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ORIGINAL RESEARCH

Interleukin-1 Trap Rilonacept Improved Health-Related Quality of Life and Sleep in Patients With Recurrent Pericarditis: Results From the Phase 3 Clinical Trial RHAPSODY

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BACKGROUND: Recurrent pericarditis is characterized by painful flares and inflammation, which negatively impact health-related quality of life. RHAPSODY (rilonacept inhibition of interleukin-1 alpha and beta for recurrent pericarditis: a pivotal symptomatology and outcomes study) evaluated the efficacy and safety of rilonacept (IL-1α and -β cytokine trap) in recurrent pericarditis. A secondary analysis of these data evaluated the patient-reported outcome questionnaire score change during the trial.

METHODS AND RESULTS: Participants completed 5 patient-reported outcome (PRO) questionnaires assessing pericarditis pain, health-related quality of life, general health status, sleep impact, and overall symptom severity. PRO score changes during the treatment run-in period (12 weeks) and the blinded randomized withdrawal period (up to 24 weeks) were evaluated using descriptive statistics and mixed model repeated measures analyses. Participants with PRO data from the run-in period (n=84) and the randomized withdrawal period (n=61; 30 rilonacept, 31 placebo) were included in analyses. Run-in baseline PRO scores indicated that pericarditis symptoms during pericarditis recurrence impacted health-related quality of life. All PRO scores significantly improved (P<0.001) on rilonacept treatment during the run-in period. For the randomized withdrawal period, PRO scores were maintained for participants receiving rilonacept. For those receiving placebo and who experienced a recurrence, PRO scores deteriorated at the time of recurrence and then improved following rilonacept bailout. At randomized withdrawal Week 24/End of Study, scores of participants who received bailout rilonacept were similar to those of participants who had continued rilonacept.

CONCLUSIONS: These results demonstrate the burden of pericarditis recurrences and the improved physical and emotional health of patients with recurrent pericarditis while on rilonacept treatment. These findings extend prior rilonacept efficacy results, demonstrating improvements in patient-reported health-related quality of life, sleep, pain, and global symptom severity while on treatment.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03737110.

Key Words: inflammation ■ interleukin-1 ■ patient-reported outcome measures ■ pericarditis ■ quality of life ■ rilonacept ■ surveys and questionnaires

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CLINICAL PERSPECTIVE

What Is New?

- These clinical trial data demonstrate the impact of recurrent pericarditis episodes on patient-reported outcomes such as pain, quality of life, and sleep.
- The study design allowed for the examination of scores on patient-reported outcomes questionnaires on and off treatment, and these new analyses show that patients have worse scores on all assessments during a recurrence, and large improvements in scores are seen while on treatment.

What Are the Clinical Implications?

- Understanding the burden of recurrence is important for clinicians; "idiopathic" recurrent pericarditis is particularly burdensome because of patient uncertainty about cause.
- The negative impact of recurrences on patients with recurrent pericarditis is substantial, and the magnitude of the improvement in health-related quality of life while on rilonacept is notably larger than that demonstrated for other cardiovascular conditions in prior research.

Nonstandard Abbreviations and Acronyms

BL	Baseline
EOS	End of Study
ISI	Insomnia Severity Index
NRS	numeric rating scale
PGIPS	Patient Global Impression of Pericarditis Symptom Severity
PRO	patient-reported outcome
RHAPSODY	rilonacept inhibition of interleukin-1 alpha and beta for recurrent pericarditis: a pivotal symptomatology and outcomes study
RI	run-in
RP	recurrent pericarditis
RW	randomized withdrawal

Recurrent pericarditis (RP) is characterized by painful, debilitating, and unpredictable flares,[1–3] which have a negative impact on health-related quality of life (HRQoL).[4,5] Up to 30% of patients who have a first pericarditis episode will experience a recurrence within 18 months of the initial episode.[6] Interleukin 1 (IL-1) is a mediator of RP disease pathophysiology, with evidence of systemic inflammation during recurrences (eg, elevated CRP [C-reactive protein] levels).[7] Rilonacept is the first US Food and Drug Administration–approved therapy for the treatment of RP and the reduction in risk of recurrence.[8] Conventional treatments (i.e., colchicine and nonsteroidal anti-inflammatory medications) do not target IL-1 specifically and are not suitable for all patients with RP because of complications and contraindications, and some patients are refractory because of inadequate treatment response and persistent underlying disease.[9] Corticosteroids are currently used as a treatment in some patients with RP but are associated with safety and toxicity issues, as well as potentiation of pericarditis recurrence and greater disease burden, and may be contraindicated in patients with comorbidities. In addition, some patients with RP become corticosteroid dependent and are unable to discontinue corticosteroid treatment.[2,3,10]

RHAPSODY (rilonacept inhibition of interleukin-1 alpha and beta for recurrent pericarditis: a pivotal symptomatology and outcomes study) was a global Phase 3 clinical trial evaluating the efficacy and safety of rilonacept, a subcutaneously injected, once-weekly cytokine trap designed to bind IL-1α/IL-1β, a cytokine family implicated in the pathophysiology of the underlying mechanism that drives autoinflammation.[8,11] Patients enrolled in RHAPSODY had a history of multiple recurrences and were experiencing an active recurrence at the time of study qualification despite being on conventional treatments, including corticosteroids. Results from RHAPSODY showed that rilonacept rapidly resolved signs and symptoms of pericarditis episodes and reduced the risk of recurrence by 96% while allowing tapering and discontinuation of corticosteroids for those patients who had previously been corticosteroid dependent.[8]

In addition to the clinical indicators of recurrence (eg, inflammation as assessed by serum CRP or cardiac imaging), a battery of patient-reported outcome (PRO) questionnaires was administered during RHAPSODY, including a daily electronic pain diary and questionnaires completed at study visits to assess HRQoL, sleep impact, and health status. The objective of the current secondary analysis of the RHAPSODY data is to characterize the effect of rilonacept treatment on patient-reported pain, HRQoL, sleep, and health status over the course of the clinical trial.

METHODS

Trial Design and Data Set for Secondary Analyses

RHAPSODY, a Phase 3 global, multicenter, double-blind, placebo-controlled, event-driven, randomized-withdrawal trial (ClinicalTrials.gov identifier: NCT03737110),[11] enrolled

participants ≥12 years of age with at least 2 prior episodes of RP and presenting with acute symptoms and evidence of systemic inflammation (elevated CRP) despite treatment with commonly used medications. The trial included 4 time periods: Screening, single-blinded treatment Run-In (RI), double-blinded Randomized Withdrawal (RW), and open-label Long-term Extension. Randomization was stratified to ensure that patients were equally divided to receive rilonacept or placebo depending on whether they were receiving or not receiving oral corticosteroids at RI Baseline (BL), and patients were blinded to the number of weeks that constituted the RI period (thus, they were unaware when randomization occurred).[8] For additional information on the time periods of RHAPSODY, please refer to Figure 3 in Klein et al.[11] The study protocol was reviewed and approved by Advarra Institutional Review Board (registration number 00000971), and all enrolled participants provided written informed consent (or assent with parental permission for participants <18 years of age). Data, analytic methods, and study materials will be made available to other researchers upon reasonable request.

The study design and results of clinical indicators of inflammation (including serum CRP and, for a subset of participants, cardiac imaging [magnetic resonance imaging or presence of pericardial effusion on echocardiogram]), are presented elsewhere.[8,11] The current secondary analysis includes additional data collected during the RI and RW periods, which characterize in greater detail the impact of rilonacept on patient-reported pain, HRQoL, sleep impact, and health status. Specifically, the analyses presented herein include data from the PRO questionnaires completed during the 12-week single-blind RI period and the double-blind event-driven RW period up to Week 24. Participants in the placebo group who experienced a documented qualifying recurrence during the RW period attended a clinic "Recurrence" visit, completed the PRO questionnaires, and then received rilonacept bailout treatment. The current analyses focus on the following study periods and timepoints: RI BL, RI Week 12/RW BL, Recurrence visit, RW Week 24, or End of Study (EOS) visit.

Assessments

The PRO questionnaires included in RHAPSODY were informed by qualitative research, including interviews with adults with RP, to develop a patient-centric conceptual model of RP.[5,12] Results from this qualitative research provided insight into the patient experience, notably the symptoms associated with RP and also the impacts, including impacts on sleep, physical functioning, emotional functioning, and other domains of quality of life.[12] All PRO questionnaires, with the exception of the daily pericarditis pain assessment, were completed by participants at clinic visits before clinician interaction.

1. A single-item 11-point numeric rating scale (NRS) for average pericarditis pain intensity, with a 24-hour recall period (0=no pain, and 10=pain as bad as it could be),[13–15] was completed by participants each evening electronically, from RI BL through the end of the RW period. The daily assessment of pain minimized the potential for recall bias that can negatively impact pain ratings. Both daily scores and weekly average scores associated with key clinic visits are reported.
2. HRQoL was assessed with the SF-36v2 at clinic visits. The SF-36v2 is a 36-item questionnaire assessing the following 8 domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. In addition to the 8 domain scores, 2 component summary scores are also calculated: Physical Component Summary and Mental Component Summary.[16,17] Scoring for the SF-36v2 is based on normative data, with 50 as the average equating to the population mean and higher scores reflecting better HRQoL.
3. General health status was assessed using the EQ-5D Visual Analogue Scale (EQ VAS) and Utility Index, from the 5-level EQ-5D (EQ-5D-5L) completed at clinic visits. For the EQ VAS, participants rate current overall health on a vertical 0 to 100 VAS, with 100=Best Health Imaginable and 0=Worst Health. The EQ-5D-5L Utility Index converts the scores for the 5 dimensions into a single summary index number (utility) that ranges from 0 to 1, with higher scores indicating better health status/functioning.[18]
4. Sleep impact was assessed by the Insomnia Severity Index (ISI) at clinic visits. The ISI is a 7-item questionnaire where each item is rated on a 5-point Likert scale ranging from 0 (no problem) to 4 (very severe problem), and total score ranges from 0 to 28, with higher scores indicating worse impact on sleep.[19] Additionally, score ranges for the total score have been previously defined to categorize severity of insomnia: 0–7=absence of insomnia, 8–14=sub-threshold insomnia, 15–21=moderate insomnia, and 22–28=severe insomnia.[19]
5. Global pericarditis symptom severity was assessed by the Patient Global Impression of Pericarditis Symptom Severity (PGIPS) at clinic visits. The PGIPS is a newly developed single-item questionnaire with a 7-point response scale ranging from absent (No RP symptoms) to very severe (RP symptoms cannot be ignored), with higher scores indicating more severe symptoms.

Statistical Analysis

Analyses were conducted using SAS version 9.4. Demographic and health information from the RI BL visit was evaluated descriptively for the full sample. To evaluate the change in the scores of the PRO questionnaires over the clinical trial RI and RW time periods, descriptive statistics and mixed model repeated measures analyses, with unstructured covariance structure, were conducted. To first evaluate the magnitude of change during the 12-week single-blind RI period, Cohen's effect size (d) was calculated with 95% CIs for the mean change between RI BL and RI Week 12 for all PRO scores. Mixed model repeated measures was used to calculate the overall change in PRO scores by treatment group during the 12-week RI period and the full study period (from RI BL to RW Week 24/EOS). The model included time (all visits from RI BL to RW Week 24/EOS), treatment group, interaction between visit by treatment group, and PRO scores (controlling for RI BL score on each PRO questionnaire/domain). Change in PRO score was assessed for statistical significance. Significance was assessed at 2-sided α of 0.05. Further descriptive analyses were conducted to evaluate the impact of having received bailout rilonacept for those participants randomized to placebo who experienced a recurrence in the RW period before Week 24.

RESULTS

The participant sample has been described previously,[8] and a summary of the patient demographic and health characteristics for the 86 participants enrolled in the RI period is presented in Table 1. The average age of participants was 45 years of age (range, 13 to 78 years), and more than half were female (57%). The median number of prior recurrences was 4 (range, 3–11), and almost half the sample was on oral corticosteroids at RI BL, with ≈22% of these patients having been on corticosteroids for >26 weeks. The most commonly reported comorbidities at RI BL were hypertension (29.1%), atrial fibrillation (19.8%), obesity (19.8%), and hyperlipidemia (17.4%). Of the participants enrolled, 84 had PRO data, and 61 were randomized into the RW study period (30 randomized to continue rilonacept; 31 randomized to placebo).

Participants in RHAPSODY were in active recurrence at the beginning of the trial. At RI BL, CRP was elevated (average 6.2 mg/dL[8]), and the average pain NRS score was 4.5±2.5. The scores on the PRO questionnaires at RI BL further quantified the magnitude and impact of an acute pericarditis recurrence: all SF-36v2 scores were below the population reference score of 50, EQ VAS (0–100) was 57.4±19.6, EQ-5D-5L Utility Index was 0.74±0.15, ISI total score was 10.8±6.1, and the PGIPS was 3.4±1.7. These data demonstrate that pericarditis recurrence negatively impacts HRQoL, sleep, and general health status (Table S1).

Table 1. Demographic and Health Characteristics of RHAPSODY Phase 3 Clinical Trial Sample

Characteristic	Patients at RI BL (n=86)
Age, y, mean±SD (range)	44.7±16.1 (13–78)
Female participants, n (%)	49 (57.0%)
CRP values, mg/dL, mean±SD (range)	3.7±5.7 (0.0–30)
Number of prior recurrences, mean±SD (range)	4.7±1.7 (3–11)
Pericardial effusion on echocardiography, n (%)	11 (12.8%)
Pericardial inflammation on MRI*, n (%)	8 (9.3%)
Concomitant medications at the qualifying recurrence episode	
Corticosteroid use, n (%)	41 (47.7%)
Analgesics (opioid and nonopioid), n (%)	10 (11.6%)
NSAIDs, n (%)	58 (67.4%)
Colchicine, n (%)	69 (80.2%)
Most frequent comorbidities (>10%) reported at BL	
Hypertension, n (%)	25 (29.1%)
Atrial fibrillation, n (%)	17 (19.8%)
Obesity, n (%)	17 (19.8%)
Hyperlipidemia, n (%)	15 (17.4%)
Anxiety, n (%)	14 (16.3%)
Depression, n (%)	12 (14.0%)
Gastroesophageal reflux disease, n (%)	12 (14.0%)
Asthma, n (%)	10 (11.6%)
Seasonal allergy, n (%)	10 (11.6%)
Drug hypersensitivity, n (%)	9 (10.5%)
Migraine, n (%)	9 (10.5%)

BL indicates baseline; CRP, C-reactive protein; MRI, magnetic resonance imaging; RHAPSODY, rilonacept inhibition of interleukin-1 alpha and beta for recurrent pericarditis: a pivotal symptomatology and outcomes; and RI, run-in.

*Cardiac MRI at RI BL assessed pericardial delayed hyperenhancement, myocardial delayed hyperenhancement, and pericardial effusion and effusion size; 29 patients had no inflammation on MRI (33.7%), and 49 patients did not have MRI (57.0%).

Changes in the scores on the PRO questionnaires during the 12-week single-blind RI period showed significant improvement (P<0.001) on rilonacept treatment (Figure 1); nearly all changes were large based on Cohen's effect sizes (d>0.80), and the remaining score changes were moderate (d=0.50–0.79).[20] The largest changes were observed for the SF-36v2 Bodily Pain subscale (d=2.63), followed by the PGIPS (d=1.82), SF-36v2 Physical Component Summary (d=1.76), and the Weekly Average Pericarditis Pain NRS (d=1.68).

In addition to an improvement on sleep impact during RI BL to RI Week 12 (as measured by the mean ISI continuous total score; d=0.82), the categorical ISI total score also improved over time. Figure 2 shows that at RI BL (left stacked bars), a quarter of patients reported a high degree of insomnia (21% "moderate insomnia," and 4% "severe insomnia"). At RI Week 12,

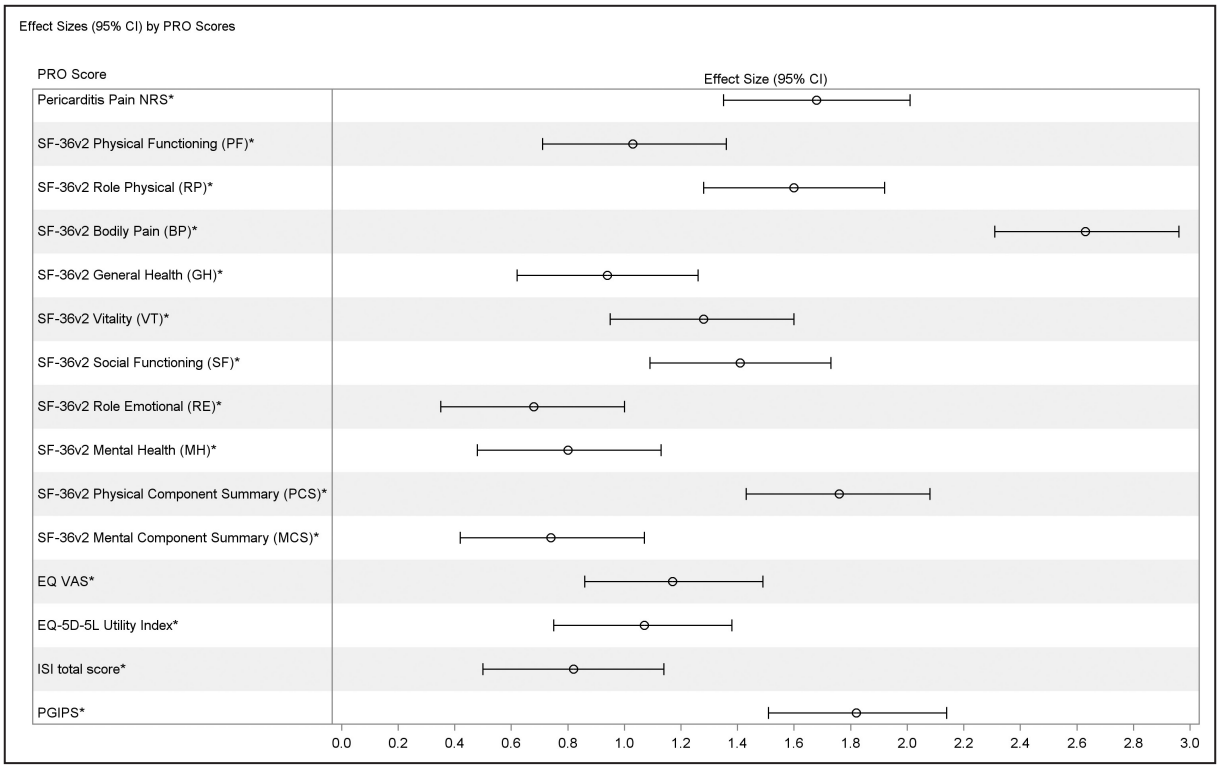

Figure 1. Effect size and 95% CIs for change in PRO scores between RI BL to RI Week 12.
Cohen's effect size d=(mean RI week 12–mean RI BL)/SD RI BL. *P<0.001. BL indicates baseline; ISI, Insomnia Severity Index; NRS, numeric rating scale; PGIPS, Patient Global Impression of Pericarditis Symptom Severity; PRO, patient-reported outcome; RI, run-in; and VAS, Visual Analogue Scale.

after rilonacept treatment (second to leftmost stacked bars), only 4% had scores for "moderate insomnia," and 0% had scores in the "severe insomnia" range. In fact, 74% of patients reported none/minimal insomnia (56% with "absence of insomnia" and 18% with "subthreshold insomnia") at RI Week 12.

The improvement in PRO scores observed in the RI period was maintained in the double-blind RW period for those participants randomized to continue rilonacept treatment. Specifically, between the start and end of the study (RI BL to RW Week 24/EOS) there were significant improvements (P<0.001) for all PRO scores for this group of participants (n=30; Table 2). Similar to the results for the full sample, for participants who continued rilonacept treatment in the RW period, the percentage of those with no insomnia increased from ≈30% at RI BL to >70% at RW Week 24/EOS (Figure 2; middle cluster of bars).

Of the 31 participants randomized to placebo, 22 had a documented qualifying recurrence before the end of the event-driven, double-blind RW period and received bailout rilonacept treatment. Trial closure was triggered, as prespecified, upon accrual of 22 adjudicated recurrences,[8] and 1 additional participant in the placebo group, who experienced a recurrence after RW Week 24, is excluded from recurrence analyses. Participants who experienced a recurrence in the RW period report incremental increases in average daily pain scores on the Pericarditis Pain NRS (ie, worsening pain) in the 2 weeks before the Recurrence visit (with data centered on the Recurrence visit) and resolution of pain in the 1 to 2 weeks following bailout rilonacept treatment (Figure 3). These patients also reported that SF-36v2 scores from the Recurrence visit are lower than RI Week 12 and similar to the scores from the RI BL visit (Figure 4). Following rilonacept bailout after the documented recurrence, scores on the SF-36v2 improved again by RW Week 24/EOS to levels similar to RI Week 12 (Figure 4). These results show that scores on the PRO reflect the health status of the participants over the trial (ie, indicate worse outcomes during recurrence, and improve during treatment with rilonacept).

Participants' scores on one particular SF-36v2 domain (Bodily Pain, which had the largest change in the RI period) improved when patients were receiving rilonacept treatment, deteriorated for patients who experienced a pericarditis recurrence in RW period (ie, those randomized to placebo who had washed off rilonacept treatment), and then improved again when back on treatment (ie, receiving bailout rilonacept) by RW Week 24/EOS, such that the scores were similar to those reported by participants who had

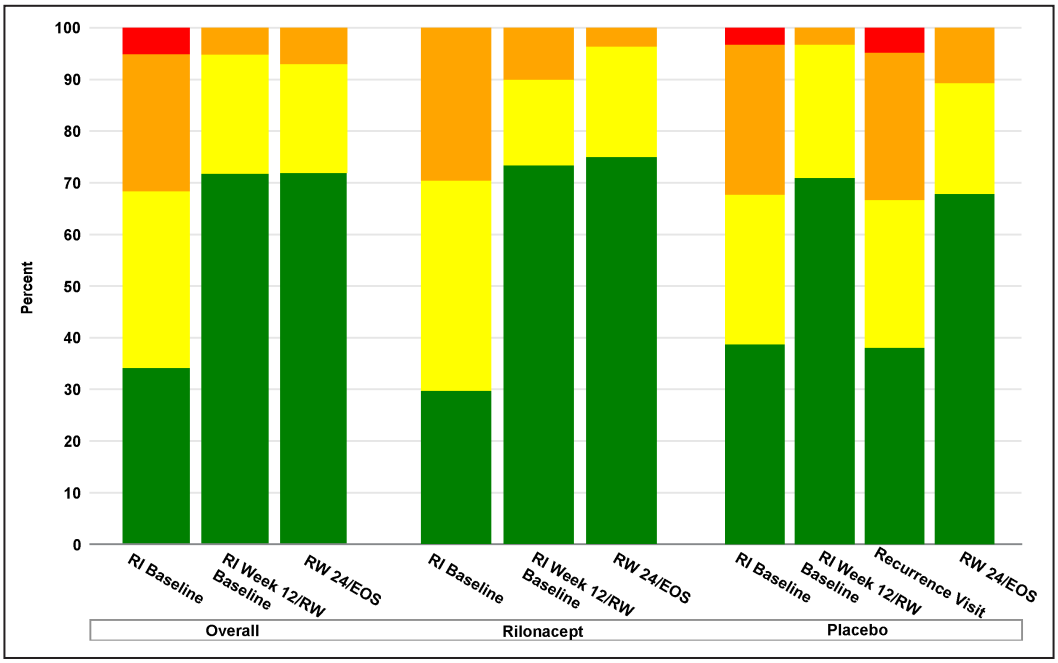

Figure 2. Percentage of participants for each ISI total score severity category over time, and by treatment group.
ISI total score categories are noted by color; Green="absence of insomnia" (0–7), Yellow="sub-threshold insomnia" (8–14), Orange="moderate insomnia" (15–21), Red="severe insomnia" (22–28). EOS indicates End of Study; ISI, Insomnia Severity Index; RI, run-in; and RW, randomized withdrawal.

not experienced a recurrence during the RW period (Figure 5).

There is a similar pattern for sleep impact. Specifically, the categorical ISI total scores from the Recurrence visit (for those who had a recurrence in the RW period) look similar to the frequency distribution across categories from RI BL (Figure 2, right cluster bars). Distribution of the categories for the placebo group at RW Week 24/EOS indicates improvement with more than half of the sample in the category "absence of insomnia."

DISCUSSION

While the primary analyses of RHAPSODY showed that rilonacept led to a rapid resolution of pericarditis recurrence and reduced the risk of subsequent recurrence,[8] this secondary analysis provides insight into both the burden of RP to patients on their daily lives during recurrence and the improvement of patient-centric outcomes while on rilonacept treatment, including improvements in patient-reported pain, symptom severity, HRQoL, and sleep.

At RI BL, patients presented with a pericarditis recurrence as evidenced by pain and systemic inflammation (elevated CRP levels). Scores on the PRO questionnaires reflected the burden of those recurrences on patients, including measurable pain severity, poor HRQoL (with scores lower than norms for the SF-36v2, including some domain scores that were more than a SD below the norm), reported sleep impacts on the ISI, and poor global health status (per scores on the EQ VAS, EQ-5D-5L Utility Index, and PGIPS). These findings align with prior research that has documented the substantial burden of the condition.[4,5]

During the 12-week single-blind RI period, the improvements in PRO scores on rilonacept treatment were both clinically and statistically ($P<0.001$) significant while concomitant medications were weaned and discontinued (including corticosteroids) over a mean period of ≈8 weeks. These results mirror the results of the primary study outcomes, which included rapid reduction in pain, normalization of CRP, and resolution of other manifestations of pericarditis.[8] At the end of the 12-week RI, average pain scores on the NRS were close to 0 (d=1.68), the averages for all domains and summary scores on the SF-36v2 had improved to the norm of 50 or above, and were statistically significant[21] (effect sizes ranged from moderate to large), and sleep impact and overall health status improved (effect sizes were large). Furthermore, the magnitude of changes in the SF-36v2 domain and component scores was larger than changes noted in

Table 2. Least-Squares Means and SE for Change Between RW Week 24 and RI BL on PRO Scores for Participants Randomized to Continue Rilonacept Treatment in the RW Period

Questionnaire score	LS mean (SE) change* Rilonacept group (n=30)
Pericarditis Pain NRS (weekly average)	−4.35 (0.13)
SF-36v2 Physical functioning	12.4 (1.2)
SF-36v2 Role physical	15.2 (1.5)
SF-36v2 Bodily pain	18.3 (1.6)
SF-36v2 General health	7.7 (1.3)
SF-36v2 Vitality	14.4 (1.4)
SF-36v2 Social functioning	14.6 (1.5)
SF-36v2 Role emotional	8.4 (1.0)
SF-36v2 Mental health	10.4 (1.0)
SF-36v2 Physical component summary	14.5 (1.3)
SF-36v2 Mental component summary	9.2 (1.0)
EQ (VAS)	27.3 (3.3)
EQ-5D-5L Utility index	0.16 (0.02)
ISI total score	−5.7 (0.8)
PGIPS	−3.27 (0.14)

BL indicates baseline; ISI, Insomnia Severity Index; LS mean, least-squares mean; NRS, numeric rating scale; PGIPS, Patient Global Impression of Pericarditis Symptom Severity; PRO, patient-reported outcome; RI, run-in; RW, randomized withdrawal; and VAS, Visual Analogue Scale.

*$P<0.001$ for all PRO scores.

interventional studies for other cardiovascular patient groups.[22–24]

Rilonacept use also was associated with improvement in sleep, which is reflected in both significant changes in the ISI continuous total score and also changes in the distribution of the categories associated with the total score. At RI BL, only approximately a quarter of all participants were in the "absence of insomnia" category (27%), but at RW Week 24/EOS, 75% of participants on rilonacept had reached this category. For participants in the placebo group who experienced a recurrence in the RW, the distribution of the ISI categories at the Recurrence visit is similar to RI BL, and the distribution at RW Week 24/EOS (following bailout rilonacept) is similar to RI Week 12. A deeper understanding of the improvements in the health status of these patients can be gleaned from responsive measures such as the ISI and sleep impact.

The improvement in these patient-centric outcomes observed in the RI period were maintained throughout the double-blind RW period in patients randomized to continue receiving rilonacept. In comparison, the majority (>70%) of the patients randomized to receive placebo in the blinded RW period experienced a documented recurrence before Week 24. These patients lost the benefit of the prior improvement in PRO scores they had garnered during the resolution of their acute episode during the RI period. When scores from RI BL, RI Week 12, Recurrence visit, and RW Week 24/EOS visits are examined for this group of participants, the changes in PRO scores tracked with the changes in the participants' health status. Specifically, scores improved while on rilonacept, deteriorated when off treatment, and then improved again following bailout

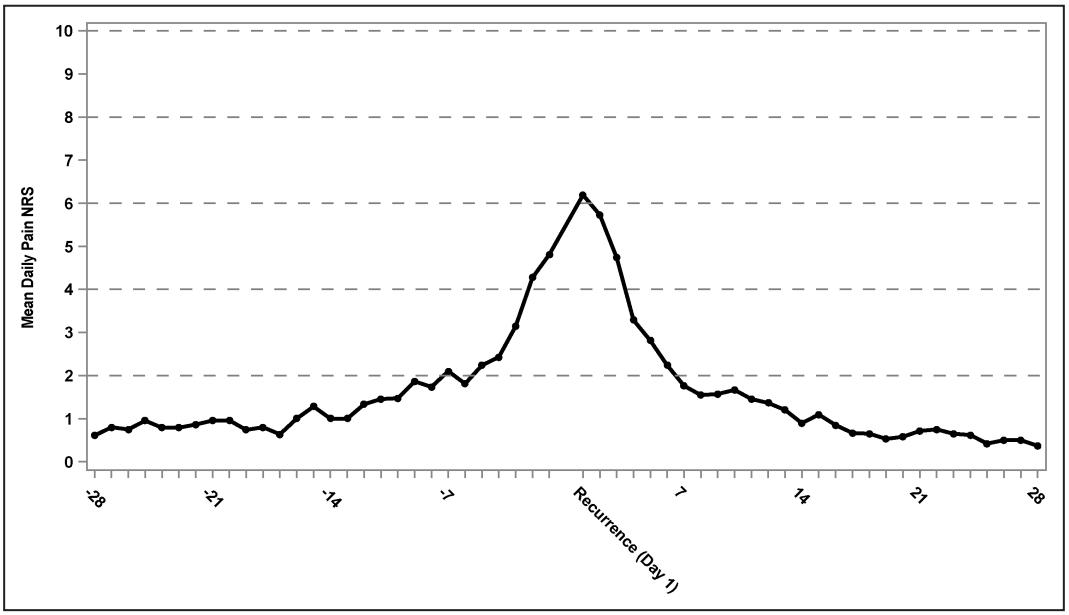

Figure 3. Daily pain scores for participants in placebo group who experienced recurrence before Week 24 of the RW (n=22), before and after Recurrence visit.
NRS indicates numeric rating scale; and RW, randomized withdrawal.

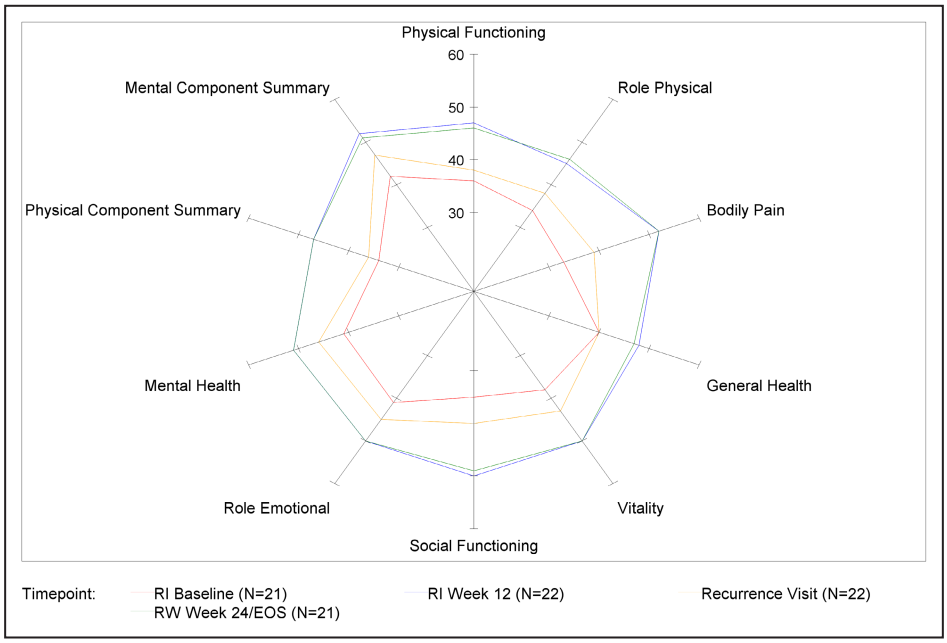

Figure 4. Spider plot for SF-36v2 scores over study timepoints for participants in placebo group who experienced recurrence Before Week 24 of the RW (n=22).
Each spoke corresponds to a subscale or domain score on the SF-36v2; scores closer to the center indicate worse HRQoL, and scores further on each spoke correspond to better HRQoL; all scores are normed such that a score of 50 is the population average. EOS indicates End of Study; HRQoL, health-related quality of life; RI, run-in; and RW, randomized withdrawal.

rilonacept monotherapy treatment to levels comparable to RI Week 12 scores, with resolution of the acute episode. In addition, there is a 1- to 2-week period of increasing daily pericarditis pain preceding a documented on-study recurrence in the RW period. The pain experienced before a documented recurrence and the unpredictable nature of the condition[4] (eg, when a recurrence might happen) underscore the HRQoL impacts that are seen in the RI BL PRO questionnaire scores for all participants in RHAPSODY. This observation of a prodrome period of increased pain could be informative in management of patients with RP.

These analyses of the PRO data demonstrate both the burden of experiencing a recurrence and the improvement across multiple aspects of physical and emotional health when the participants are not experiencing a recurrence and are in clinical remission. The burden of RP on patients' HRQoL has been reported previously, including in a real-world patient survey[4] and in the Phase 2 clinical trial of rilonacept using the PROMIS Global Health questionnaire.[4,5] This is further demonstrated in RHAPSODY using the SF-36v2, and expanded to include evaluations for changes in sleep impact with the ISI, as well as general health using the EQ VAS and EQ-5D-5L Utility Index and pericarditis symptom severity using the PGIPS and Pericarditis Pain NRS. Furthermore, the negative impact of recurrences in patients with RP is substantial, and the magnitude of the change in HRQoL while on rilonacept is notably larger than demonstrated in prior research for other cardiovascular conditions.

The physical and emotional burden of RP should not be underestimated, especially because the condition is usually diagnosed as "idiopathic," or having unknown cause, resulting in great uncertainty as to the long-term clinical outcomes for those affected.[7,25] Patients with RP (and frequently their physicians) become frustrated when usual medical management fails and recurrences are frequent and prolonged, often requiring hospital admissions. Thus, this "idiopathic" condition fuels concern not just about long-term outcomes but also about important domains in everyday life (eg, employment, sentimental personal relationships, family planning, etc).[26–28]

Strengths of the study include the availability of data from multiple PRO questionnaires to provide the additional context of the patient experience during the time of the trial beyond the pain/inflammatory outcome measures and adjudicated events. In addition, the inclusion of the SF-36v2 and EQ-5D-5L allows for comparison to other clinical studies

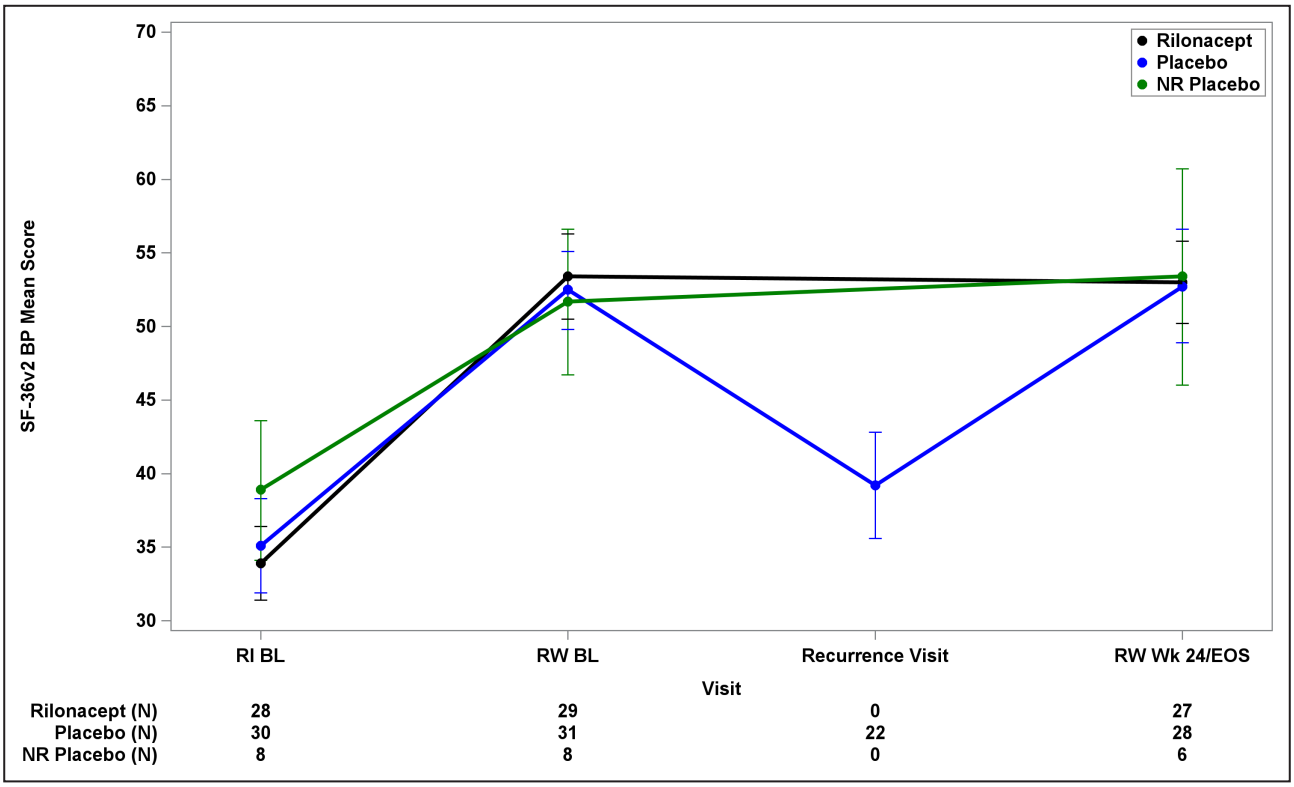

Figure 5. Mean scores (and 95% CI error bars) for SF-36v2 Bodily Pain domain for RI BL, RW BL, Recurrence visit, and RW Week 24/EOS, for 3 groups of participants: Rilonacept only, placebo, and placebo without recurrence before Week 24.
BL indicates baseline; BP, bodily pain; EOS, End of Study; NR, no recurrence; RI, run-in; and RW, randomized withdrawal.

involving cardiovascular therapies. Another strength is that the completion of the PRO questionnaires at the Recurrence visit provided researchers insight into the negative impact of recurrence at 2 different timepoints, one in which several treatments were used concomitantly and the other most commonly following rilonacept monotherapy. One limitation is that these results report secondary, post hoc analyses; while the trial was powered to detect statistical differences for the Pericarditis Pain NRS, it was not powered to detect statistical differences for the other PRO questionnaires. Another limitation is that the data included in the analyses for the RW time period do not include the full 24 weeks for all participants, given that the event-driven study design required the halting of the trial at the 22nd recurrence.[8,11] In addition, while the majority of participants enrolled in the trial had a diagnosis of idiopathic RP (which is similar to prevalence reported in other studies[2]), 15% were postpericardiotomy and postinfarction syndrome. The results reported herein should be generalizable to all types of pericarditis, although the results for postpericardiotomy and postinfarction syndrome are less robust. Finally, the sample size of the study precluded additional subgroup analyses, including comparisons between sexes or age groups; however, based on the primary efficacy analyses, there were no differences between these subgroups.[8]

CONCLUSIONS

These findings expand upon the efficacy results from RHAPSODY, which demonstrated resolution of patient-reported pain and indicators of inflammation; the new analysis provides reinforcing evidence of the detrimental impact a recurrence of RP imposes on patients' lives, and the significant improvements in quality of life, sleep, and general health while receiving rilonacept. The majority of patients who interrupted rilonacept treatment because of randomization to placebo experienced a recurrence, and for these negative changes in health status, PRO scores mirrored their initial presentation. The results presented provide support for the potential broad impact of rilonacept treatment on patients' lives, by demonstrating that HRQoL, sleep, pain, and global symptom severity improve while on treatment, which may result in an improvement of, or return to, normal daily activities for these patients.

APPENDIX

RHAPSODY Investigators

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ARTICLE INFORMATION

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Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. PRO scores of Phase 3 clinical trial sample at RI BL, RI Week 12, mean change, and effect size

PRO score	RI BL		RI Week 12		Change between RI Week 12 and RI BL		Effect size (95% CI)*
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Pericarditis Pain NRS	82	4.5 (2.5)	73	0.4 (0.6)	71	-4.2 (2.5)	1.68 (1.35–2.01)†
SF-36v2 Physical Functioning	79	40.0 (9.8)	77	49.9 (8.4)	73	10.1 (9.2)	1.03 (0.71–1.36)†
SF-36v2 Role Physical	79	35.1 (8.5)	77	48.9 (7.9)	73	13.6 (9.3)	1.60 (1.28–1.92)†
SF-36v2 Bodily Pain	79	34.6 (7.1)	77	53.2 (7.3)	73	18.7 (10.4)	2.63 (2.31–2.96)†
SF-36v2 General Health	79	41.9 (8.2)	77	49.4 (8.8)	73	7.7 (8.1)	0.94 (0.62–1.26)†

Table S1. PRO scores of Phase 3 clinical trial sample at RI BL, RI Week 12, mean change, and effect size

PRO score	RI BL		RI Week 12		Change between RI Week 12 and RI BL		Effect size (95% CI)*
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
SF-36v2 Vitality	79	39.5 (10.4)	77	53.1 (9.4)	73	13.3 (9.9)	1.28 (0.95–1.60)†
SF-36v2 Social Functioning	79	36.7 (10.5)	77	51.7 (7.3)	73	14.8 (10.6)	1.41 (1.09–1.73)†
SF-36v2 Role Emotional	79	44.1 (11.2)	77	52.2 (6.9)	73	7.6 (9.9)	0.68 (0.35–1.00)†
SF-36v2 Mental Health	79	43.5 (11.7)	77	53.3 (7.7)	73	9.4 (9.0)	0.80 (0.48–1.13)†
SF-36v2 Physical Component Summary	79	36.0 (7.8)	77	49.4 (7.9)	73	13.7 (8.6)	1.76 (1.43–2.08)†

Table S1. PRO scores of Phase 3 clinical trial sample at RI BL, RI Week 12, mean change, and effect size

PRO score	RI BL		RI Week 12		Change between RI Week 12 and RI BL		Effect size (95% CI)*
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
SF-36v2 Mental Component Summary	79	44.0 (12.1)	77	53.6 (8.1)	73	9.0 (9.3)	0.74 (0.42–1.07)†
EQ VAS	81	57.4 (19.6)	78	79.8 (17.0)	76	23.0 (23.1)	1.17 (0.86–1.49)†
EQ-5D-5L Utility Index	81	0.74 (0.15)	78	0.90 (0.09)	76	0.16 (0.10)	1.07 (0.75–1.38)†
ISI total score	79	10.8 (6.1)	78	5.4 (4.7)	74	-5.0 (6.4)	0.82 (0.50–1.14)†

Table S1. PRO scores of Phase 3 clinical trial sample at RI BL, RI Week 12, mean change, and effect size

PRO score	RI BL		RI Week 12		Change between RI Week 12 and RI BL		Effect size (95% CI)*
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
PGIPS	81	3.4 (1.7)	81	0.4 (0.6)	78	-3.1 (1.6)	1.82 (1.51–2.14)†

*Cohen's effect size d=(Mean RI Week 12 – Mean RI BL)/SD RI BL

†p<0.001

Abbreviations: BL=Baseline; CI=confidence interval; ISI=Insomnia Severity Index; NRS=numeric rating scale; PGIPS=Patient Global Impression of Pericarditis Symptom Severity; PRO=patient-reported outcome; RI=Run-In; SD=standard deviation; VAS=Visual Analogue Scale