Absence of Pericarditis Recurrence in Rilonacept-Treated Patients with COVID-19 and mRNA Vaccinations: Experience from Phase 3 RHAPSODY Long-Term Extension

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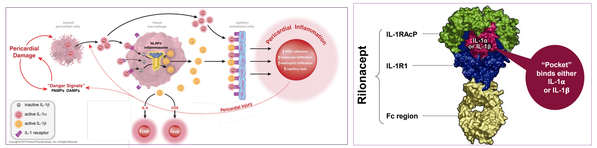
BACKGROUND

Clinical Considerations

- It is unknown if patients with recurrent pericarditis (RP) might be at increased risk of triggered recurrence after SARS-CoV-2 vaccination or during or after COVID-19 infection.
- Questions exist regarding the use of IL-1 antagonists in the setting of COVID-19 infection.
- There is limited information regarding the efficacy and safety of SARS-CoV-2 vaccination while patients are receiving rilonacept.
- The recently-completed 2-year long-term extension of the Phase 3 trial RHAPSODY took place from May 2020 to June 2022, during the peak of COVID-19 prevalence, and may provide additional on-treatment efficacy and safety information.
- The known efficacy of rilonacept in treating and preventing pericarditis recurrence could inform COVID-19 disease and vaccine management in patients with recurrent pericarditis.

Role of IL-1

FIGURE 1. ILLUSTRATIONS OF THE ROLE OF IL-1 IN RP AND IL-1 INHIBITION WITH RILONACEPT



Rilonacept

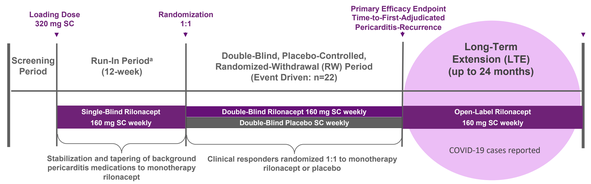
- Rilonacept is an interleukin-1α (IL-1α) and interleukin-1β (IL-1β) cytokine trap approved in the US for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and children 12 years and older. It is also approved for treatment of cryopyrin-associated periodic syndromes (CAPS) in adults and children 12 years and older as well as the maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing 10 kg or more.[1]
- Rilonacept binds IL-1α or IL-1β and prevents engagement with the cell-surface receptor for IL-1, thus inhibiting IL-1 activity.[2]

METHODS

- RHAPSODY was a Phase 3, double-blind, placebo-controlled, event-driven, randomized withdrawal (RW) trial of rilonacept in patients with RP, which also included a long-term extension (LTE) phase, allowing up to 24 months of additional open-label rilonacept treatment (**Figure 2**)[3].
- All suspected pericarditis recurrence events in the RW period were formally adjudicated by the Clinical Endpoint Committee (CEC).
- RHAPSODY Results (RW period)
  - Rilonacept treatment resulted in a 96% reduction in the risk of pericarditis recurrence (Hazard ratio in a Cox proportional-hazards model, 0.04; 95% CI, 0.01-0.18; P<0.0001 by log-rank test).
    - There were too few recurrence events in the rilonacept group to allow for the median time to the first adjudicated recurrence to be calculated.
    - The median (95% CI) time to the first adjudicated recurrence in the placebo group was 8.6 (4.0-11.7) weeks.
  - 2 of 30 patients (7%) in the rilonacept group had a pericarditis recurrence, as compared with 23 of 31 patients (74%) in the placebo group.
    - The two recurrence events in the rilonacept group were associated with temporary interruptions of the trial-drug regimen of one to three weekly doses.
  - Rilonacept was well-tolerated
    - The most common adverse events with rilonacept were injection-site reactions and upper respiratory tract infections.
    - No cases of COVID-19 were reported before conclusion of the RW period (May 2020), at which time COVID-19 was prevalent.
- Long Term Extension
  - A long-term extension (LTE) enabled up to 24 months further open-label rilonacept treatment from May 2020 until June 2022. 74 of 75 eligible patients opted to participate in the LTE.
  - SARS-CoV-2 vaccinations (reported as concomitant medication) and COVID-19 cases (reported as adverse events) occurring during the LTE were examined in this post-hoc analysis.

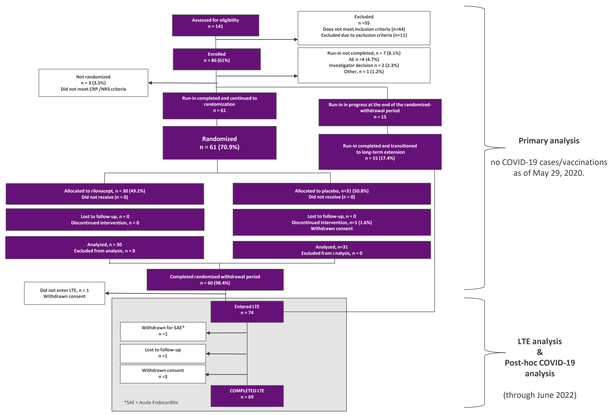
METHODS (cont.)

FIGURE 2. RHAPSODY DESIGN



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

FIGURE 3. PATIENT DISPOSITION CONSORT DIAGRAM



COVID-19 DISEASE SEVERITY REPORTING

- COVID-19 cases were reported by investigators as adverse events (AEs) and were not adjudicated. Method of disease diagnosis (e.g., rapid antigen versus polymerase chain reaction [PCR] test) was not reported.
- AEs were reported as mild, moderate, or severe according to FDA AE-reporting guidelines; the WHO classification of COVID-19 infection were available in the prespecified study eCRF.[4]
- Per FDA guidance:
  - Mild: easily tolerated, does not interfere with normal daily activities, does not require intervention
  - Moderate: causes some interference with daily activities; minimal, local or noninvasive intervention indicated
  - Severe: as a consequence of the event, daily activities are limited or completely halted; hospitalization or prolongation of hospitalization indicated

RESULTS

- No COVID-19 cases were reported during the run-in period nor the randomized withdrawal period (n=86), which closed May 29, 2020.
- The SARS-CoV-2 vaccine did not become available until November 2020, and, as such, no subjects were vaccinated during those trial periods.
- 47/74 subjects were vaccinated during the LTE while receiving rilonacept treatment: mRNA vaccine series (n=34), VAXZEVRIA (n=1), J&J (n=1), and "unknown"(n=11).

- A COVID-19 AE was reported in 22% (16/74) of subjects participating in the LTE period
  - The infection rate was 33% in unvaccinated (n=27) / partially-vaccinated (n=3) subjects (n=10/30) **Figure 4.**
  - The infection rate was 14% in fully-vaccinated (≥14 days beyond second serial dose) subjects (n= 6/44) **Figure 4.**
    - Of fully-vaccinated subjects, 1 case occurred ~11 months post-primary-vaccination cycle; a second case occurred 14 months post-primary-vaccination cycle. **Table 1.**
  - COVID-19 event severity was mild (n= 13), moderate (n=2), or severe (n=1).
  - All cases resolved, except one prolonged severe AE complicated by comorbidities; the subject discontinued rilonacept treatment and completed the study one month later.

- Of the 16 LTE subjects with a COVID-19 diagnosis:
  - 12 subjects were receiving rilonacept at the time
    - 10 continued rilonacept; 1 interrupted rilonacept for ~4 weeks; 1 permanently discontinued rilonacept.
    - None experienced a pericarditis recurrence during/after the COVID-19 adverse event.
  - 2 subjects had previously interrupted rilonacept for off-treatment observation.
    - One pericarditis recurrence occurred in the peri-COVID-19 period (18 days after infection), but the patient had discontinued rilonacept > 4.5 months prior.
    - No pericarditis recurrence occurred in the other subject (>6 months).
  - 2 COVID-19 cases occurred after the end-of-rilonacept-treatment visit but during the 4-week safety follow-up period (prior to end-of-study visit).
    - Neither subject experienced a pericarditis recurrence during/after the COVID-19 adverse event.

FIGURE 4. COVID-19 STATUS OF SUBJECTS ENROLLED IN RHAPSODY LTE (n = 74)

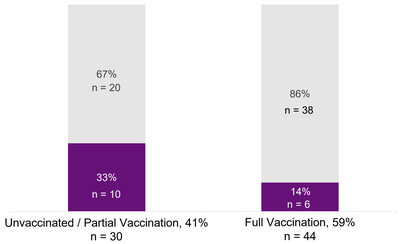


TABLE 1. SUBJECTS WHO HAD RECEIVED FULL-COURSE SARS-COV-2 VACCINATION AND DEVELOPED COVID-19

COVID-19 AE Case	Time Between Last Booster Inoculation & COVID-19 AE (months)	Severity of Disease
Subject #1	2.5	Mild
Subject #2	3.5	Mild
Subject #3	5	Moderate
Subject #4	6	Mild
Subject #5	11	Mild
Subject #6 [§]	14	Mild

AE = Adverse Event

[§] COVID-19 AE was reported during the safety follow-up period, one month after the subject had stopped rilonacept treatment

CONCLUSIONS

In patients on rilonacept in this study, although numbers are small:

- SARS-CoV-2 Vaccination:
  - Treatment with rilonacept did not appear to interfere with the protective effect of SARS-CoV-2 vaccination.
  - Subjects who were vaccinated experienced fewer cases of COVID-19 compared to subjects who were unvaccinated or incompletely vaccinated.
- COVID-19 Cases:
  - Adverse events related to SARS-CoV-2 infection were uncommon in this study population.
  - Rilonacept treatment was safely continued in patients with COVID-19.
- Pericarditis Recurrences:
  - No pericarditis recurrences occurred during rilonacept treatment – regardless of COVID-19 events or vaccination.
  - One pericarditis recurrence occurred in the peri-COVID-19 period (18 days after infection), but the patient had discontinued rilonacept > 4.5 months prior.

LIMITATIONS

- The present report is an observational post-hoc assessment of adverse events reported during the Long-term Extension of RHAPSODY.
- Sample size was limited (44 subjects were fully vaccinated, and 30 subjects were not fully vaccinated: 3 were partially vaccinated and 27 were unvaccinated).

CLINICAL IMPLICATIONS [‡]

- Patients with RP should receive SARS-CoV-2 vaccination to reduce the risk of COVID-19.
  - Vaccination was well tolerated, and rilonacept does not appear to interfere with vaccine efficacy.
- In order to reduce the risk of pericarditis recurrence, patients receiving rilonacept who develop COVID-19 should not interrupt rilonacept treatment.
  - Continued rilonacept treatment reduces risk of pericarditis recurrence.

[‡]Based on the assessment of data by the clinical authors

DISCLOSURES

- Antonio Brucato reports institutional funding from Kiniksa Pharmaceuticals as an investigative site; an unrestricted research grant from Sobi and Acarpia and travel and accommodation for advisory committee from Sobi and Kiniksa
- Lucia Trotta reports no disclosures
- Michael Arad reports no disclosures
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- Eliyazar Gaddam reports no disclosures
- Antonella Insalaco reports advisory board from Sobi Pharmaceuticals outside the current work
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- Martin LeWinter reports grants and advisory board, consulting, and other fees from Kiniksa Pharmaceuticals outside the submitted work and consulting fees from Sobi Pharmaceuticals outside the current work
- David Lin reports no disclosures
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- Yishay Wasserstrum reports no disclosures
- Allan Klein reports grants and other from Kiniksa Pharmaceuticals during the conduct of the study and other fees from Cardiol Therapeutics, Sobi and Pfizer outside of the current work
- Massimo Imazio reports other fees from Kiniksa Pharmaceuticals and Sobi outside the submitted work
- JoAnn Clair is employed by Kiniksa Pharmaceuticals, Corp.
- * Manoj Samant was an employee of Kiniksa at the time of the study
- Sheldon Wang is employed by Kiniksa Pharmaceuticals Corp.
- John F. Paolini is employed by Kiniksa Pharmaceuticals Corp. and is an inventor on patents and pending patent applications licensed to Kiniksa Pharmaceuticals covering methods of using rilonacept for treating recurrent pericarditis

- This study was sponsored by Kiniksa Pharmaceuticals (UK), Ltd.

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