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: **R**ilonacept in**H**ibition of interleukin-1 **A**lpha and beta for recurrent **P**ericarditis: a pivotal **S**ymptomatology and **O**utcomes stu**DY**

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- Rilonacept in Recurrent Pericarditis is for Investigational Use Only; Clinicaltrials.gov: NCT03980522

Recurrent Pericarditis and the Role of IL-1

Recurrent Pericarditis (RP)

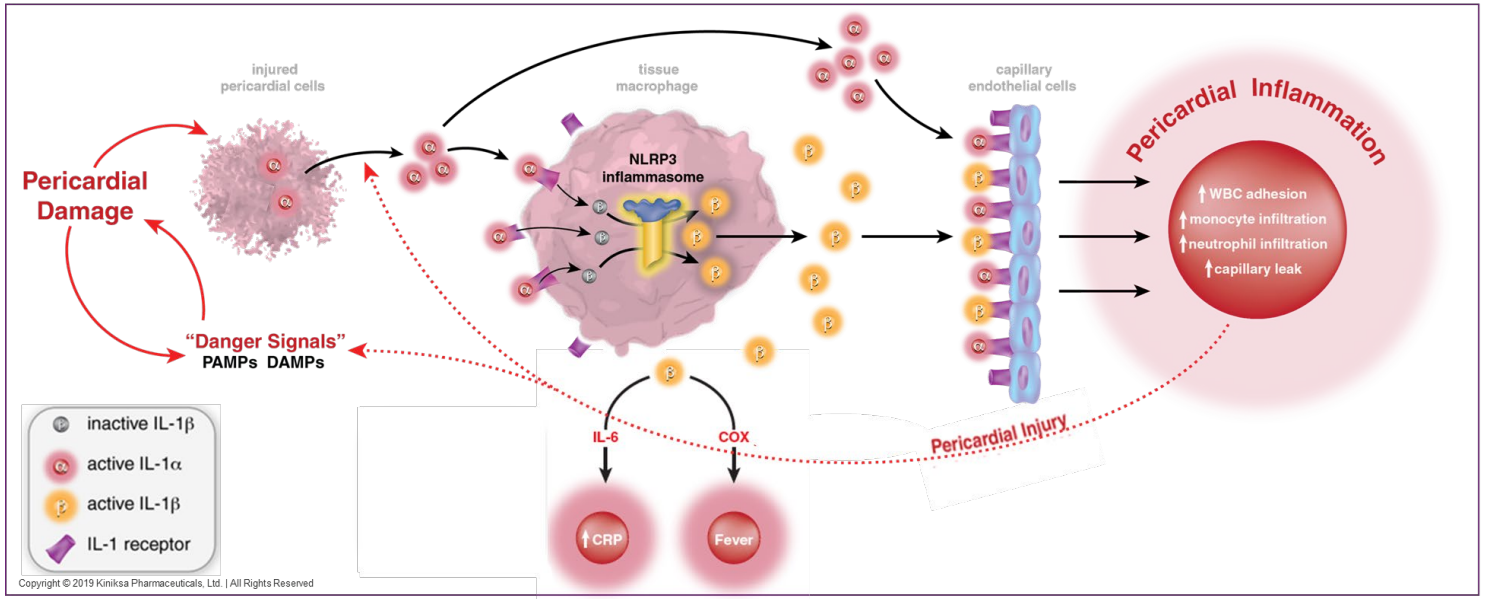
- Chronic, debilitating autoinflammatory disease often requiring months to years of treatment[1-3]
- No FDA-approved therapies
- Non-specific immunosuppressants commonly used: NSAIDs/colchicine/corticosteroids
  - Corticosteroids associated with significant morbidity[1-2]

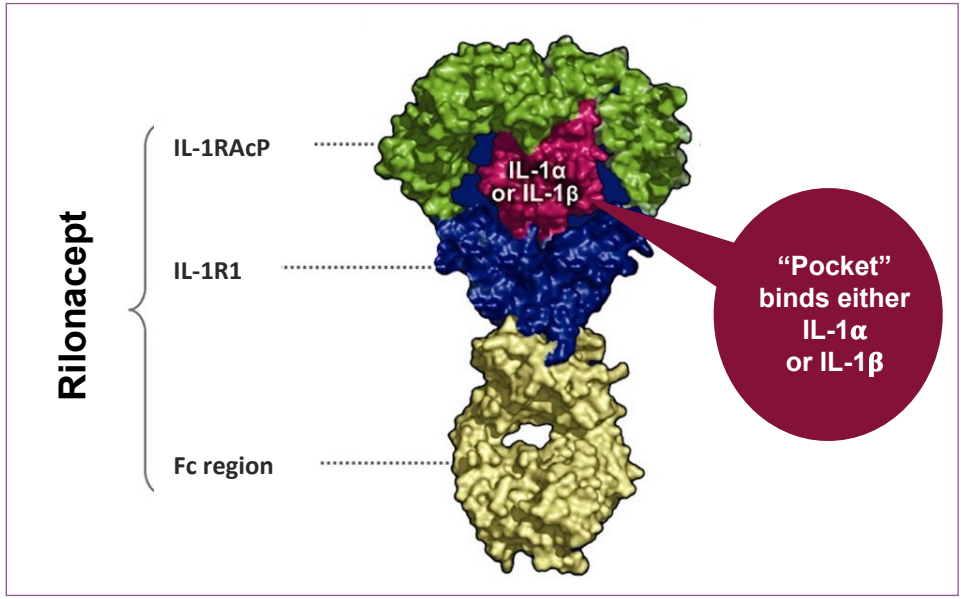
Role of IL-1

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

Rilonacept

- Once-weekly IL-1α and IL-1β cytokine trap





[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

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

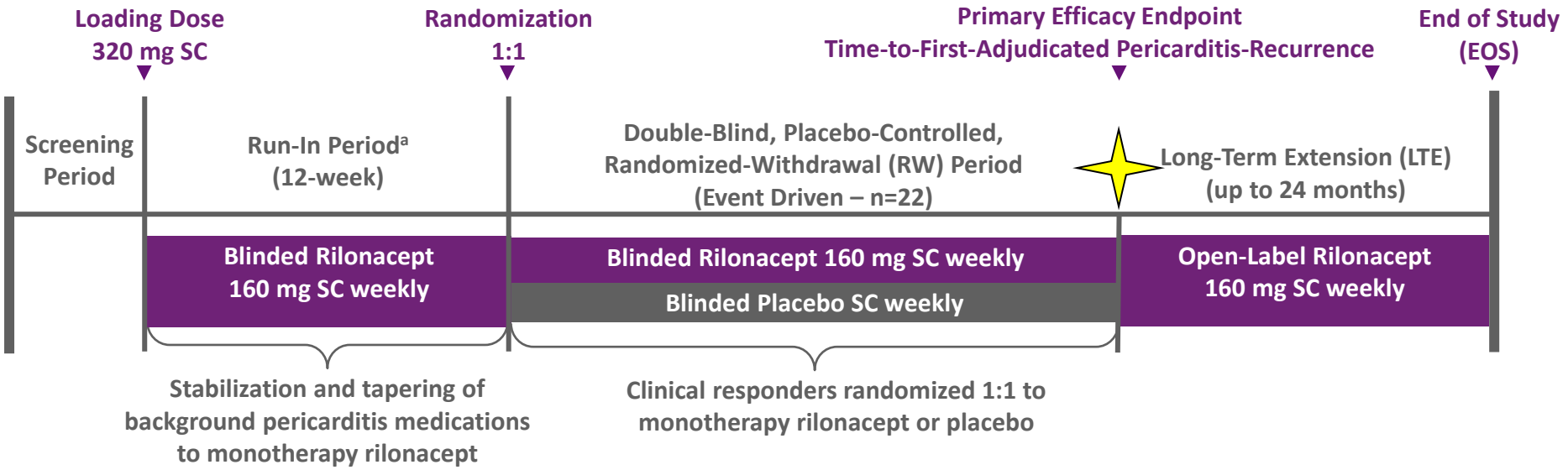
- Weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS
- CRP level ≤0.5 mg/dL
- On monotherapy study drug without a recurrence

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

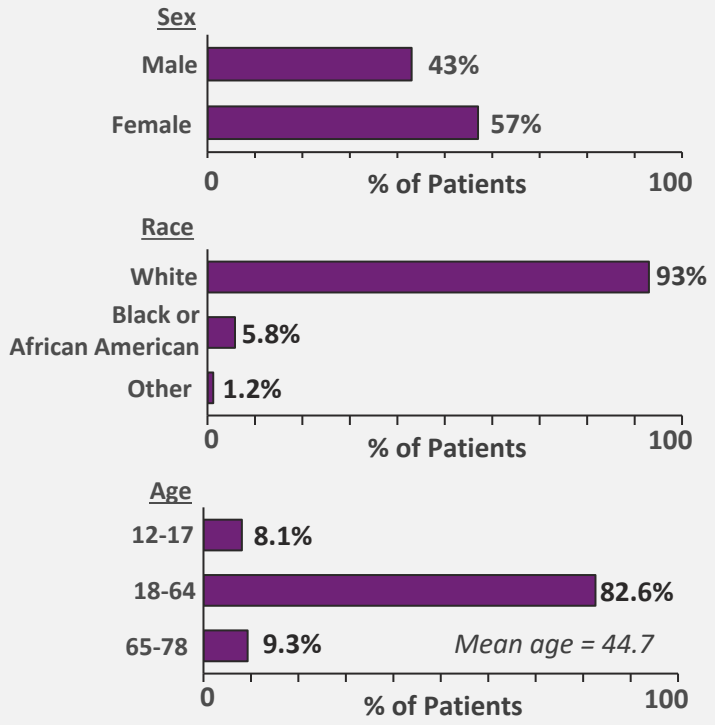
Hypothesis

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

[1] Klein and Imazio et al. AHJ 2020

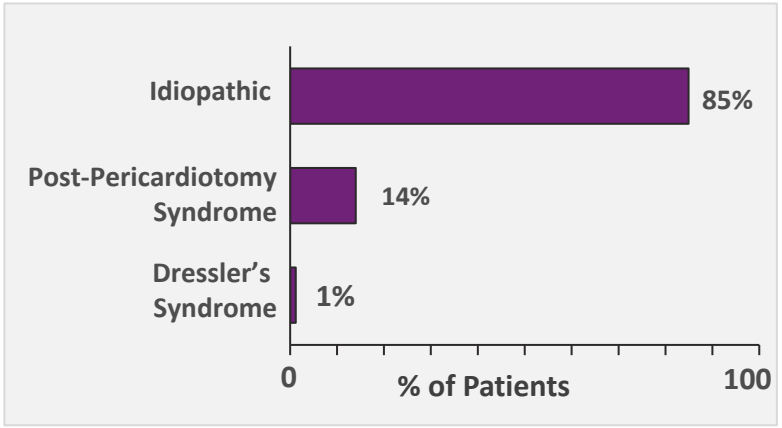
Baseline Demographics and Clinical Characteristics

Baseline Demographics (n=86)

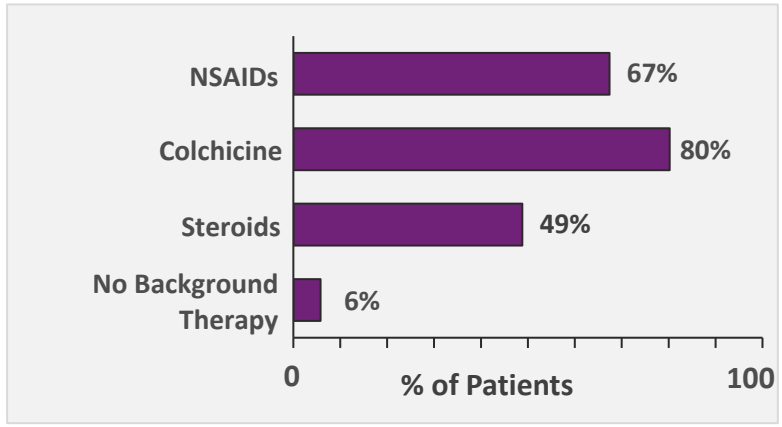


Total Number of Episodes Including Index and Qualifying Episodes	Run-in Period (n=86)
Mean	4.7

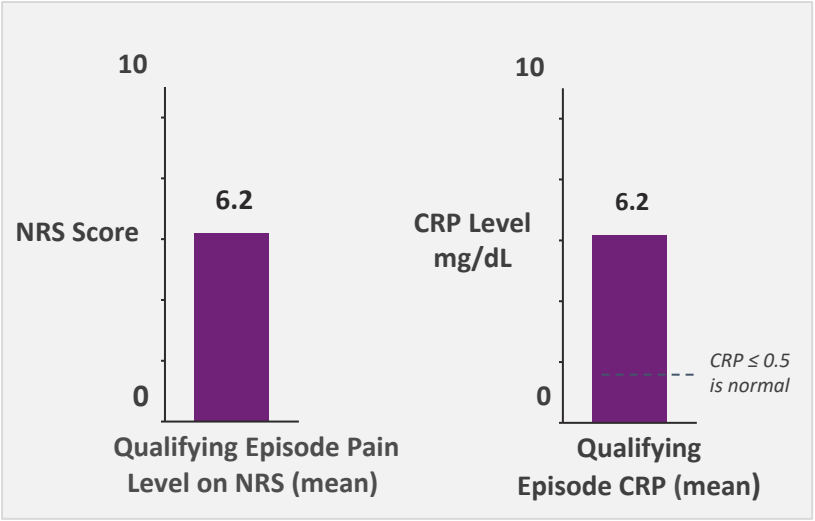
Prior Pericarditis History at Baseline (n=86)



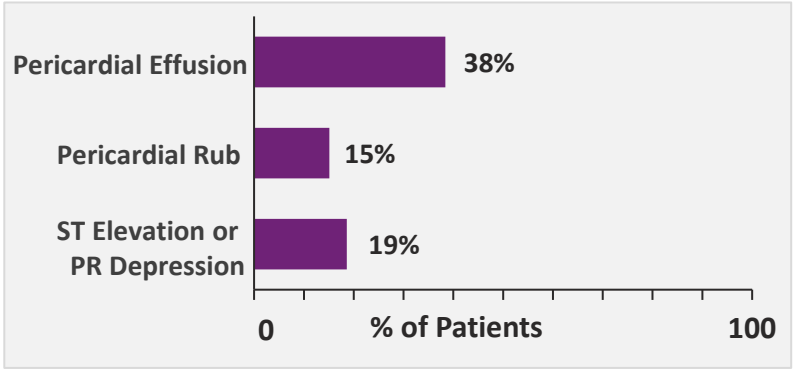
SoC Received at Qualifying Episode (n=86)



Qualifying Episode NRS & CRP (n=86)

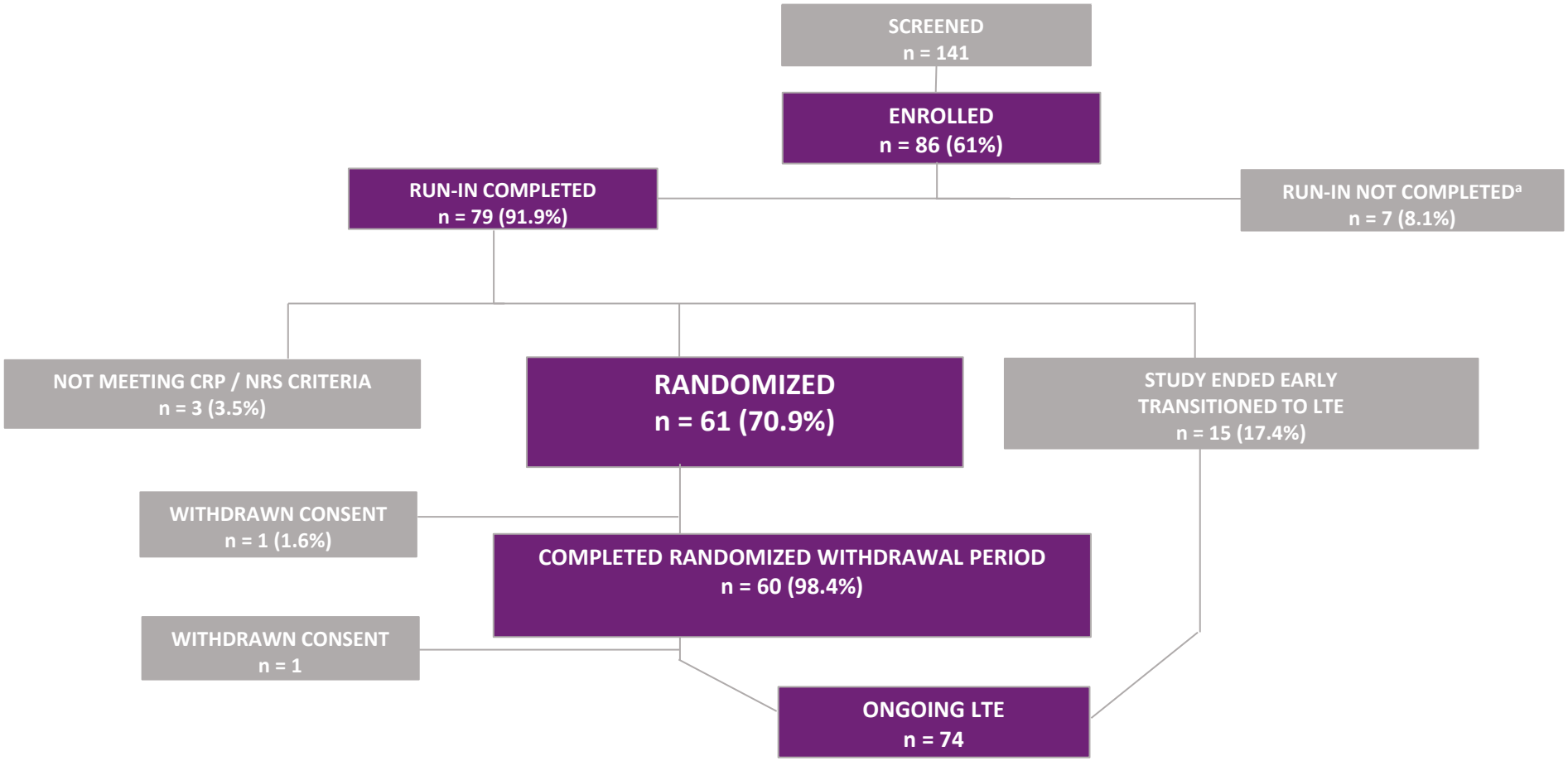


Pericarditis Manifestations at Qualifying Episode (n=86)



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

Patient Disposition CONSORT Diagram



Key Points

- 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)

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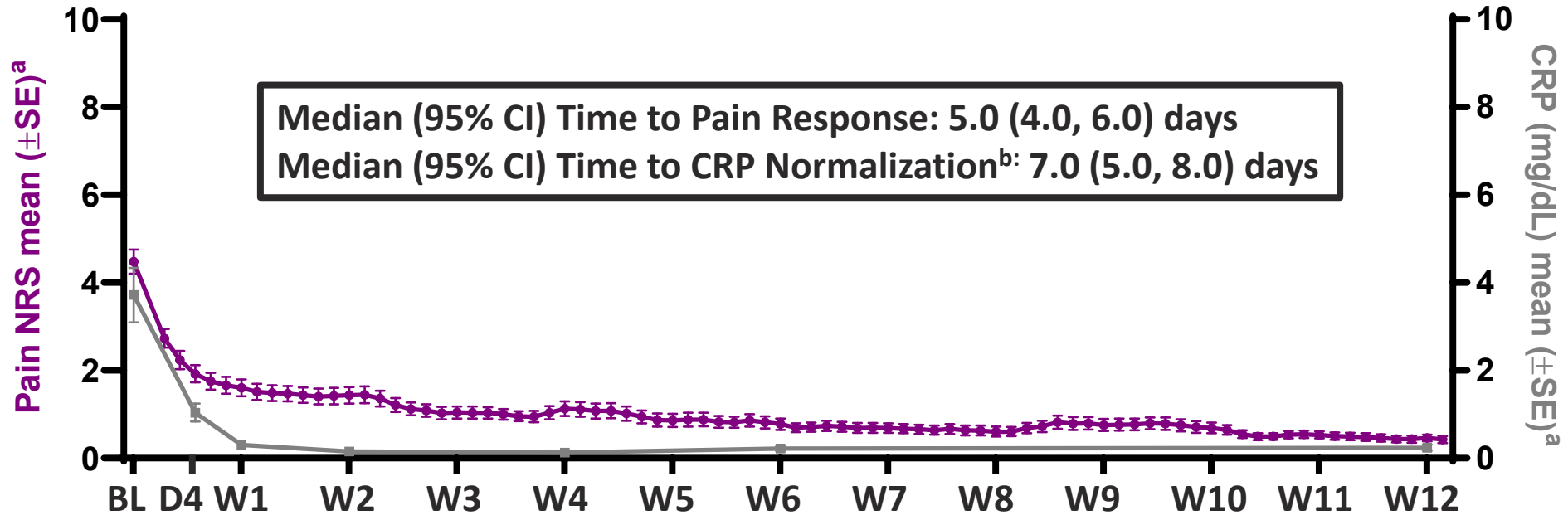

CRP	# of Patients	85	79	82	81		79		82						81
	CRP Mean	3.7	1.0	0.30	0.15		0.13		0.22						0.24
Pain NRS	# of Patients	84		84	84	83	83	84	83	83	82	81	82	82	78
	Pain Mean	4.5		1.60	1.43	1.04	1.13	0.86	0.78	0.68	0.61	0.76	0.69	0.53	0.46

[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

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)

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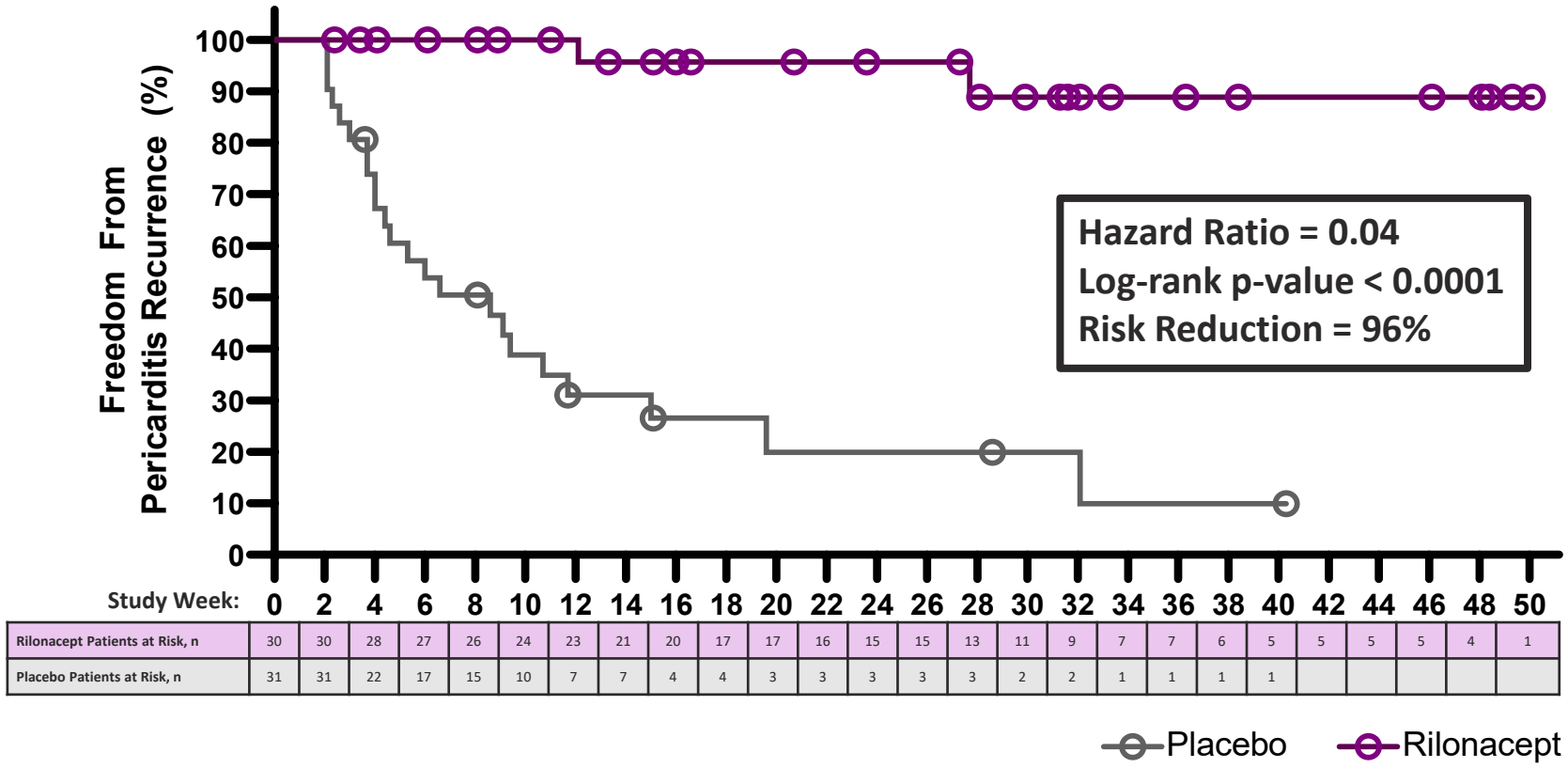

Study Week:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Rilonacept Patients at Risk, n	30	30	28	27	26	24	23	21	20	17	17	16	15	15	13	11	9	7	7	6	5	5	5	5	4	1
Placebo Patients at Risk, n	31	31	22	17	15	10	7	7	4	4	3	3	3	3	3	2	2	1	1	1	1					

	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

Key Points

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

[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)

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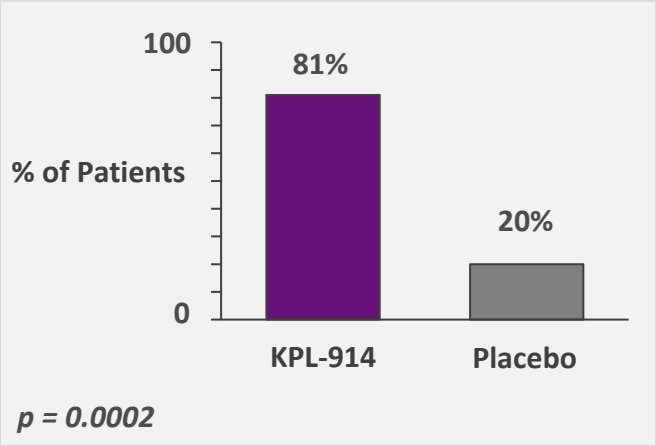
Proportion of Patients Who Maintained Clinical Response at Week 16

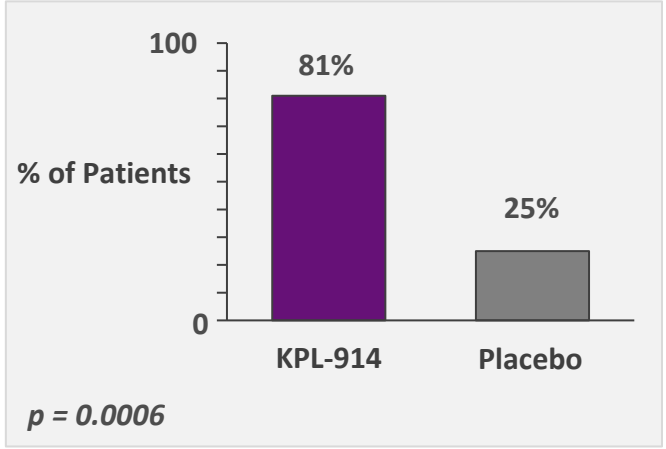


Data at Weeks 8 and 24 were consistent (Week 8, p < 0.0001; Week 24, p=0.0022)[b]

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

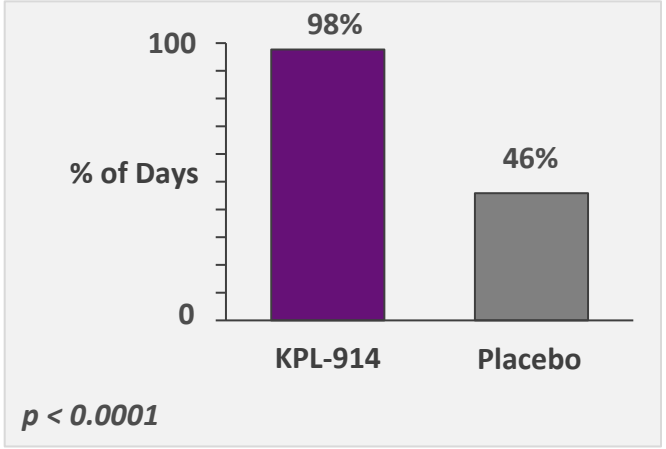


Data at Weeks 8 and 24 were consistent (Week 8, p < 0.0001; Week 24, p=0.0002)[b]

PGIPS:

- Patient Global Impression of Pericarditis Severity

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



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

[a]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.

[b]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

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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

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 CAPS[a]

[a]Cryopyrin-Associated Periodic Syndromes; Arcalyst [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals; 2016.

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

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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