Efficacy and Safety of Rilonacept in Recurrent Pericarditis: A Multicenter Phase 2 Clinical Trial

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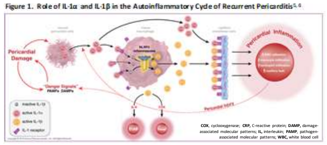
BACKGROUND

- Recurrent pericarditis (RP) is characterized by the recurrence of pericarditis signs and symptoms after a symptom-free period of ≥4 to 6 weeks[1]
- RP affects 15% to 30% of patients with acute pericarditis[2]
- Conventional treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids (CS)[3]
- Recurrent pericarditis is associated with a high burden of disease
  - Debilitating chest-pain that limits physical activity and activities of daily living, leads to emergency visits and overall reduces quality of life (QOL)[4]
  - Potentially life-threatening complications including tamponade and constrictive pericarditis
  - Limited efficacy data and side effects of conventional therapeutic options, especially corticosteroids
  - Need for invasive surgery, i.e., pericardiectomy, for patients refractory to conventional treatments

- Interleukin-1 (IL-1) is a family of cytokines which mediates the pathophysiology of recurrent pericarditis (**Figure 1**)
- Rilonacept inhibits IL-1 signaling by acting as a soluble decoy receptor that binds IL-1α and IL-1β, thus preventing interaction with IL-1 cell surface receptors
- 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 in-line to the Fc portion of human IgG1 (**Figure 2**)

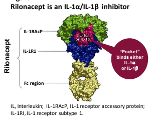
Figure 1. Role of IL-1α and IL-1β in the Autoinflammatory Cycle of Recurrent Pericarditis[5,6]



COX, cyclooxygenase; CRP, C-reactive protein; DAMP, damage-associated molecular patterns; IL, interleukin; PAMP, pathogen-associated molecular patterns; WBC, white blood cell

- Tissue damage caused by IL-1α and IL-1β in the pericardium stimulates additional IL-1α and IL-1β, thereby creating a self-perpetuating cycle of pericardial inflammation
- Arcalyst® (rilonacept, Regeneron, Tarrytown, NY) is approved in the US for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS); Arcalyst® is a registered trademark of Regeneron
- Rilonacept is being investigated for the treatment of RP by Kiniksa Pharmaceuticals, Ltd.

Figure 2
Rilonacept is an IL-1α/IL-1β inhibitor



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

METHODS

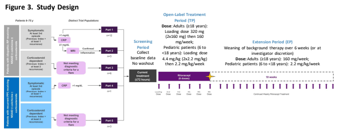
Study Objectives

- Evaluate the efficacy and safety of rilonacept in patients with RP, assessing:
  - Improvement of pericarditis symptomatology with rilonacept administration
  - Feasibility of weaning from corticosteroids while receiving rilonacept in patients with corticosteroid-dependent RP of idiopathic or post-pericardiotomy syndrome (PPS) etiology
  - Safety of rilonacept

Study Design

- Open-label, single-active-arm, 5-part pilot study explored clinical and biochemical endpoints of pericarditis and collected inter- and intra-patient variability data for baseline and on-treatment parameters (**Figure 3**)
- Eligible patients were adults (18 to 75 y) or children (≥6 to <18 y) with RP due to idiopathic or PPS etiology, presenting with at least a third pericarditis episode or with at least 3 prior episodes if not in an active episode but CS-dependent at the time of enrollment
- All patients at study entry were allowed concomitant NSAIDs and/or colchicine and/or CS (in any combination) as long as the dosages were stable for ≥7 days; CS-dependent patients must have been on CS at enrollment
- Serial MRIs were performed on a subset of patients at enrollment and Final Visit

Figure 3. Study Design



CRP, C-reactive protein; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PPS, post-pericardiotomy syndrome; RP, recurrent pericarditis.

Treatment and Procedures

- In the TP:
  - No changes in concomitant medications were allowed during the 6-week open-label treatment period (TP)
  - Adults (≥18 y) received a loading dose of 320 mg (2 × 160 mg) rilonacept, administered via SC injection on day 0, followed by 160 mg SC weekly for 5 additional doses
- In the optional 18-week treatment extension period (EP), during which weekly rilonacept continued, investigators were encouraged to wean patients from concomitant medications according to the following recommended schedule:
  - NSAIDs and colchicine: tapered and withdrawn within 15 days of EP entry
  - CS: taper by 5 mg and 0.2 mg/kg each week in adults and children, respectively; discontinue within 6 weeks of EP entry
  - Treatment was similar to TP: rilonacept 160 mg SC weekly for 18 additional doses
- Patients who completed TP and EP received rilonacept for a total of 6 months

Efficacy Assessments

- For continuous variables (e.g., change from baseline), summary statistics were calculated as mean and median; for categorical variables, frequency and percentage were calculated
- Primary endpoints
  - Patients with active pericarditis (Parts 1, 2, and 4): pain numeric rating scale (NRS) and C-reactive protein (CRP) levels at baseline and on treatment
  - Patients with corticosteroid (CS)-dependent non-active pericarditis (Part 3 and 5): disease activity during and after CS taper
- Secondary endpoints
  - Improvement in pericarditis manifestations other than pain and CRP (pericardial rub, ECG changes, pericardial effusion)
  - Change in patients' quality of life using validated Patient-Reported Outcomes Measurement Information System (PROMIS®) Questionnaire (v1.2) to assess overall physical and mental well-being[7]
  - Use of concomitant CS (prednisone)
  - Changes in the use of other concomitant medications for pericarditis

Safety Assessments

- Adverse events (AEs) were recorded with the level of severity (i.e., mild, moderate, or severe) and relationship to study drug based on investigators' judgement (i.e., not related, unlikely related, possibly related, or related)

RESULTS

Table 1. Baseline Demographics

General Characteristics	All Patients (n=25)
Unique patients, n	25
Mean age (range), yrs	42.8 (26-62)
Sex (male/female)	10/15
Race (white/African American)	22/3
Mean pericarditis episodes at enrollment[a] (range)	4.3 (3-10)
Mean disease duration (range), yrs	2.2 (0.2-7.9)

[a]Includes index, recurrent, and qualifying (if applicable) episodes

Table 2. Clinical Characteristics

	Idiopathic RP			PPS	
Disease Status:	Active[a]	Active[b]	CS-dep[c]	Active[d]	CS-dep[e]
CRP requirement (mg/dL):	>1	≤1	N/A	>1	N/A
N:	12	3	6	1	3
Mean NRS[f] (SD)	4.6 (1.7)	4.7 (3.1)	1.2 (0.8)	4.0 (N/A)	2.0 (2.7)
Mean CRP (SD), mg/dL	4.9 (5.8)	0.5 (0.4)	0.2 (0.1)	1.1 (N/A)	0.1 (0.1)

[a]Part 1; [b]Part 2; [c]Part 3; [d]Part 4; [e]Part 5; [f]11-point numeric scale, ranging from zero (0, no pain) to ten (10, pain as bad as possible); CRP, C-reactive protein; CS-dep, corticosteroid-dependent; NRS, numeric rating scale; CS-dep, corticosteroid-dependent; PPS, post-pericardiotomy syndrome

Figure 4
Pericarditis Manifestations at Baseline; All Patients

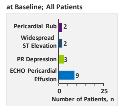
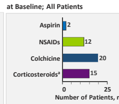
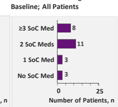


Figure 5
SoC Medications Received at Baseline; All Patients



[a]Mean baseline prednisone dose among patients receiving prednisone: 12.7 mg/day (range from 1 to 50 mg/day)

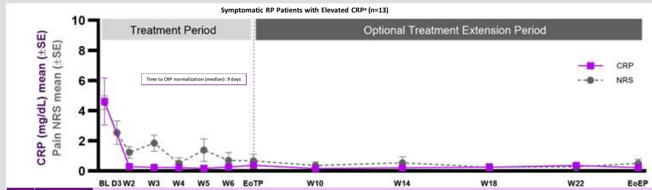
Figure 6
SoC Medication Categories at Baseline; All Patients



RESULTS, continued

Rapid, sustained, and clinically meaningful reductions in patients' pericarditis pain and CRP in symptomatic RP with elevated CRP >1 mg/dL (Parts 1 and 4)

Figure 7. Rapid Reduction in NRS Scores (Pain) and CRP Levels in Symptomatic Patients with Elevated CRP After the First Dose and Sustained Throughout EP (Parts 1 and 4)

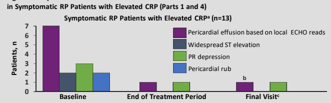


		BL	D3	W2	W3	W4	W5	W6	EoTP	W10	W14	W18	W22	EoEP
CRP	# of Patients	13		11	13	8	12	7	12	11	10	7	11	12
	CRP Mean	4.62		0.29	0.23	0.22	0.17	0.27	0.38	0.16	0.22	0.25	0.37	0.22
Pain NRS	# of Patients	13	11	13	13	8	13	10	9	11	11	8	11	12
	Pain Mean	4.5	2.5	1.2	1.8	0.5	1.4	0.7	0.7	0.4	0.5	0.3	0.3	0.5

[a]Parts 1 and 4 combined. Patients with elevated CRP and symptomatic disease (Parts 1 and 4) are most representative of real-world recurrent pericarditis. Inclusion and exclusion criteria for the ongoing Phase 3 study RHAPSODY align with this patient population (clinicaltrials.gov/NCT03737110).
EoTP, end of treatment period; EoEP, end of extension period

- Reductions in average pericarditis pain observed as soon as after the first (loading) dose of rilonacept
- Reductions maintained throughout the study (**Figure 7**)
- Reductions in pain were clinically meaningful and averaged 4 points on an 11-point pain NRS (ranging from 0-10)
- Resolution or improvement of pericardial effusion and other pericarditis manifestations (**Figure 8**)

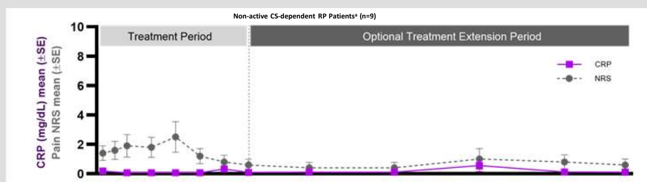
Figure 8. Improvement or Resolution of Pericardial Effusion and Other Pericarditis Manifestations in Symptomatic RP Patients with Elevated CRP (Parts 1 and 4)



[a]Part 1 and 4; [b]Patient with effusion at baseline, no effusion at EoT Visit and trivial effusion (not pathological) at Final Visit; [c]n=12; one patient discontinued study drug in TP due to SAE; no effusion at baseline or EoT Visit

Corticosteroid-dependent patients who entered the study without an active pericarditis episode maintained low average pain and CRP levels without disease recurrence despite tapering off the corticosteroids while rilonacept treatment continued (Parts 3 and 5)

Figure 9. NRS Scores (Pain) and CRP Levels Remained Low in Non-Active CS-dependent Patients During TP and Throughout EP (Parts 3 and 5)



		BL	D3	W2	W3	W4	W5	W6	EoTP	W10	W14	W18	W22	EoEP
CRP	# of Patients	9		8	9	5	9	5	9	7	8	4	8	8
	CRP Mean	0.19		0.07	0.07	0.07	0.07	0.33	0.09	0.10	0.11	0.56	0.12	0.12
Pain NRS	# of Patients	9	8	8	8	4	9	9	5	8	8	4	8	8
	Pain Mean	1.4	1.6	1.9	1.8	2.5	1.2	0.8	0.6	0.4	0.4	1.0	0.8	0.6

[a]Part 3 and Part 5 combined
EoTP, end of treatment period; EoEP, end of extension period

Table 3. Corticosteroid-Dependent Patients (Parts 3 and 5): Pericarditis Medication During TP and EP Combined

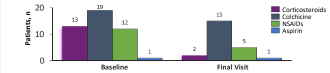
	Medications					
	At least 1	Analgesics	Aspirin	NSAIDs	Colchicine	CS
Dose stopped	7/8 (87.5)	0/0	0/1	2/5 (40.0)	1/7 (14.3)	7/8 (87.5)
Dose decreased	4/8 (50)	0/0	1/1 (100)	2/5 (40)	1/7 (14.3)	1/8 (12.5)
Dose increased	0/8	0/0	0/1	0/5	0/7	0/8
Starting new	0/8	0/8	0/8	0/8	0/8	0/8

Improvement in manifestations other than pain and elevated CRP in CS-dependent patients (Part 3 and 5)

- 2 patients in Part 3 had effusion at BL; in one patient, effusion resolved during rilonacept treatment; the second patient had a trivial/physiologic effusion at Final Visit

All patients on CS at baseline who completed the Extension Period reduced or stopped CS during treatment with rilonacept, and none of these patients experienced a pericarditis recurrence while on rilonacept treatment

Figure 10
Concomitant Pericarditis Medications in All Patients who Completed the Extension Period



Of 13 patients on CS at baseline who completed EP, 11 discontinued CS, and the remaining two successfully reduced the dose (Table 4)

- None of the patients in EP required initiation of prednisone for pericarditis
- There were no pericarditis recurrences based on Investigator's judgement after prednisone taper or discontinuation in EP

Table 4. Corticosteroid Use in All Patients

	Idiopathic			PPS		Idiopathic or PPS
Disease Status:	Active[a]	Active[b]	CS-dep[c]	Active[d]	CS-dep[e]	All[a-e]
CRP requirement (mg/dL):	>1	≤1	N/A	>1	N/A	N/A
N:	12	3	6	1	3	25
Baseline						
Pts on prednisone[f], n	4	2	6	0	3	15
Mean dose (mg/day)	8.4	40.0	8.9	0	7.7	12.7
Min	1.0	30.0	2.5	0	3.0	1.0
Max	12.5	50.0	30	0	15.0	50.0
Corticosteroid Changed During TP and EP Combined						
Prednisone dose decreased[g,h]	**0/3**	**1/2 (50.0)**	**1/5 (20.0)**	**0/0**	**0/3**	**2/13 (15.4)**
Prednisone stopped[g,h]	**3/3 (100)**	**1/2 (50.0)**	**4/5 (80.0)**	**0/0**	**3/3 (100)**	**11/13 (84.6)**
Prednisone dose increased[g]	0/3	0/2	0/5	0/0	0/3	0/13
Prednisone initiated[i]	0/11	0/3	0/5	0/1	0/3	0/23

[a]Part 1; [b]Part 2; [c]Part 3; [d]Part 4; [e]Part 5; [f]2 patients on prednisone at baseline did not enter EP (one in Part 1 and in Part 3)
[g]Refers to patients who entered the study on prednisone; [h]1 patient decreased prednisone dose in TP, and 1 stopped prednisone in TP (both in Part 2);
[i]Refers to all patients in EP; CS-dep, corticosteroid-dependent; PPS, post-pericardiotomy syndrome

Rilonacept improved quality of life as assessed by PROMIS® questionnaire

- Increased PROMIS®v.1.2 Global Health scores reflect improvement in quality of life with rilonacept treatment (**Table 5**)
- At baseline, mean scores across all patients were below 50, which is the mean score for the general US population[7]
- In symptomatic patients with active RP of idiopathic or PPS etiology (Parts 1, 2, and 4), the mean Physical and Mental Global Health baseline scores were 39.9 and 44.5, respectively, and improved to 51.3 and 50.5, respectively, at the Final Visit
- In CS-dependent patients with RP of idiopathic or PPS etiology without an active pericarditis episode (Parts 3 and 5), the mean Physical and Mental Global Health baseline scores were 43.3 and 46.5, respectively, and improved to 46.8 and 50.7, respectively, at the Final Visit

Table 5. PROMIS® Scale (v1.2)[a]: Global Health by Symptomatic Patients (Parts 1, 2, 4) and CS-Dependent (Parts 3, 5)

	Idiopathic or PPS	
	Active[b] (n=16)	CS-dependent[c] (n=9)
Global Physical Health, mean (SD)		
Baseline	39.94 (8.941)	43.3 (5.311)
End of TP	51.35 (7.962)	45.09 (4.057)
Final Visit	51.32 (6.564)	46.81 (9.266)
Global Mental Health, mean (SD)		
Baseline	44.5 (10.484)	46.49 (7.767)
End of TP	50.13 (11.325)	47.91 (5.509)
Final Visit	50.54 (10.995)	50.66 (6.299)

[a]PROMIS® - Patient Reported Outcomes Measurement Information System. The higher the score, the better global health is. US national average score for Global Physical and Mental Health is 50 (SD 10); [b]Part 1, 2, and 4; [c]Part 3 and 5; PPS, post-pericardiotomy syndrome

Annualized incidence of pericarditis episodes decreased from 3.9 episodes/year prior to the study to <0.18 episodes/year during rilonacept treatment in the study (Table 6)

Table 6. Annualized Incidence of Pericarditis Episodes Prior to and During the Study

	Idiopathic			PPS	
Disease Status:	Active[a]	Active[b]	CS-dep[c]	Active[d]	CS-dep[e]
CRP requirement (mg/dL):	>1	≤1	N/A	>1	N/A
N:	12	3	6	1	3
Prior to the study[f]					
Pericarditis episodes per year, mean (SD)	4.4 (4.68)	2.0 (1.75)	4.5 (2.58)	1.3 (N/A)	3.7 (3.02)
During the study[g]					
Patients with pericarditis episodes, n	1[h]	0	0	0	0
Pericarditis episodes per year, mean (SD)	0.18 (0.62)	0	0	0	0

[a]Part 1; [b]Part 2; [c]Part 3; [d]Part 4; [e]Part 5; [f]Episodes at enrollment include index, prior recurrences, and current episode; [g]Episodes during the study include recurrences during TP and EP combined. Pericarditis recurrence during the study was based on Investigator's judgement; [h]Patient had a mild pericarditis recurrence in TP, 5 days duration, with NRS pain increase from 0 to 2, CRP 0.10 mg/dL, not requiring addition of new medication to treat pericarditis

Rilonacept was generally well-tolerated (Table 7): majority of AEs were mild

Table 7. Adverse Events

	Idiopathic			PPS		Idiopathic or PPS		
Disease Status:	Active[a]	Active[b]	CS-dep[c]	Active[d]	CS-dep[e]	Active[a,b,d]	CS-dep[c,e]	All
CRP requirement (mg/dL):	>1	≤1	N/A	>1	N/A	N/A	N/A	N/A
N:	12	3	6	1	3	16	9	25
≥1 TEAE, n (%)	12 (100)	3 (100)	6 (100)	1 (100)	3 (100)	16 (100)	9 (100)	25 (100)
≥1 treatment-related TEAE, n (%)	9 (75)	2 (66.7)	3 (50)	1 (100)	2 (66.7)	12 (75)	5 (55.6)	17 (68)
≥1 serious TEAE, n (%)	2 (16.7)	0	0	0	0	2 (12.5)	0	2 (8)
≥1 treatment-related serious TEAE, n (%)	1 (8.3)	0	0	0	0	1 (6.3)	0	1 (4)
≥1 TEAE leading to treatment discontinuation, n (%)	1 (8.3)	0	0	0	0	1 (6.3)	0	1 (4)
≥1 TEAE leading to death, n (%)	0	0	0	0	0	0	0	0
TEAEs by severity, n (%)								
Mild	9 (75)	3 (100)	4 (66.7)	1 (100)	2 (66.7)	13 (81.3)	6 (66.7)	19 (76)
Moderate	2 (16.7)	0	2 (33.3)	0	0	2 (12.5)	2 (22.2)	4 (16)
Severe	1 (8.3)	0	0	0	1 (33.3)	1 (6.3)	1 (11.1)	2 (8)
Reactions at injection site[f], n (%)	5 (41.7)	1 (33.3)	3 (50)	1 (100)	2 (66.7)	7 (43.8)	5 (55.6)	12 (48)

[a]Part 1; [b]Part 2; [c]Part 3; [d]Part 4; [e]Part 5; [f]Includes injection site bruising, erythema, pain, reaction, joint warmth, and application site bruising and erythema;

- There were 2 serious treatment-emergent AEs reported in Part 1, both of which resolved
  - 1 patient with subcutaneous abscess (possibly related to study drug that resolved with medical management) discontinued rilonacept treatment
  - 1 patient with atypical chest pain (not related to study drug) continued rilonacept treatment
- AEs observed with rilonacept treatment are consistent with the known safety profile of rilonacept
- The most common AEs were observed in the general disorders and administration site conditions (injection site reactions), infections and infestations, and musculoskeletal and connective tissue disorders classes

DISCLOSURES AND ACKNOWLEDGEMENTS

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AK - research grant and advisory board for Kiniksa, advisory board for Sobi and Pfizer, and royalties from Kluwers Lippincott and Elsevier; PC – advisory board for Kiniksa and Sobi; SAL – advisory board for Kiniksa and Sobi, consultant for Sobi; AA – research grant and advisory board for Kiniksa; MML – advisory board and consultant for Kiniksa; SC and AB – consultant for Kiniksa; FF, RP, KW, and JFP – employees of Kiniksa Corp.; DL and AE – no disclosures;
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CONCLUSIONS

- Rapid improvements in both patient-reported outcomes (pain, QoL) and other clinical manifestations of pericarditis (CRP levels, pericardial effusions, ECG changes, pericardial rubs, pericardial inflammation by MRI) persisted throughout the 6-month study period[a]
  - In symptomatic RP patients with elevated CRP:
    - Clinically meaningful reductions in pain NRS scores and CRP levels were seen as early as after the first rilonacept administration and maintained throughout the 6 month duration of the study
    - Median time to CRP normalization was 9 days
  - In CS-dependent RP patients:
    - Low NRS and CRP levels maintained throughout the 6-month duration of the study
- Treatment with rilonacept allowed for discontinuation of corticosteroids without pericarditis recurrences, including patients who had been corticosteroid-dependent for disease control, suggesting a potential corticosteroid-sparing effect of rilonacept which could offer a clinically meaningful advantage over existing therapies by allowing for a reduction in corticosteroid dose or even by obviating corticosteroid use altogether, thus eliminating or reducing the risk of significant corticosteroid-associated morbidity
- Reduced annualized incidence of pericarditis episodes from 3.9 episodes/year prior to the study to <0.18 episodes/year during the study while on rilonacept treatment as compared to patients' own natural history in the period prior to study entry; these data thus provide supportive evidence that the reductions in the markers of pericardial inflammation (pain, CRP, clinical manifestations) observed during the trial were in fact due to a treatment effect of rilonacept and not due to spontaneous resolution.
- Safety data from this study are consistent with the known safety profile of rilonacept

Results from this study support the design of RHAPSODY, an ongoing, double-blind, placebo-controlled randomized withdrawal (RW) pivotal Phase 3 pivotal study with an open-label extension, intended to evaluate the efficacy and safety of rilonacept treatment in patients with recurrent pericarditis

[a]Interpretation of efficacy and safety outcomes is limited by small number of patients in each study part, open-label study design, and single-active-treatment arm design