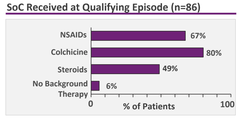
Once-weekly IL-1α/IL-1β trap rilonacept resolves active episodes and decreases recurrence risk.

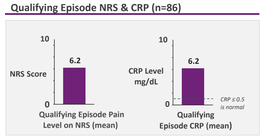
Baseline Demographics and Clinical Characteristics

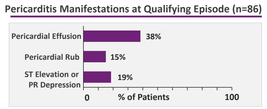


Total Number of Episodes Including Index and Qualifying Episodes	Run-in Period (n=86)
Mean	4.7







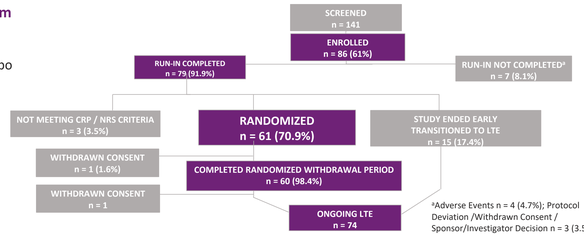


CRP = C-reactive protein; NRS = Numerical Rating Scale; SoC = Standard of Care; NSAIDs = nonsteroidal anti-inflammatory drugs

RESULTS

Patient Disposition CONSORT Diagram

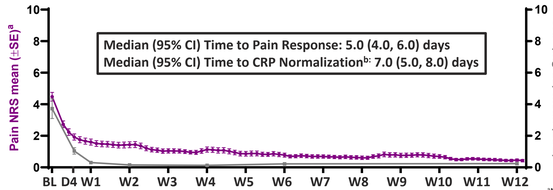
- Of 86 enrolled patients, 79 (91.9%) completed the run-in
- 61 patients were randomized; 31 placebo and 30 rilonacept
- Event-driven trial: 15 patients transitioned from run-in to LTE after randomization stopped



[a]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)

- 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



		BL	D4	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
CRP	# of Patients	85	79	82	81		79		82						81
	CRP Mean	3.7	1.0	0.30	0.15		0.13		0.22						0.24
Pain NRS	# of Patients	84		84	84	83	83	84	83	83	82	81	82	82	78
	Pain Mean	4.5		1.60	1.43	1.04	1.13	0.86	0.78	0.68	0.61	0.76	0.69	0.53	0.46

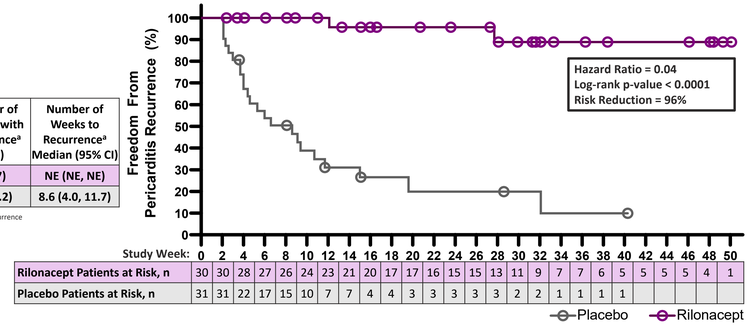
[a]Mean pain NRS and CRP at BL differs from those at qualifying episode: investigator could temporarily manage pericarditis episode with SOC prior to enrollment
[b]CRP ≤0.5 mg/dL

Rilonacept Reduced the Risk of Pericarditis Recurrence Primary Efficacy Endpoint (Randomized Withdrawal Period; n=61)

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

	Number of Patients with Recurrence[a] n (%)	Number of Weeks to Recurrence[a] Median (95% CI)
Rilonacept	2 (6.7)	NE (NE, NE)
Placebo	23 (74.2)	8.6 (4.0, 11.7)

[a]First adjudicated pericarditis recurrence
NE, not estimable

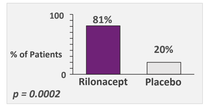


	Study Week: 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Rilonacept Patients at Risk, n	30	30	28	27	26	24	23	21	20	17	17	16	15	15	13	11	9	7	7	6	5	5	5	5	4	1
Placebo Patients at Risk, n	31	31	22	17	15	10	7	7	4	4	3	3	3	3	3	2	2	1	1	1	1					

Patients Receiving Rilonacept Maintained Improvements in Symptoms and Disease Severity

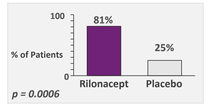
Major Secondary Efficacy Endpoints (Randomized Withdrawal Week 16)

Proportion of Patients Who Maintained Clinical Response[a] at Week 16



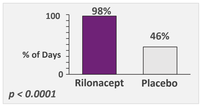
Data at Weeks 8 and 24 were consistent (Week 8, p < 0.0001; Week 24, p=0.0022)[d]

Proportion of Patients with Absent/Minimal Pericarditis Symptoms[b] at Week 16



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

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



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

[a]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
[b]Based on 6-point Patient Global Impression of Pericarditis Severity (PGIPS)
[c]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.
[d]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

- 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 Cryopyrin-Associated Periodic Syndromes (CAPS)[9]

Category of Treatment-Emergent Adverse Events (TEAEs)[a]- n (%)	Run-In	Randomized Withdrawal		Overall Study
	Rilonacept (N = 86)	Rilonacept Before Bailout (N = 30)	Placebo Before Bailout (N = 31)	Rilonacept or Placebo (N = 86)
Any TEAE[b]	69 (80.2)	24 (80.0)	13 (41.9)	74 (86.0)
TEAE by maximum severity[c]				
Mild	52 (60.5)	16 (53.3)	9 (29.0)	47 (54.7)
Moderate	15 (17.4)	8 (26.7)	4 (12.9)	25 (29.1)
Severe	2 (2.3)	0	0	2 (2.3)
Drug related TEAE[d]	46 (53.5)	10 (33.3)	1 (3.2)	50 (58.1)
Serious TEAE	1 (1.2)	1 (3.3)	1 (3.2)	5 (5.8)
Drug related serious adverse event	**0**	**0**	**0**	**0**
TEAEs leading to dose interruption	0	1 (3.3)	0	1 (1.2)
TEAEs leading to study drug discontinuation	4 (4.7)	0	0	4 (4.7)
TEAEs leading to death	0	0	0	0
TEAEs of infection or infestation	14 (16.3)	12 (40.0)	3 (9.7)	29 (33.7)
TEAEs of upper respiratory tract infection	**12 (14.0)**	**7 (23.3)**	**0**	**19 (22.1)**
TEAEs of injection-site reaction	**28 (32.6)**	**5 (16.7)**	**0**	**29 (33.7)**

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

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
- Reduced Risk of Recurrence[a]
- Corticosteroid-Sparing
- Improved Quality of Life

[a]While on treatment

- **Recurrent pericarditis episodes resolved with addition of rilonacept**
  - Rapid (after first dose) and sustained reductions in pain NRS and CRP
  - Resolution of pericarditis manifestations, where present at baseline
- **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
- **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
- **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

References

1. Adler EHJ 2015; 2. Soler-Soler Heart 2004; 3. Imazio Lancet 2014; 4. Brucato JAMA 2016; 5. Brucato IEM 2018; 6. Dinarello NRDD 2012; 7. Chiabrando JACC 2020; 8. Klein Circulation 2019 JACC; 9. Arcalyst [package insert]. Kiniksa Pharmaceuticals (UK), Ltd.; 2021

Disclosures

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 presenter, Randy Perrin, is an employee of Kiniksa Pharmaceuticals Corp. The study was funded in full by Kiniksa Pharmaceuticals, Ltd.