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KPL-404 Single-Ascending-Dose Phase 1 Data

May 2021

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KPL-404

Monoclonal antibody inhibitor interaction between CD40 and CD40L

Disease Area: External proof-of-concept previously established in broad range of autoimmune diseases: Sjogren's disease, systemic lupus, rheumatoid arthritis, solid organ transplant and Graves' disease[1]

Scientific Rationale[2,3]: Attractive target for blocking T-cell dependent, B-cell–mediated autoimmunity

Status: Phase 1 single-ascending-dose study in healthy volunteers completed and supports further development in patients with optionality for testing SC and/or IV dosing; Expect to initiate Phase 2 proof-of concept trial in patients in 2H 2021

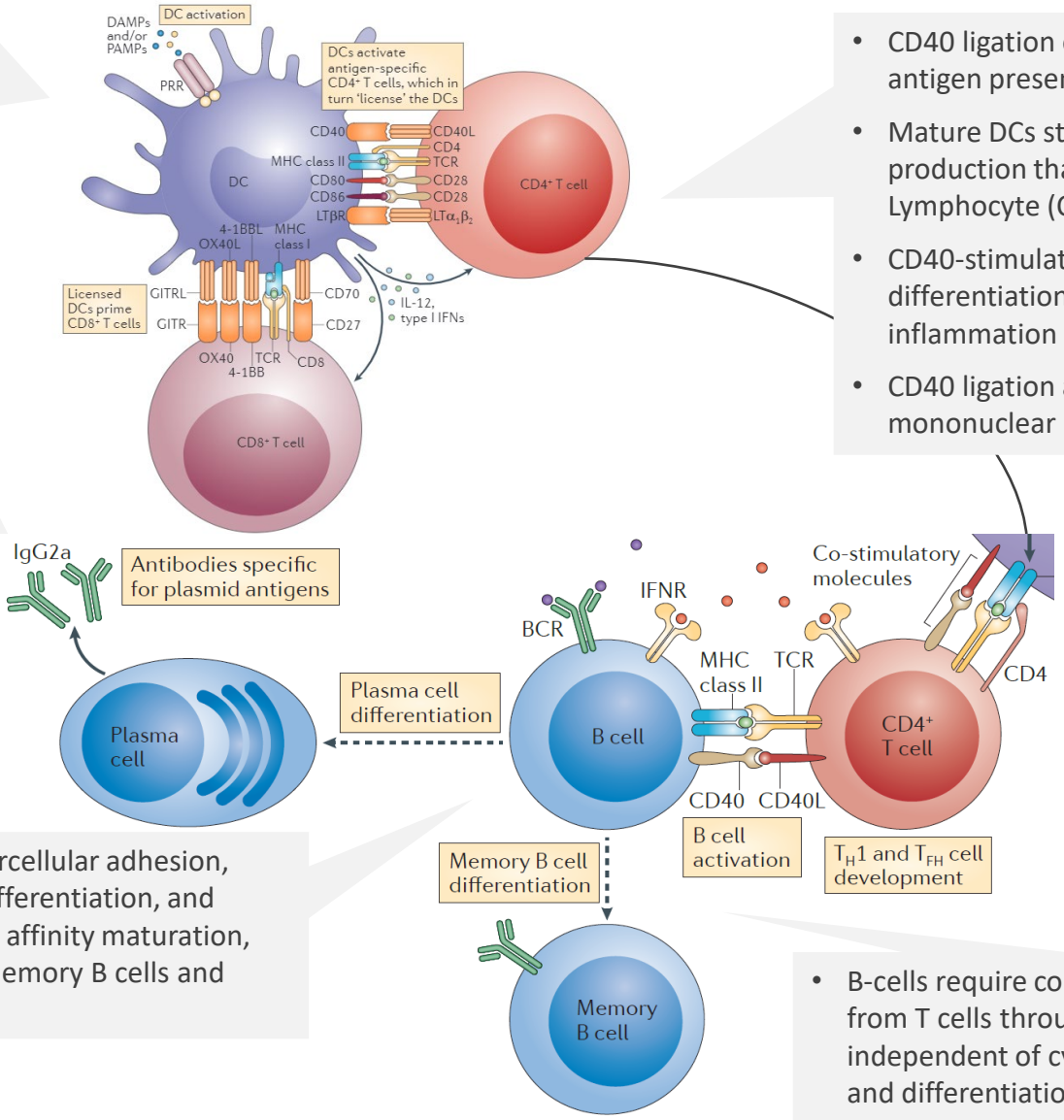
Economics: Clinical and regulatory milestones and royalty on annual net sales

Rights: Worldwide

1) Poster presentation at the Keystone Symposia: Antibodies as Drugs: New Horizons in the Therapeutic Use of Engineered Antibodies: KPL-404, a CD40 antagonist, blocked antigen-specific antibody responses in an in vivo NHP model and demonstrated strong PK/PD correlation; 2) Elgueta, et al. Immunol Rev 2009, 229 (1), 152-172; 3) Peters, et al. Semin Immunol 2009, 21 (5) 293-300; CD40L = CD40 ligand; RO = receptor occupancy; TDAR = T-cell Dependent Antibody Response

CD40/CD40L is an Essential Immune Pathway for T-Cell Priming and T-Cell Dependent B-Cell Responses

- CD40 is expressed on the surface of dendritic cells, B-cells, antigen-presenting cells and non-immune cell types
- Its ligand, CD40L (CD154), is expressed by activated T-cells, platelets, and other cell types



- CD40 ligation on DCs induces cell maturation by promoting antigen presentation and enhancing their costimulatory activity
- Mature DCs stimulate activated T-cells to increase IL-2 production that facilitates T-helper cells (Th) and cytolytic T-Lymphocyte (CTL) expansion
- CD40-stimulated DCs also secrete cytokines favoring Th1 cell differentiation and promoting Th cell migration to sites of inflammation
- CD40 ligation also provides a pro-inflammatory signal within the mononuclear phagocyte system

- Humoral immunity is dependent on a thriving B cell population and activation by Th cells; blockade of CD40/CD40L interaction has been shown to completely ablate primary and secondary TDAR response

- CD40 engagement triggers B-cell intercellular adhesion, sustained proliferation, expansion, differentiation, and antibody isotype switching leading to affinity maturation, which is essential for generation of memory B cells and long-lived plasma cells

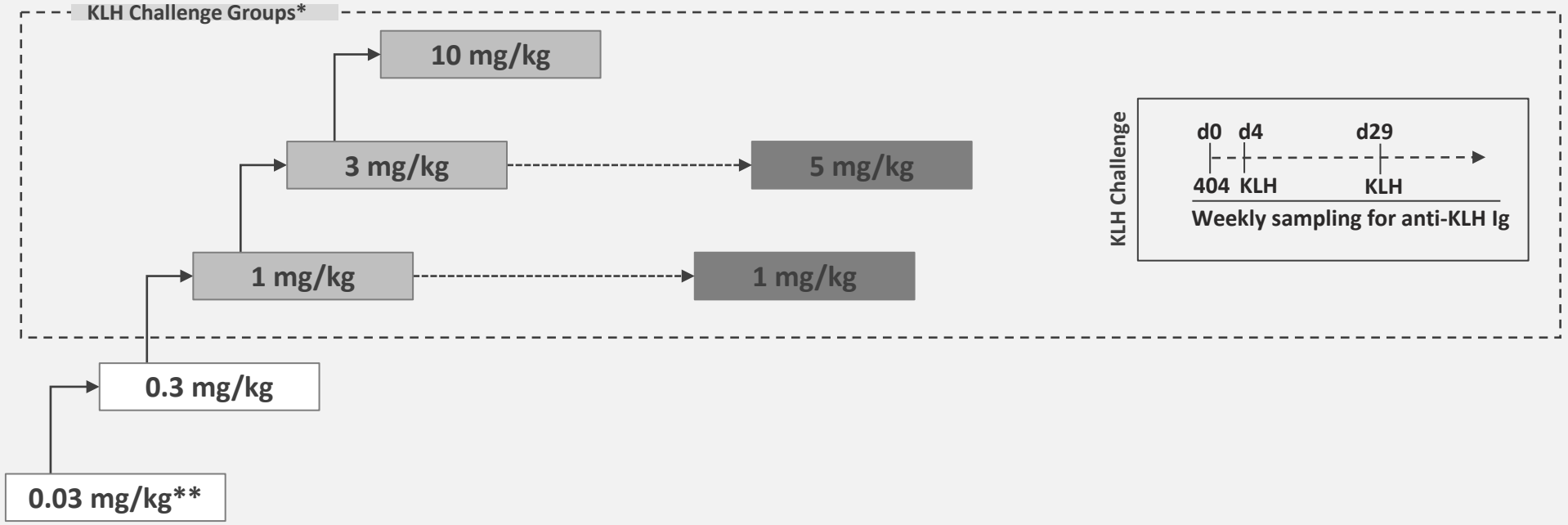
- B-cells require contact-dependent stimulus from T cells through CD40/CD40L interaction independent of cytokines to trigger growth and differentiation

Sources: Elgueta et al., Immunol Rev, 2009; Peters et al., Semin Immunol, 2009; Kambayashi et al., Nature Reviews: Immunology, 14, 2014; Desmet et al., Nature Reviews: Immunology, 12, 2012

KPL-404 Single-Ascending-Dose Phase 1 Study

First-in-human study to provide safety data and pharmacokinetics as well as receptor occupancy and TDAR

Part A (Single IV dose) | Part B (Single SC Dose)



- **Primary endpoints:** Safety and Tolerability
- **Secondary endpoints:** PK and ADA / CD40 RO in blood / Serum anti-KLH Ig levels
- **Exploratory endpoints:** Serum CXCL13 levels

Notes: Unless otherwise noted dose groups included 6 active/2 placebo subjects; *1° KLH challenge for all SAD dose groups except 0.03 and 0.3 mg/kg, 2° KLH re-challenge only in 1, 3, and 10 mg/kg IV; ** Cohort included 2 active and 2 placebo subjects

SAD = single-ascending-dose; TDAR = T-cell dependent antibody response; KLH = keyhole limpet hemocyanin; RO = receptor occupancy; ADA = anti-drug antibodies

Final Data from KPL-404 Single-Ascending-Dose Phase 1 Study

The randomized, double-blind, placebo-controlled first-in-human (FIH) study is designed to investigate the safety, tolerability, PK and PD properties of single-ascending intravenous (IV) and subcutaneous (SC) doses of KPL-404 in healthy subjects.

- 2 single-ascending-dose arms (SAD):
  - Single-dose KPL-404 0.03 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg or 10 mg/kg IV and
  - Single-dose KPL-404 1 mg/kg or 5 mg/kg SC

Primary Endpoint: Safety and tolerability of single ascending intravenous (IV) and subcutaneous (SC) doses of KPL-404 in healthy subjects.

- KLH challenge in 1 mg/kg, 3 mg/kg, and 10 mg/kg IV and 1 mg/kg and 5 mg/kg SC cohort

Secondary Endpoints: Pharmacokinetics and anti-drug antibody response following single IV and SC doses of KPL-404 in healthy subjects, serum anti- keyhole limpet hemocyanin (KLH) IgG levels

Exploratory Endpoint: Receptor occupancy of KPL-404 on CD40 in healthy subjects

Preliminary Data:

- All dose escalations occurred as per protocol with no dose limiting safety findings. All 6 subjects dosed with KPL-404 3 mg/kg IV showed full receptor occupancy through Day 29, which corresponded with complete suppression of the T-cell Dependent Antibody Response (TDAR) to KLH through Day 29. Consistent dose relatedness was shown in the lower dose level cohorts, including 0.03 mg/kg, 0.3 mg/kg, 1 mg/kg IV and 1 mg/kg SC. Data collection for the higher dose level cohorts, 10 mg/kg IV and 5 mg/kg SC, is ongoing.
- The data to-date support subsequent study in patients, including potential IV or SC monthly administration. Kiniksa expects final data and safety follow-up from all cohorts in the first half of 2021.

Final Data:

- KPL-404 showed dose-dependent increases in concentration across cohorts. All dose escalations occurred as per protocol with no dose-limiting safety findings.
- KPL-404 was well-tolerated, and there were no serious adverse events.
- Subjects dosed with KPL-404 10 mg/kg IV showed full RO through at least Day 71 and complete suppression of TDAR after KLH challenge and re-challenge through at least Day 57.
- Subjects dosed with KPL-404 5 mg/kg SC showed full RO through Day 43 and suppression of TDAR after KLH challenge through at least Day 29. These data confirm and extend previously-reported 3 mg/kg IV cohort data, in which RO and suppression of TDAR after KLH challenge were demonstrated through Day 29.
- The 3 mg/kg IV dose level had previously demonstrated complete suppression of memory TDAR response to a re-challenge on Day 29.
- Anti-drug antibodies to KPL-404 were suppressed for at least 57 days at 10 mg/kg IV; the suppression of antibody responses to the drug itself is an independent indicator of target engagement and pharmacodynamic effect.

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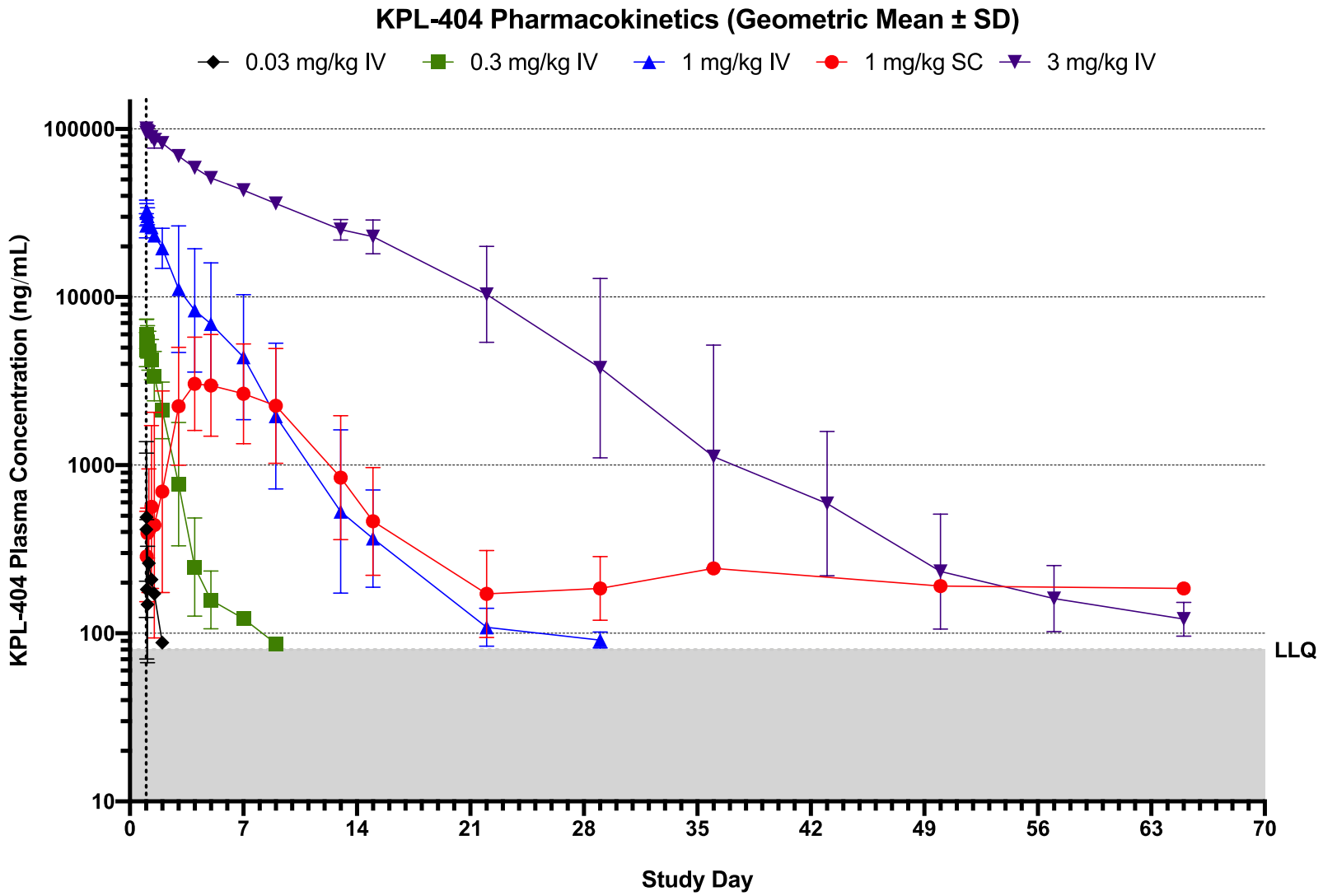
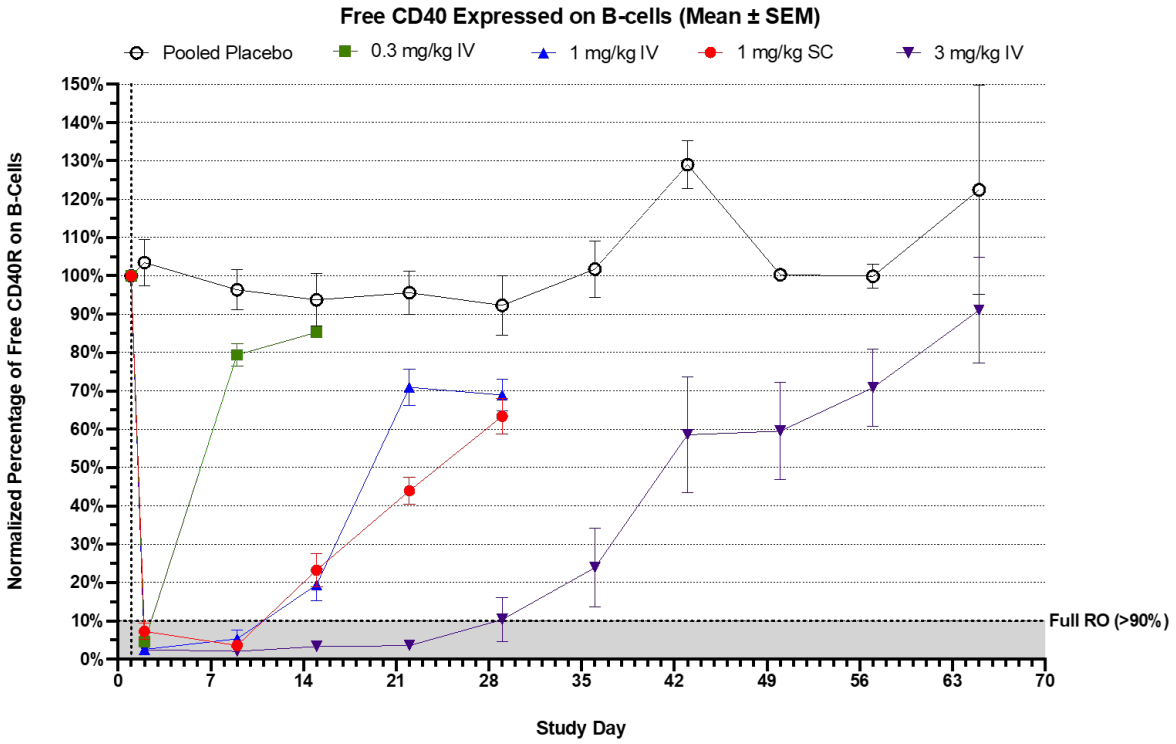
Preliminary Data from KPL-404 Single-Ascending-Dose Phase 1 Study

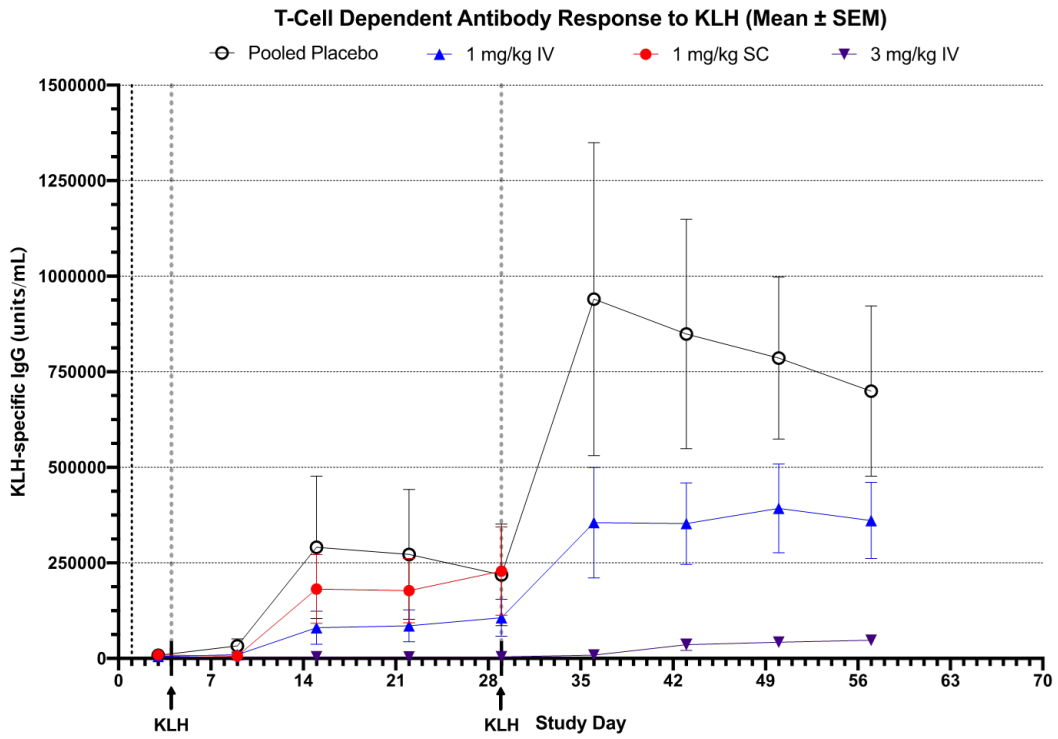
Pharmacokinetic summary



Preliminary Data from KPL-404 Single-Ascending-Dose Phase 1 Study

Receptor occupancy and KLH antigen challenge TDAR summary

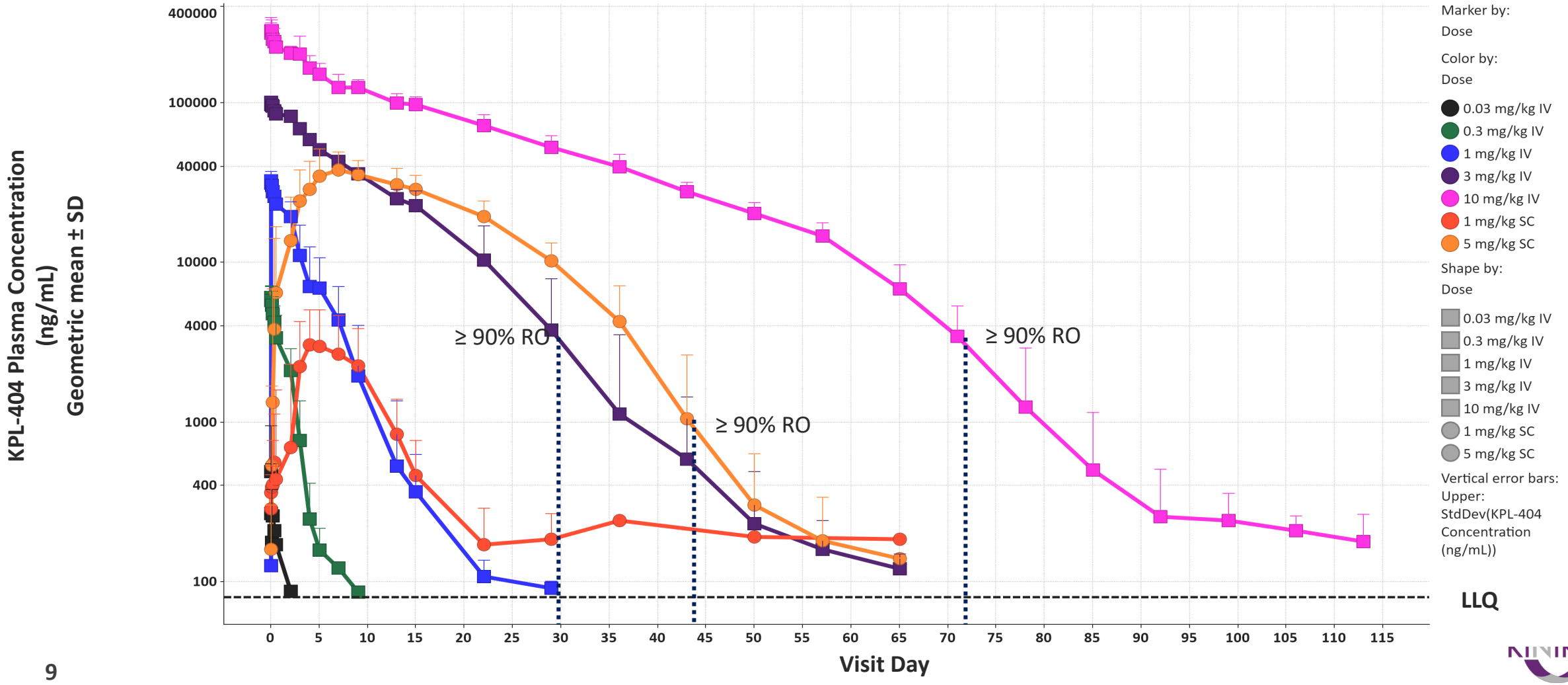




1) Free CD40R = inverse of receptor occupancy; KLH = keyhole limpet hemocyanin; TDAR = T-cell dependent antibody response

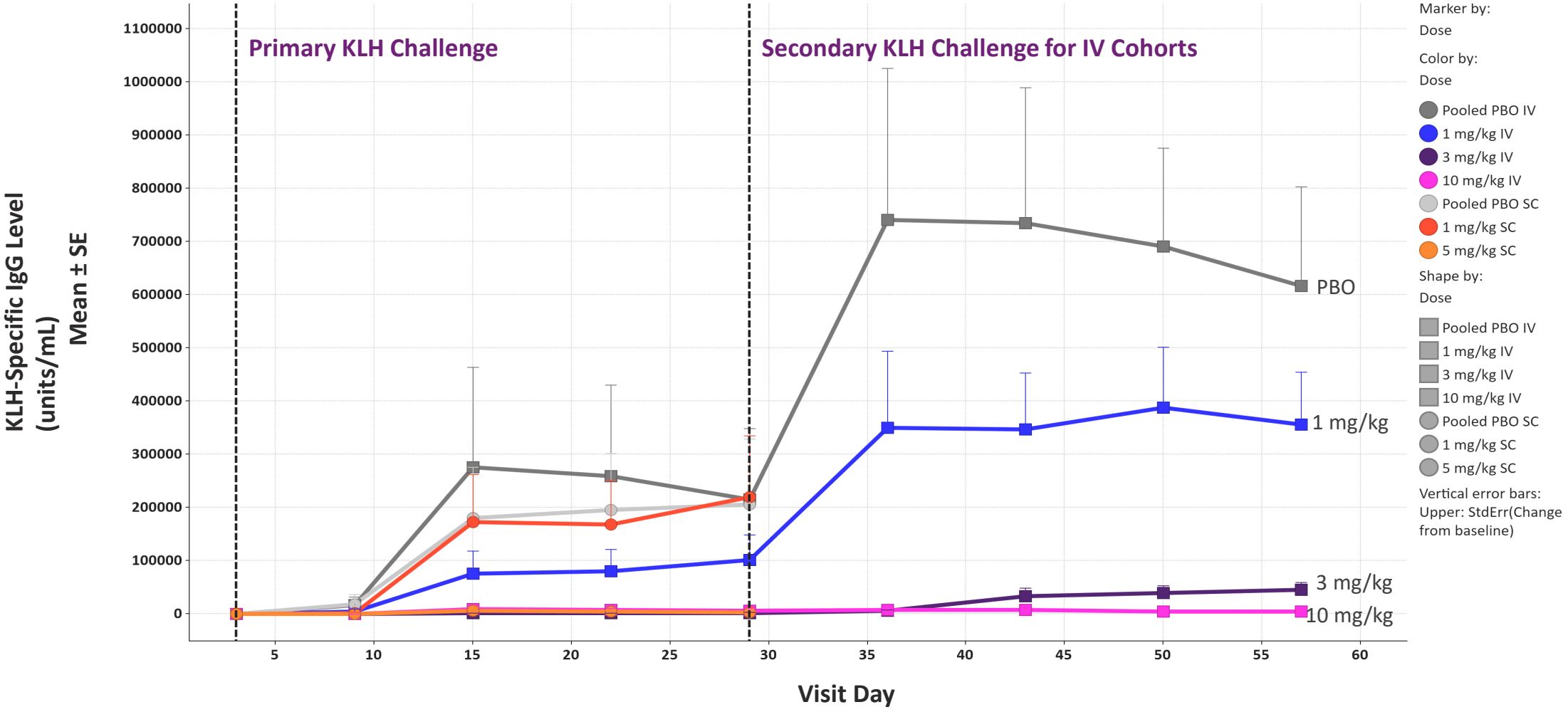
Final Data from KPL-404 Single-Ascending-Dose Phase 1 Study

Pharmacokinetic profiles for KPL-404



Final Data from KPL-404 Single-Ascending-Dose Phase 1 Study

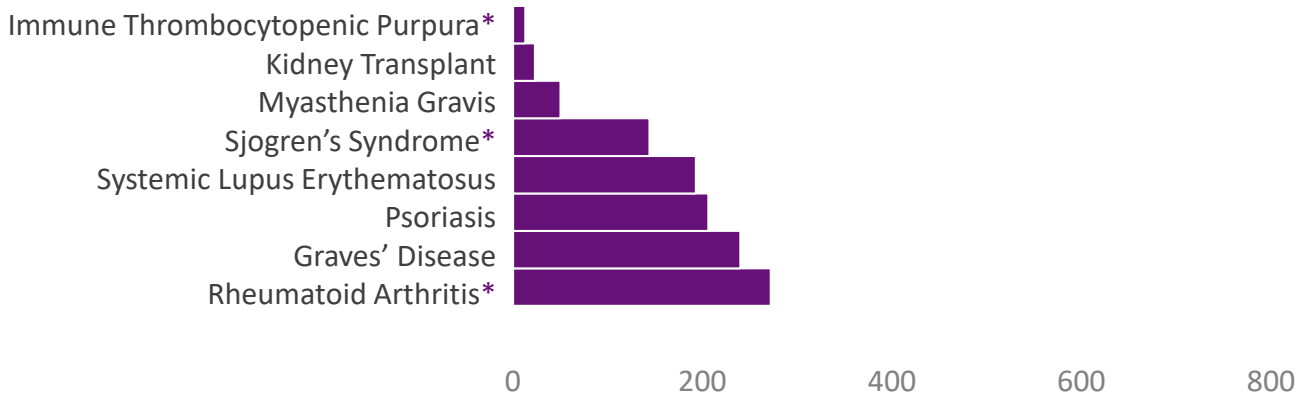
T-Cell Dependent Antibody Response (TDAR) for KLH antigen challenge



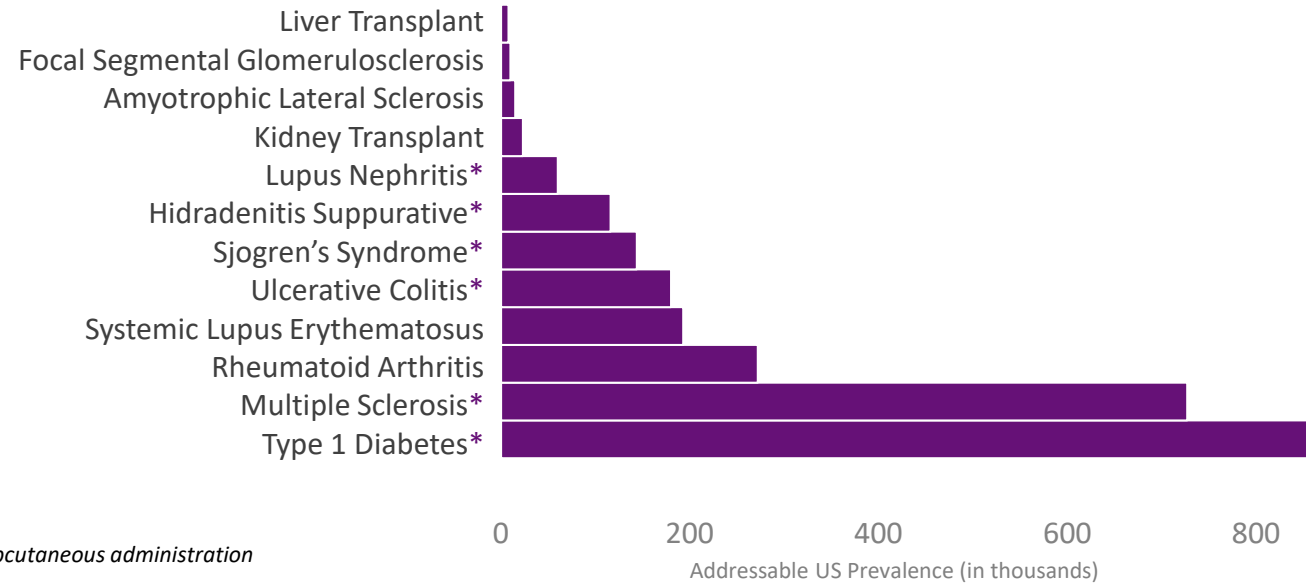
KLH = keyhole limpet hemocyanin

Potential for Evaluation of KPL-404 in a Broad Range of Autoimmune Diseases

Indications with Published Data[1]



Indications with Pending Data & Trials Ongoing[1]



Indication Selection Criteria

- **Robust Data or proof-of-concept supporting mechanism**
- **Differentiation vs. Competitors**
- **Commercial Attractiveness**

**Indications evaluated with subcutaneous administration*

1) With the CD40 mechanism

Sources: 2019 numbers: https://unos.org/data/transplant-trends/; Hunter et al. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014; Rheumatol Int. 2017 Sep;37(9):1551-1557; Overall Prevalence: Maciel et al, Arthritis Care Res (Hoboken) 2017; Qin et al, Ann Rheum Dis 2015; UpToDate; Baldini et al. Prevalence of Severe Extra-Glandular Manifestations in a Large Cohort of Patients with Primary Sjögren's Syndrome; 2012 ACR/ARHP Annual Meeting, ABSTRACT NUMBER: 2185; Wallin et al. The prevalence of MS in the United States A population-based estimate using health claims data, Neurology, March 5, 2019; Somers et al.; Prevalence of Systemic Lupus Erythematosus in the United States: Preliminary Estimates from a Meta-Analysis of the Centers for Disease Control and Prevention Lupus Registries; 2019 ACR/ARP Annual Meeting ABSTRACT NUMBER: 2886; Garg et al. JAMA Dermatol. 2017;153(8):760-764. doi:10.1001/jamadermatol.2017.0201 Sex- and Age-Adjusted Population Analysis of Prevalence Estimates for Hidradenitis Suppurativa in the United States; MayoClinic.org; Yale J Biol Med. 2013 Jun; 86(2): 255–260. N Engl J Med 2016;375:2570-81; https://www.diabetesresearch.org/diabetes-statistics; Nephcure.org; Kitiyakara C, Eggers P, Kopp JB. Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. Am J Kidney Dis. 2004 Nov;44(5):815-25; Rachakonda et al. J Am Acad Dermatol . 2014 Mar;70(3):512-6. doi: 10.1016/j.jaad.2013.11.013. Epub 2014 Jan 2. Psoriasis prevalence among adults in the United States; Yeung et al. Psoriasis severity and the prevalence of major medical co-morbidities: a population-based study; JAMA Dermatol. 2013 Oct 1; 149(10): 1173–1179; Hoover etal. Kidney Int. 2016 Sep; 90(3): 487–492. Insights into the Epidemiology and Management of Lupus Nephritis from the U.S. Rheumatologist's Perspective.

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