Dose-dependent Suppression of T Cell-Dependent Antibody Response in Healthy Volunteers by KPL-404, an Anti-CD40 Monoclonal Antibody, Supports Phase 2 Study in Patients with Rheumatoid Arthritis

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*Denotes those who were employed at Kiniksa when the work was conducted.

BACKGROUND

- **CD40 – CD154 (CD40L) Costimulatory Interaction**
  - **Essential mediator of primary and secondary humoral immune responses to T-cell dependent antigens.**
  - **Actively targeted for treatment of autoimmune diseases in which abnormal B- and T-cell activation plays a role in pathogenesis.**
  - **Blockade ablates primary and secondary T-cell dependent antibody response (TDAR).**
  - **Several CD40-CD154-targeting agents are under clinical investigation in other diseases:**
    - Sjogren's syndrome (SS)[1]
    - Rheumatoid arthritis (RA)[2]
    - Grave's disease[3]
    - Lupus nephritis[4]
    - Liver and renal transplant[5]
    - Systemic lupus erythematosus[6]
- **An unmet need remains in patients with failure and/or inadequate response (IR) to biological disease-modifying antirheumatic drugs (bDMARD-IR) and/or Janus kinase inhibitors (JAKi-IR).**
  - The CD40 - CD154 costimulatory interaction is linked to inflammation and joint destruction in RA via production of autoantibodies and inflammatory mediators.
  - KPL-404 is a humanized IgG4 antibody engineered to bind CD40 without triggering Fc effector functions.
- **In a first-in-human Phase 1 single ascending dose study, 52 healthy volunteers received single doses of KPL-404 administered either subcutaneously (SC) or intravenously (IV) with no dose-limiting safety findings, infectious episodes, or toxicities.**
  - Pharmacodynamic assessments suggested full target engagement and dose-dependent suppression of TDAR for primary and secondary KLH challenge were achieved at pharmacologically relevant concentrations (Figure 1).

METHODS

- A PK model was used to simulate multiple dosing scenarios, including: 2.5, 5, and 10 mg/kg SC qwk, q2wk, and q4wk, as well as 10 mg/kg IV q4wk.
- The model was used to identify optimal Phase 2 dosing schedules by generating 1000 virtual subjects using the typical parameter estimates with between-subject variability included.

PRIOR KPL-404 PHASE 1 (SINGLE ASCENDING DOSE) DATA

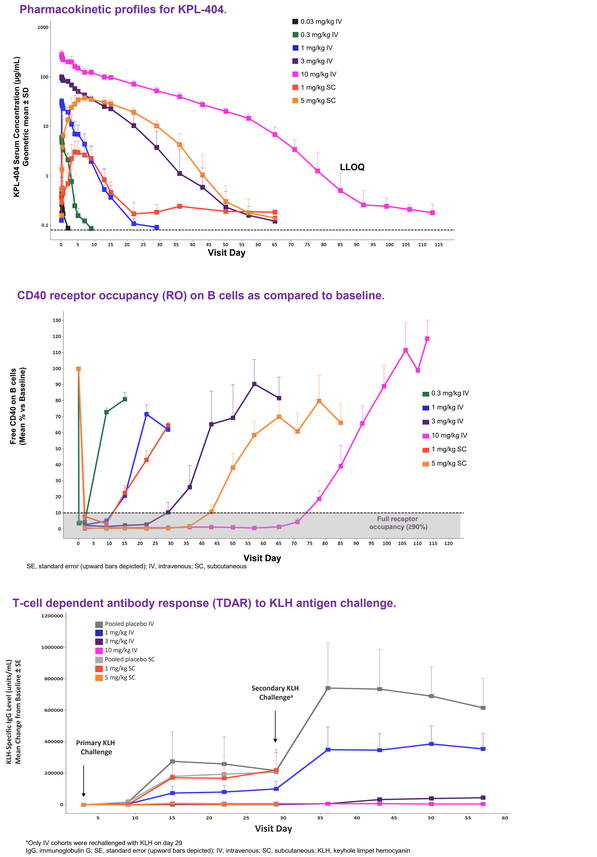


FIGURE 1. RESULTS FROM KPL-404 PHASE 1: SAFETY, TOLERABILITY, PK, RO, AND TDAR SUPPRESSION

DISCLOSURES

This study was sponsored by Kiniksa Pharmaceuticals.

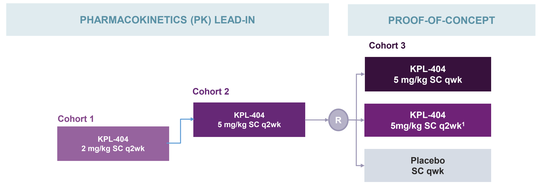
REFERENCES

1. 1. Fisher 2020, Lancet Rheumatol. 2. Karnell 2019, Sci Transl Med. 3. Kahaly et al, 2020, J Clin Endocrinol Metab 4. Jayne, 2021, Annals of the Rheumatic Diseases [abstract] 5. Espie et al, 2020, Am J Transplant 6. Furie et al, 2021, Rheumatology

RESULTS

- **Following SC administration, all subjects were predicted to achieve complete ADA suppression for the full dosing interval at/above 2.5 mg/kg SC q2wk.**
- **At 2 mg/kg SC q2wk (starting dose level), simulated steady-state 8-week data predicted PK in a sub-therapeutic range for most subjects and an approximately 31- and 18-fold safety margin relative to preclinical NOAEL dose.**
- **At 5 mg/kg SC q2wk, 100% of patients were predicted to be in a therapeutic range, indicating a potential practical efficacious dose level.**
- **At 5 mg/kg SC qwk, 100% of patients were predicted to be in the supratherapeutic range.**
- **These results support a Multiple Ascending Dose (MAD) Phase 2 study design, with PK lead-in comprised of 2 Cohorts at 2 and 5 mg/kg SC q2wk (each randomized 6:2) and a Proof-of-Concept phase (Cohort 3) comprised of up to 75 subjects randomized 1:1:1 to 5 mg/kg qwk, 5 mg/kg q2wk, and placebo SC.**
- **The ongoing study will evaluate efficacy (Disease Activity of 28 joints using C-reactive protein [DAS28-CRP]), safety, PK, and pharmacodynamics (PD) of escalating doses levels of KPL-404 compared with placebo in patients with moderate to severe RA (bDMARD-IR or JAKi-IR).**
- **The study also allows the flexibility of optional cohorts including additional dosing regimens and/or subpopulations identified based on clinical response and biomarkers.**

FIGURE 2. STUDY DESIGN OF THE PHASE 2 TRIAL OF KPL-404 IN RHEUMATOID ARTHRITIS



PATIENT POPULATION:
- Active RA who have an inadequate response to or are intolerant to a Janus kinase inhibitor (JAKi) or at least one biologic disease-modifying anti-rheumatic drug (bDMARD). Subjects who have failed both bDMARD and JAKi are excluded from the study.

DISEASE CRITERIA:
- Six or more swollen joints and ≥ 6 tender joints at screening and baseline line visits; levels of high sensitivity C-reactive protein ≥ 5 mg/L; seropositivity for serum RF and/or ACPA at screening.

COHORTS 1-2 (PK Lead-In)
- Each cohort will each sequentially randomize 8 patients
- Primary Endpoints:
  - Incidence of treatment-emergent adverse events (TEAEs)
  - Pharmacokinetics (C_{max}, $AUC_{(0-t)}$)
- Secondary Endpoint:
  - Change from baseline in DAS28-CRP at Week 12

COHORT 3 (Proof of Concept)
- Cohort 3 will randomize up to 75 patients
- Primary Endpoint:
  - Change from baseline in DAS28-CRP at Week 12
- Secondary Endpoints :
  - Incidence of treatment-emergent adverse events (TEAEs)
  - Pharmacokinetics (C_{max}, $AUC_{(0-t)}$)

Objectives: Evaluate safety, efficacy, and PD compared with placebo across the estimated therapeutic range and to characterize PK across varying dose levels of KPL-404

1) The 5 mg/kg SC q2wk group will receive weekly administrations of alternating active investigational product and matching blinded placebo
SC = subcutaneous; q2wk = every other week; AUC = Area Under the Curve; RF = Rheumatoid Factor; ACPA = anti-citrullinated protein antibodies, PD = Pharmacodynamics; PK = Pharmacokinetics; R = Randomization; SRC = Safety Review Committee