Novel Clinical Trials in Recurrent Pericarditis: Studies Assessing Efficacy and Safety of the Investigational IL-1 Receptor Antagonist KPL-387 in Recurrent Pericarditis

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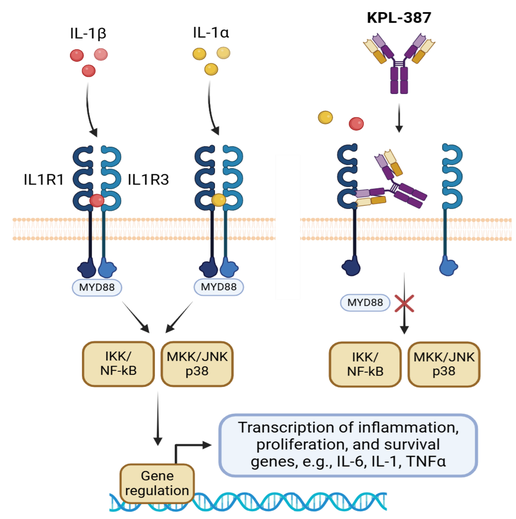
The KPL-387 development program will evaluate the efficacy and safety of KPL-387 across the spectrum of clinical presentations of pericarditis.

BACKGROUND

Recurrent Pericarditis

- Recurrent pericarditis (RP) predominantly shows features consistent with an IL-1-mediated autoinflammatory disease that may require prolonged treatment (median of 3.8 yrs) to mitigate adverse impacts on quality of life[1-3]
- Data implicating IL-1α and IL-1β in RP pathophysiology informed a novel approach to disease control, decreasing prolonged corticosteroid use[4-6]
- In AIRTRIP, anakinra (± colchicine) significantly reduced recurrence risk versus placebo in idiopathic RP patients flaring despite glucocorticoids[7]
  - ~45% of patients on anakinra during the Randomized-Withdrawal Period also received concomitant colchicine, as monotherapy was not obligatory
- In RHAPSODY, once-weekly rilonacept was effective not only as a third-line therapy (after glucocorticoids) but also as a second-line therapy (instead of glucocorticoids) in treatment of RP and as a monotherapy in reducing recurrence risk[4]
- Physicians in the US are recognizing the paradigm shift in RP treatment, increasingly utilizing these IL-1 pathway inhibitors earlier in the disease as a steroid-sparing therapy[8-9]
- KPL-387 is an investigational fully human IgG2 monoclonal antibody that binds interleukin-1 receptor, inhibiting IL-1α and IL-1β signaling (**Figure 1**).

Figure 1. KPL-387 Mechanism of Action

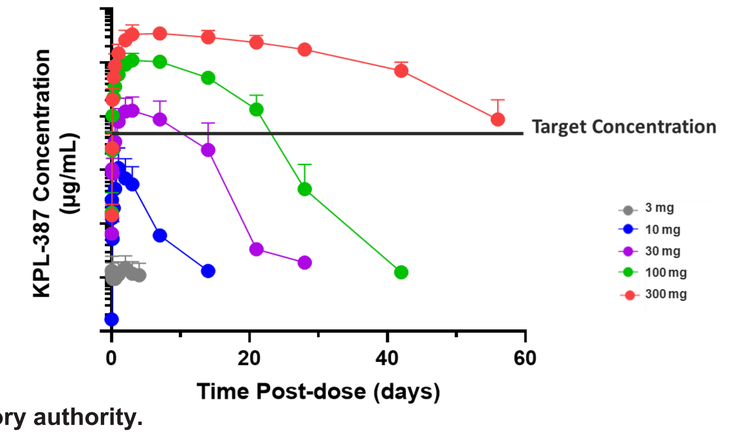


IgG2, immunoglobulin G2; IKK, IkappaB kinase; IL-1R1, interleukin-1 receptor 1; IL-1R3, interleukin-1 receptor 3; IL-6, interleukin 6; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; JNK, jun N-terminal kinase; MYD88, myeloid differentiation primary response 88; MKK, mitogen-activated protein kinase; NF-KB, nuclear factor-kappa B; p38, p38 mitogen-activated protein kinase; TNFα, tumor necrosis factor-alpha.

KPL-387 Phase 1 Data

- In Phase 1 (n=112; placebo-controlled): the safety, tolerability, PK, PD, and immunogenicity of KPL-387 administered as single ascending doses (subcutaneous or intravenous) and as multiple ascending doses (subcutaneous) were evaluated.
  - The single-dose PK of KPL-387 300mg SC demonstrated sustained serum concentrations above the target concentration, supporting a once-monthly SC dosing paradigm (**Figure 2**)

Figure 2. Topline Phase 1 SAD (SC) Pharmacokinetics



KPL-387 is an investigational product; the efficacy and safety have not been evaluated by any regulatory authority.

METHODS

KPL-387 Clinical Development Program: A comprehensive suite of studies

- The Phase 2/3 (Phase 2 Dose-Focusing / Phase 3 Pivotal) Study, the Phase 2 Transition to KPL-387 Monotherapy Dosing and Administration Study, and several Long-Term Extensions (LTE).

KPL-387 Phase 2/3 Recurrent Pericarditis Clinical Trial (NCT07010159)

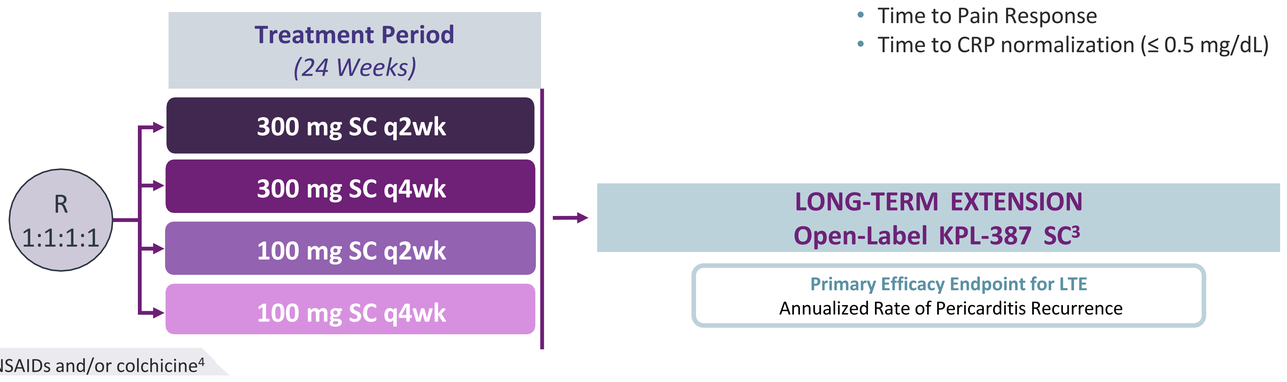
(International Co-principal Investigators: Prof. Antonio Brucato, MD & Dr. Allan Klein, MD)

Phase 2 Dose-Focusing

Population: Up to ~80 patients diagnosed with RP presenting at screening with a qualifying pericarditis episode[1] despite treatment with conventional oral therapies[4]

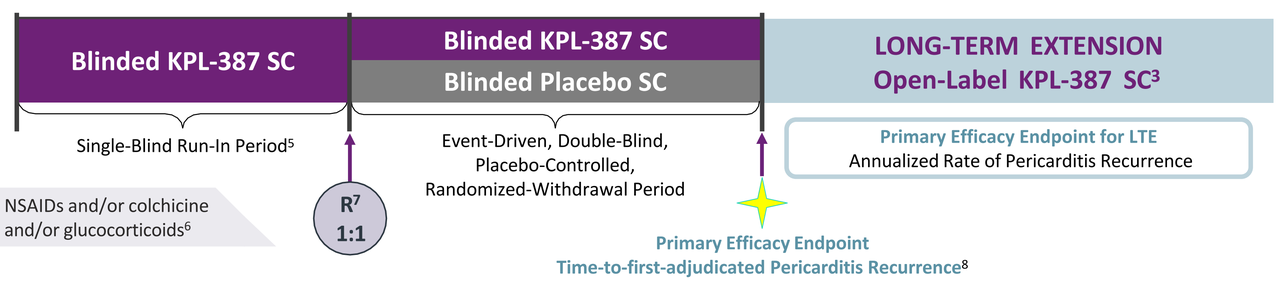
Primary Efficacy Endpoint
- Time to Treatment Response[2]

Key Secondary Endpoints
- Time to Pain Response
- Time to CRP normalization (≤ 0.5 mg/dL)



Phase 3 Pivotal

Population: Up to ~85 patients diagnosed with RP presenting at screening with a qualifying pericarditis episode[1] despite treatment with conventional oral therapies[6]



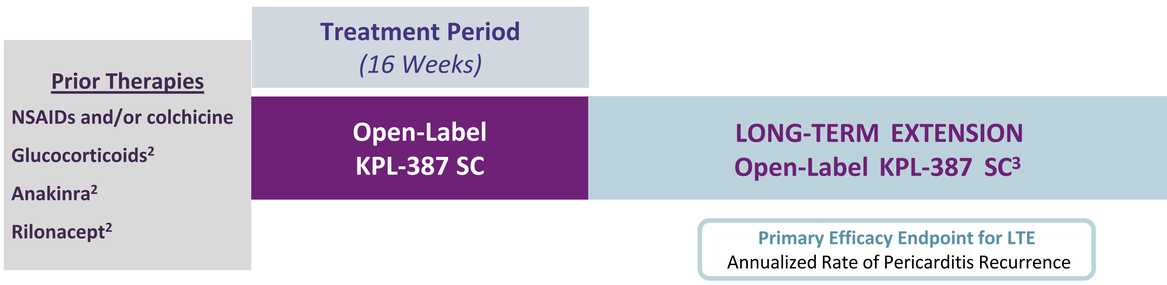
CRP, C-reactive protein; LTE, Long-Term Extension; NRS, numerical rating scale (for chest pain); NSAID, non-steroidal anti-inflammatory drug; q2wk, every two weeks; q4wk, every four weeks; R, randomization; RP, recurrent pericarditis; RW, Randomized Withdrawal; SC, subcutaneous.
[1]At least 1 day with NRS ≥4 and CRP ≥1 mg/dL.
[2]Defined as Pain Response (NRS score ≤ 2 on the 11-point daily pericarditis pain NRS) and at least one CRP level ≤ 0.5 mg/dL within 7 days before or after the Pain Response.
[3]Up to 24 months or the time KPL-387 is approved for commercial use in that region to treat pericarditis.
[4]KPL-387 will be added to conventional oral pericarditis medications (NSAIDs and/or colchicine) from baseline to Week 1; oral medications will be weaned off to achieve KPL-387 monotherapy by Week 2. Participants previously treated with glucocorticoids must have discontinued their use at least 72 hours prior to first study drug administration.
[5]Duration of the run-in period undisclosed in order to maintain study subjects blinded to the start of the randomized-withdrawal period.
[6]KPL-387 will be added to conventional oral pericarditis medications (NSAIDs and/or colchicine and/or corticosteroids, in any combination) from baseline; oral medications will then be weaned.
[7]Patients with Clinical Response (NRS ≤2 and CRP ≤ 0.5 mg/dL, while on KPL-387 monotherapy) will be randomized (1:1) into the RW Period and receive continued blinded KPL-387 or placebo.
[8]Defined as the time from randomization in the RW Period to the date of the first Pericarditis Recurrence for each participant. Only CEC-confirmed Pericarditis Recurrences will be considered as events for the primary efficacy analysis in the pivotal portion.

Phase 2 Transition to KPL-387 Monotherapy Dosing & Administration Study

(International Co-principal Investigators: Prof. George Lazaros, MD & Dr. Dor Lotan, MD)

Population: Up to ~80 participants with well-controlled RP[1] receiving standard therapies: NSAIDs and/or colchicine, glucocorticoids, and/or IL-1 pathway inhibition (anakinra or rilonacept)[2]

Study Objective: To evaluate the efficacy/safety of dosing regimens used to transition patients with well-controlled RP to KPL-387 monotherapy from stable prior treatment with standard therapies



CRP, C-reactive protein; LTE, Long-Term Extension; NRS, numerical rating scale (for chest pain); NSAID, non-steroidal anti-inflammatory drug; RP, recurrent pericarditis; SC, subcutaneous.
[1]No recurrence within 3 months prior to baseline; CRP < 0.5 mg/dL within 14 days of Baseline and NRS ≤ 3 at Baseline; no clinical worsening or suspicion of impending recurrence.
[2]Glucocorticoids or IL-1 pathway inhibitors may be used alone or in combination with NSAIDs and/or colchicine.
[3]Up to 24 months or the time KPL-387 is approved for commercial use in that region to treat recurrent pericarditis.

SUMMARY

- The KPL-387 development program will evaluate the efficacy and safety of KPL-387 across the spectrum of clinical presentations of pericarditis.
  - Primary data for demonstrating the efficacy and safety of KPL-387 in the treatment of RP and reduction in risk of recurrence will be based on the Pivotal Phase 3 (Double-Blind, Placebo-Controlled, Randomized-Withdrawal) portion of the Phase 2/3 clinical trial.
  - The Transition to KPL-387 Monotherapy Dosing & Administration Study will provide supplemental information on the efficacy and safety of dosing regimens used to transition patients from standard therapies to KPL-387 monotherapy.
  - The LTEs will evaluate the long-term efficacy and safety of KPL-387 during up to 24 months of additional open-label KPL-387 or until commercial approval of KPL-387 in that region for pericarditis.
- KPL-387 could be an important advancement in the treatment options available to patients with RP, potentially enabling once-monthly dosing with a single self-injection in a liquid formulation as an autoinjector, throughout the duration of the disease.

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DISCLOSURES

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