Safety, Tolerability, Pharmacokinetics, Receptor Occupancy, and Suppression of T-cell-Dependent Antibody Response in a Phase 1 Study with KPL-404, an anti-CD40 Monoclonal Antibody

Manoj Samant[1], Alistair Wheeler[2], Guang-Liang Jiang[1], Moses Njenga[1], Madeline Spiers[1], Arian Pano[1], John F. Paolini[1]

[1]Kiniksa Pharmaceuticals Corp.; [2]Kiniksa Pharmaceuticals, Ltd

BACKGROUND

CD40/CD40L pathway

- 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 cluster of differentiation (CD)40/CD40L-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]

KPL-404

- A humanized IgG4 monoclonal antibody that binds CD40, interferes with the CD40/CD40L pathway, and blocks T-cell–dependent, B-cell–immune responses.
- CD40 receptor binding (*in vitro*) as well as PK, RO, and TDAR were previously characterized in a cynomolgus monkey study[7]; the study demonstrated that KPL-404:
  - Has comparable binding affinity for human and cynomolgus monkey CD40.
  - Blocks antigen-specific primary and secondary antibody responses.
  - Was well-tolerated with systemic administration, i.e., no changes in body weight, hematology parameters, or injection-site issues.
- Non-human primate PK and receptor occupancy (RO) data informed the dosing regimen for the first-in-human clinical trial.

Hypothesis & Aims

- KPL-404 binds CD40 and blocks activation of the CD40/CD40L pathway, implicated in immune-mediated diseases; the clinical rationale for investigating interruption of this pathway is well established.
- This is the first-in-human phase 1 clinical trial to investigate the safety and tolerability, pharmacokinetics, RO, and TDAR suppression of KPL-404 in healthy participants.

METHODS

Study Design and Participants

- Phase 1, randomized, double-blind, placebo-controlled, first-in-human study of KPL-404 in healthy volunteers (NCT04497662)
  - Two study centers: one in Australia, one in the United States.
  - Males and females, aged 18-55 years, body mass index 18.0-32.0 kg/m^2.
  - A total of 52 participants (intravenous [IV] cohorts, n=36; subcutaneous [SC] cohorts, n=16) received 1 dose of study drug (KPL-404 or placebo) and had at least 1 assessment.
  - No participants prematurely discontinued the study for any reason.
- Healthy participants were randomly assigned to receive KPL-404 or placebo in two single-ascending-dose arms:
  - Single IV dose cohorts receiving 0.03 mg/kg (n=2), 0.3 mg/kg (n=6), 1 mg/kg (n=6), 3 mg/kg (n=6), or 10 mg/kg (n=6) or PBO (n=2 per cohort).
  - Single SC dose cohorts receiving 1 mg/kg (n=6) or 5 mg/kg (n=6) or PBO (n=2 per cohort).

Primary Endpoint

- Safety

Secondary Endpoints

- Pharmacokinetics (PK)
- Immunogenicity/anti-drug antibodies (ADAs)
- Pharmacodynamics (PD)
- TDAR to keyhole limpet hemocyanin (KLH) antigen challenge, measured as KLH titers (secondary challenge in selected cohorts)

Exploratory Endpoints

- CD40 RO

Assessments

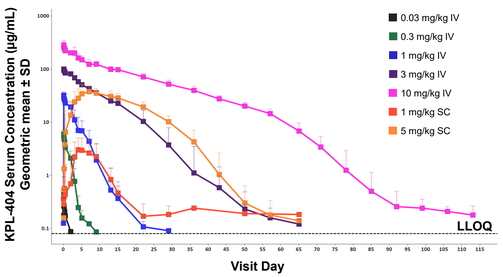
- Complete PK analysis in all patients following single IV or SC administration of KPL-404
- CD40 RO was monitored in all cohorts except 0.03 mg/kg.
  - Determined by flow cytometry-based assay performed on whole blood samples and measured as free CD40 on CD19-positive B cells. Binding of KPL-404 resulted in reduction of CD40 on B cells, and mean fluorescence intensity reduction of CD40 was measured and converted into Antibody Binding Capacity (ABC) using Quantum Simply Cellular (QSC) beads.
- KLH-induced primary immune response was monitored in cohorts receiving 1, 3, and 10 mg/kg IV and in cohorts receiving 1 and 5 mg/kg SC. KLH-induced secondary immune response was monitored in cohorts receiving 1, 3, and 10 mg/kg IV only.
- Development of ADAs was monitored in all patients.
- Safety
  - Number of participants with treatment-emergent adverse events in each cohort vs (pooled) IV and SC placebo groups from first day of dosing through day 65.
  - Clinical laboratory tests, vital signs measurements, 12-lead ECGs, physical examination findings.

RESULTS

Serum PK Parameters

- The PK profile of KPL-404 in serum after IV or SC administration had low to moderate variability between individuals.
- C_{max} increased almost dose-proportionally, and $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ increased more than dose-proportionally over the dose range of 0.03 to 10 mg/kg.
- Elimination was dose-dependent and consistent with target-mediated drug disposition (TMDD).
- Bioavailability of the SC formulation was estimated to be 66%.

Figure 1. Pharmacokinetic profiles for KPL-404.



SD, standard deviation (upward bars depicted); IV, intravenous; SC, subcutaneous; LLOQ, lower limit of quantitation

Table 1. Summary of Serum PK parameters of KPL-404.

Part	Cohort (N=6)	KPL-404 Dose (mg/kg)	C_{max} (µg/mL)	T_{max} # (h)	$AUC_{0\text{-}t}$ (h*µg/mL)	$AUC_{0\text{-}inf}$ (h*µg/mL)	$t_{1/2}$ (h)	CL or CL/F (L/h)	Vd or Vd/F (L)
A	1*	0.03	0.854 (45.7)	1.00 (1.00, 1.00)	3.20 (110.7)	7.33[a] (.)	12.8[a] (.)	0.280[a] (.)	5.16[a] (.)
	2	0.3	6.26 (18.2)	1.75 (1.50, 2.00)	152 (37.6)	156 (37.5)	22.5 (48.1)	0.156 (35.5)	4.45 (18.9)
	3	1	34.8 (12.1)	2.00 (1.50, 3.00)	2230 (32.6)	2240 (32.3)	74.3 (32.8)	0.0358 (47.1)	4.05 (78.8)
	4	3	102 (4.4)	1.50 (1.00, 3.05)	20300 (16.2)	20300 (16.2)	109 (20.8)	0.0119 (24.2)	1.81 (20.1)
	5	10	319 (15.1)	3.00 (1.05, 49.00)	96200 (12.7)	96300 (12.7)	168 (33.0)	0.00854 (17.0)	2.02 (27.8)
B	1	1	3.91 (52.4)	71.92 (48.00, 192.00)	772 (71.5)	644[b] (60.2)	82.8[b] (15.5)	0.168[b] (53.7)	19.6[b] (54.5)
	2	5	43.7 (31.5)	142.97 (96.00, 188.82)	19300 (27.5)	19400 (27.5)	122 (14.9)	0.0206 (26.7)	3.67 (35.5)

Part A cohorts are administered IV infusion; Part B cohorts are administered SC injection.
Values are presented as mean (CV%) except for T_{max} where median (min, max) are shown.
Mean t_{max} for 10 mg/kg cohort excluding the 49-hour half-life of one patient is 3.52 hours.
* N = 2
[a] n = 1, [b] n = 5

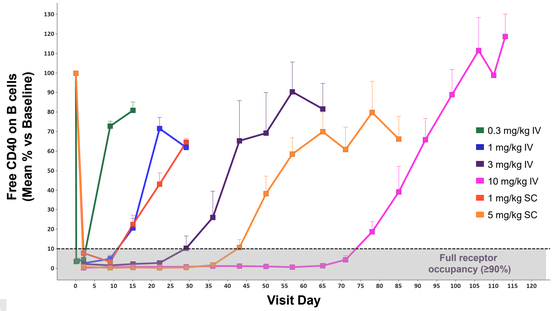
Receptor Occupancy (RO, Figure 2) and T-cell Dependent Antibody Response (TDAR, Figure 3)

- For participants receiving 1, 3, and 10 mg/kg IV, full RO was observed through days 9, 29, and 71, respectively.
- For participants receiving 1 and 5 mg/kg SC, full RO was observed through days 9 and 43, respectively.
- For participants receiving 1, 3, and 10 mg/kg IV, complete TDAR suppression was observed through days 9, 36, and 57, respectively.
- Recall responses at day 29 were abrogated in the arms dosed with 3 and 10 mg/kg IV on day 1 and were attenuated in the 1 mg/kg IV compared to placebo.
- For participants receiving 1 and 5 mg/kg SC, complete TDAR suppression was observed through at least days 9 and 29, respectively; SC cohorts were not rechallenged with KLH on day 29.
- The TDAR suppression correlated with the observed full RO.
- The suppression of TDAR is a phamacodynamic marker for target engagement.

Key Points

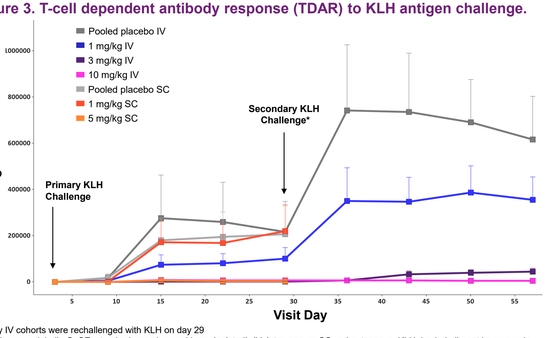
- Extent and duration of full CD40 RO was serum concentration dependent.
- KPL-404 suppressed TDAR (both primary and recall) when the receptor was fully occupied.

Figure 2. CD40 receptor occupancy (RO) on B cells as compared to baseline.



SE, standard error (upward bars depicted); IV, intravenous; SC, subcutaneous

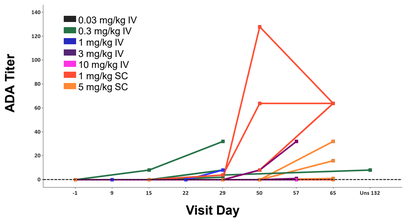
Figure 3. T-cell dependent antibody response (TDAR) to KLH antigen challenge.



*Only IV cohorts were rechallenged with KLH on day 29
IgG, immunoglobulin G; SE, standard error (upward bars depicted); IV, intravenous; SC, subcutaneous; KLH, keyhole limpet hemocyanin

Anti-Drug Antibodies (ADA)

Figure 4. ADA titer over time in participants with detectable ADA.



- In participants receiving IV KPL-404 administration, ADAs were observed (at least one postdose timepoint) in 0/2 at 0.03 mg/kg, 5/6 at 0.3 mg/kg, 1/6 at 1 mg/kg, 2/6 at 3 mg/kg, and 0/6 at 10 mg/kg.
- In participants receiving SC KPL-404 administration, ADAs were observed (at least one postdose timepoint) in 4/6 at 1 mg/kg, 3/6 at 5 mg/kg.
- In general, no consistent trends in serum KPL-404 PK parameters (C_{max}, AUCs) were observed due to ADA status, suggesting no impact of ADA status on PK of KPL-404 after either IV or SC administration.
- ADAs to KPL-404 were completely suppressed while concentrations of KPL-404 were above approximately 0.2 µg/mL.
- ADAs to KPL-404 were suppressed for at least 50 days at 5 mg/kg SC and at least 57 days at 10 mg/kg IV.
- Suppression of ADA to KPL-404 is an independent indicator of target engagement and pharmacodynamic effect.

Table 2. Adverse Events Reported by ≥5% of Healthy Participants Receiving KPL-404 IV, KPL-404 SC, and Placebo.

	KPL-404 IV						KPL-404 SC		
	0.03 mg/kg N=2 n (%)	0.3 mg/kg N=6 n (%)	1 m/kg N=6 n (%)	3 mg/kg N=6 n (%)	10 mg/kg* N=6 n (%)	Pooled placebo N=10 n (%)	1 mg/kg N=6 n (%)	5 mg/kg* N=6 n (%)	Pooled placebo N=4 n (%)
Participants with AEs	0	1 (16.7)	2 (33.3)	1 (16.7)	5 (83.3)	2 (20.0)	1 (16.7)	4 (66.7)	2 (50.0)
Participants with AEs related to KPL-404	0	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (16.7)	3 (50.0)	0
Participants with serious AE	0	0	0	0	1 (16.7)#	0	0	0	0
Preferred term									
Catheter-site pain	0	0	0	0	1 (16.7)	0			
Catheter-site swelling	0	0	0	0	1 (16.7)	0			
Infusion-site thrombosis	0	0	0	0	0	1 (10.0)			
Injection-site pain	0	0	0	0	0	1 (10.0)			
Cough	0	0	0	1 (16.7)	0	0			
Rhinorrhea	0	0	0	0	1 (16.7)	0			
Sinus congestion	0	0	0	0	1 (16.7)	0			
Contusion	0	0	0	0	1 (16.7)	0			
Patella fracture	0	0	0	0	1 (16.7)	0			
Headache	0	0	0	0	1 (16.7)	0			
Vision blurred	0	0	0	0	1 (16.7)	0			
Diarrhea	0	1 (16.7)	0	0	0	0			
Neck pain	0	0	0	0	0	1 (10.0)			
Aspartate aminotransferase increased							0	1 (16.7)	0
Myalgia							1 (16.7)	0	0
Dermatitis contact							0	0	1 (16.7)
Venous thrombosis							1 (16.7)‡	0	0
Headache							0	3 (50.0)	0
Dizziness							0	1 (16.7)	0
Paresthesia							1 (16.7)	0	0
Presyncope							0	1 (16.7)	0
Fatigue							1 (16.7)	0	0
Injection-site pain							0	1 (16.7)	0
Injection-site rash							0	1 (16.7)	0
Vessel puncture–site pain							0	0	1 (25.0)
Flatulence							1 (16.7)	0	0
Seasonal allergy							1 (16.7)	0	0

*The 10 mg/kg IV group and 5 mg/kg SC group were tested at a different study center in another country; the increased number of AEs in these groups could be impacted.
#Patella fracture; AE was severe and was considered unrelated to KPL-404 by the investigator.
‡Nonserious event of superficial vein thrombosis, which began 22 days after dosing; the participant was treated with NSAIDS and warm compresses on day 26 and resolved on day 29.

- Headache was the only AE considered related to KPL-404 occurring in more than one participant during the study.
- There were no dose-limiting or dose-related safety findings in healthy participants after IV or SC administration of KPL-404.

CONCLUSIONS

- The pharmacokinetics of KPL-404 followed a TMDD model, with higher dose cohorts showing slower elimination and longer duration of detectable concentrations with both IV and SC administration.
- Full CD40 receptor occupancy was maintained through day 43 after single SC dose of 5 mg/kg and through at least day 71 after single IV dose of 10 mg/kg.
- Pharmacodynamic assessments suggested full target engagement and dose-dependent suppression of TDAR for primary and secondary KLH challenge were achieved at pharmacologically relevant concentrations.
- KPL-404 was well tolerated with no safety signals based on the evaluation of AEs, clinical laboratory findings, and vital signs measurements in participants receiving KPL-404 versus participants receiving placebo.
- The magnitude and duration of memory immune response suppression by KPL-404 support the further study of practical chronic KPL-404 dosing regimens using both SC as well as IV administration.
- The involvement of the CD40-CD154 pathway in pathophysiology of multiple autoimmune diseases, including rheumatoid arthritis, Sjögren's syndrome, Graves' disease, and lupus supports further development of KPL-404 in a broad range of immune-mediated/autoimmune diseases.

DISCLOSURES

All authors disclose employment by Kiniksa Pharmaceuticals
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REFERENCES

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 7. Muralidharan, 2019, Keystone Symposia **[abstract]**

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