First-in-Human Phase 1 Randomized Trial with the Anti-CD40 Monoclonal Antibody KPL-404: Safety, Tolerability, Receptor Occupancy, and Suppression of T-Cell–Dependent Antibody Response

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CL, clearance
CL/F, apparent clearance
Cmax, maximum concentration
ELISA, enzyme-linked immunosorbent assay
Fc, fragment crystallizable
FIH, fist in human
λz, apparent terminal elimination rate constant
IV, intravenous
KLH, keyhole limpet hemocyanin
LLOQ, lower limit of quantification
NOAEL, no observed adverse effect level
PD, pharmacodynamic
PK, pharmacokinetic
RO, receptor occupancy
tmax, time to maximum concentration
TDAR, T-cell–dependent antibody response
TEAE, treatment-emergent adverse event
TMDD, target-mediated drug disposition
Uns, unscheduled visit
Vd, volume of distribution
Vd/F, apparent volume of distribution

**Recommended section assignment:** Inflammation, Immunopharmacology, and Asthma
ABSTRACT

Blockade of the cluster of differentiation 40 (CD40)–CD40L interaction has potential for treating autoimmune diseases and preventing graft rejection. This first-in-human, randomized, double-blind, placebo-controlled study (NCT04497662) evaluated safety, pharmacokinetics, receptor occupancy, and pharmacodynamics of the humanized anti-CD40 monoclonal antibody KPL-404. Healthy volunteers were randomized to one of two single-ascending-dose groups: single intravenous (IV) KPL-404 dose 0.03, 0.3, 1, 3, or 10 mg/kg or single subcutaneous (SC) KPL-404 dose 1 or 5 mg/kg. There were no dose-limiting or dose-related safety findings. Nonlinear dose-dependent changes in various pharmacokinetic parameters were identified following the range of IV doses. At the 10 mg/kg IV dose level, the $t_{1/2}$ was approximately 7 days, and full receptor occupancy was observed through Day 71, with complete suppression of T-cell–dependent antibody response (TDAR) to keyhole limpet hemocyanin (KLH) challenge on Day 1 and rechallenge on Day 29 through Day 57. With KPL-404 5 mg/kg SC, full receptor occupancy was observed through Day 43, with complete suppression of TDAR through at least Day 29. Antidrug antibodies to KPL-404 were suppressed for 57 days with 10 mg/kg IV and for 50 days with 5 mg/kg SC, further confirming prolonged target engagement and pharmacodynamics. These findings support continued investigation of KPL-404 IV and SC administration in a broad range of indications.
SIGNIFICANCE STATEMENT

This first-in-human clinical trial of KPL-404, a fully humanized IgG4 monoclonal antibody, was designed with two independent (by route of administration) placebo-controlled single-ascending-dose-level groups, one with four intravenous single-dose cohorts and another with two subcutaneous single-dose cohorts. The pharmacokinetic profile, duration of full CD40 receptor occupancy, and magnitude and duration of memory immune response suppression observed confirm pharmacodynamic activity regardless of administration route. These data provide evidence that chronic KPL-404 dosing regimens (intravenous or subcutaneous) could be practical.
Introduction

CD40 is a cell surface receptor that belongs to the tumor necrosis factor receptor superfamily. It is primarily known as a costimulatory receptor that regulates the activity of dendritic cells, monocytes, platelets, macrophages, and B cells as well as nonhematopoietic cells such as myofibroblast, fibroblast, epithelial, and endothelial cells (Laman et al., 1996; Inwald et al., 2003; Danese et al., 2004; Hernandez et al., 2007; Phipps, 2008; Karnell et al., 2019b). Interactions between CD40 and its ligand CD154 (CD40L), found on T cells, antigen-presenting cells, and natural killer cells, have an essential role in the promulgation of primary and secondary humoral immune responses to T-cell–dependent antigens (Karnell et al., 2019b). Various diseases characterized by autoimmune pathology (e.g., systemic lupus erythematosus, lupus nephritis, rheumatoid arthritis, Graves’ disease) have been found to exhibit evidence of CD40/CD40L pathway dysregulation (Boumpas et al., 2003; Huber et al., 2012; Fisher et al., 2020; Kahaly et al., 2020). Blockade of the CD40–CD40L interaction suppresses primary and secondary T-cell–dependent antibody responses (TDAR); thus this pathway has become a promising target for pharmacologic modulation in autoimmune diseases associated with abnormal B- and T-cell activation (Boumpas et al., 2003; Karnell et al., 2019a; Fisher et al., 2020; Kahaly et al., 2020) and for prolongation of graft survival in transplantation (Lowe et al., 2012; Cordoba et al., 2015; Harland et al., 2020).

Historically, a key safety concern with targeting CD40L was the formation of immune complexes composed of anti-CD40L antibody and soluble CD40L, which can result in thromboembolic events from platelet aggregation (Robles-Carrillo et al., 2010). Early studies involving non-silenced immunoglobulin G1 (IgG1) anti-CD40L antibodies
revealed unexpected thromboembolic events and fatalities, leading to eventual
termination of some programs (Boumpas et al., 2003; Law and Grewal, 2009). This
safety concern has likely been mitigated by the engineering of next generation anti-
CD40L antibodies that do not trigger fragment crystallizable (Fc) region–mediated
signaling (e.g., VIB4920) (Karnell et al., 2019a) or, alternatively, by targeting CD40
instead (e.g., iscalimab, bleselumab, BI 655064) (Visvanathan et al., 2019; Fisher et al.,
2020; Vincenti et al., 2020). To date, thromboembolic events have not been reported in
clinical trials involving these therapies (Schwabe et al., 2018; Karnell et al., 2019a;
Visvanathan et al., 2019; Espié et al., 2020; Fisher et al., 2020; Harland et al., 2020;
Kahaly et al., 2020).

KPL-404 is a humanized IgG4 monoclonal antibody engineered to bind CD40
and interfere with CD40–CD40L interaction and downstream T-cell–dependent B-cell–
immune responses without triggering significant B-cell depletion (i.e., “non-depleting”) or
Fc effector functions. The murine antibody 2C10 and 2C10R4 (its primatized derivative)
have been shown to be potent immunomodulatory anti-CD40 antibodies with utility in
nonhuman primate models of allo- and xenotransplantation (Lowe et al., 2012;
Mohiuddin et al., 2014; Mohiuddin et al., 2016; Längin et al., 2018). KPL-404 was
engineered as a humanized antibody by grafting the complementarity-determining
regions from 2C10 onto human germline IgG4 scaffold sequences. In vitro and in vivo
data from primate studies have confirmed the anti-CD40 blocking activity of KPL-404 at
pharmacologically relevant concentrations, with potent inhibitory effects on both primary
and secondary antibody responses; these effects were observed without concomitant
depletion of B cells (e.g., KPL-404 is “non-depleting”). These data provided support for
the clinical testing of KPL-404 in humans (Marken et al., 2021; Muralidharan et al., 2022).

This first-in-human phase 1 trial in healthy volunteers investigated KPL-404 safety, tolerability, pharmacokinetic (PK) characteristics, receptor occupancy (RO), and pharmacodynamic (PD) effect (measured by suppression of TDAR after keyhole limpet hemocyanin [KLH] challenge and inhibition of anti-KPL-404 antibodies [ADAs] to KPL-404).

Materials and Methods

Study Design

This was a phase 1, randomized, double-blind, placebo-controlled study of KPL-404 in healthy volunteers (NCT04497662). The study was conducted at two centers, one in Australia and one in the United States, between October 2019 and March 2021. Institutional review board approval was granted by Bellberry Limited Human Research Ethics Committee (Eastwood, South Australia) for the Australia site and by IntegReview IRB (Austin, TX) for the US site. All study activities were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

The study design included two single-ascending-dose groups consisting of intravenous (IV) dose cohorts (0.03 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg) and subcutaneous (SC) dose cohorts (1 mg/kg or 5 mg/kg). In the 0.03 mg/kg IV cohort, participants were randomized 1:1 to KPL-404 or placebo; all other cohorts used 3:1 (KPL-404:placebo) randomization. Each participant received a single administration of
KPL-404 or placebo. The study consisted of 3 periods: screening (up to 28 days before
dosing), domiciled treatment (4-6 days, depending on dose cohort), and safety
evaluation. Duration of the safety evaluation period varied by dose cohort and
corresponded to an amount of time necessary to allow for KPL-404 serum concentration
assessments until up to 5.5 estimated half-lives (IV 0.03 and 0.3 mg/kg, 29 days; IV 1
and 3 mg/kg, 65 days; IV 10 mg/kg, 113 days; SC 1 mg/kg, 65 days; SC 5 mg/kg, 85
days).

Study participants were administered the KPL-404 dose under observation while
domiciled in the clinical study facility. The lowest dose level IV cohort was 0.03 mg/kg;
the KPL-404 dose level was increased in successive cohorts after observations for
safety and tolerance in previous dose level cohorts. Sentinel dosing was used within
each cohort, and available safety and PK data were assessed after each dose level to
support the decision to proceed with escalation to the next planned dose. The lowest
dose level SC cohort (1 mg/kg) was enrolled only after review of the 1 mg/kg IV safety
data. The IV study medication (KPL-404 and placebo) was administered with infusion
pump over 60 minutes; SC study medication (KPL-404 or placebo) was given as single
or multiple SC injections depending on the total required volume.

Dose Selection

Selection of KPL-404 doses was based on nonclinical PK/PD research
(Muralidharan et al., 2022), and safety data from an 8-week repeated-dose toxicity study
(unpublished data), and on predicted human PK and an anticipated therapeutic dose of
KPL-404 derived from PK modeling.
Using the predicted exposures following a starting dose of 0.03 mg/kg IV in humans, the safety margins were estimated to be 10,058-fold for $C_{\text{max}}$ and 101,158-fold for area under the curve (AUC) relative to the no-observed-adverse-effect-level (NOAEL) dose determined in the pivotal toxicology study. The highest IV or SC doses were not expected to exceed the exposures achieved at the NOAEL dose, and the $C_{\text{max}}$ and AUC fold-safety margins for the predicted KPL-404 exposures for the 10 mg/kg IV dose relative to the NOAEL dose were 28.3 μg/mL and 293 h·μg/mL, respectively.

**Participants**

Eligible participants were healthy male and female volunteers who were between ages 18 and 55 years and had a body mass index between 18.0 and 32.0 kg/m². Participants receiving IV doses of 0.03 mg/kg, 0.3 mg/kg, 1 mg/kg, and 3 mg/kg and SC doses of 1 mg/kg were enrolled by the US center, and participants receiving 10 mg/kg IV and 5 mg/kg SC were enrolled by the Australia center. All inclusion and exclusion criteria are provided. (see Supplemental Data, Appendix S1).

**Safety Assessments**

Safety assessments included adverse event (AE) monitoring, concomitant medications, clinical laboratory analyses (including clinical chemistry, hematology, coagulation panel, urinalysis, serology, and ADAs), vital signs measurements, electrocardiograms, and physical examination findings. All AEs that occurred between administration of study treatment and end-of-study visit were recorded, whether considered related to study treatment or not.
Pharmacokinetic Assessments

The primary purpose of the proposed Phase 1 FIH study was to evaluate safety and tolerability of single ascending intravenous (IV) and subcutaneous (SC) doses of KPL-404 in healthy volunteers, with the PK component intended to determine the extent and duration of exposure by dose and route of administration. Blood samples for PK assessments were collected post-dose by venipuncture or cannulation at various times over periods ranging from 15 to 113 days, depending on study cohort. KPL-404 serum concentrations were determined using a validated enzyme-linked immunosorbent assay (ELISA) (see Supplemental Data, Appendix S2).

Pharmacodynamic Assessments

**CD40 Receptor Occupancy on B Cells.** CD40 RO on whole-blood B cells was assessed to evaluate the engagement of KPL-404 to its target. RO was determined by flow cytometry pre-dose and at various times post-dose up to 113 days depending on the cohort (see Supplemental Data, Appendix S2). CD40 RO was evaluated in all cohorts except the 0.03 mg/kg IV cohort, given that the degree of CD40 RO at this starting dose was expected to be at such a low level that it might not have been accurately detected by RO assay.

**TDAR to KLH Antigen Challenge.** Select cohorts underwent KLH challenge for quantification of humoral immune response suppression. Three IV cohorts (1, 3, 10 mg/kg on Day 1) underwent a primary KLH challenge on Day 4 and rechallenge (without re-dosing KPL-404) on Day 29. Both SC cohorts underwent a primary KLH challenge on
Day 4 only (no rechallenge). Each challenge was an intramuscular injection of 1 mg (0.5 mL) in the deltoid. Samples for anti-KLH immunoglobulin G (IgG) titers (see Supplemental Data, Appendix S2) were obtained on Days 3, 9, 15, 22, and 29; additional samples were obtained from the rechallenged cohorts on Days 36, 43, 50, and 57.

**Immunogenicity Assessments**

All participants were monitored for development of ADAs pre-dose and at various points through Day 65, depending on dose group. Putative-positive samples were assessed in a confirmatory assay; presence of ADA was declared only if the confirmatory antibody test was positive (see Supplemental Data, Appendix S2).

**Data Analysis and Sample Size**

No formal sample size calculations were performed. The sample size was considered sufficient to adequately assess the safety, PK, PD, and immunogenicity of KPL-404; the study size is consistent with dose escalation studies for safety and PK. Summary statistics are provided for study endpoints.

Principal KPL-404 pharmacokinetic parameters ($C_{\text{max}}$, $\text{AUC}$, $t_{1/2}$) were calculated by a model-independent noncompartmental analysis employing Phoenix WinNonlin Version 8.0 (Certara USA; Princeton, NJ, USA) using the actual sample collection times (see Supplemental Data, Appendix S3).

Pharmacokinetic parameters were summarized for each cohort by geometric mean with coefficient of variation (CV%, calculated by SD/mean × 100), median, and
minimum/maximum. For calculation of PK parameters, a below-the-limit-of-quantitation result was treated as zero if it occurred before the first quantifiable concentration or as missing if it occurred afterward. All statistical data were generated with SAS Version 9.4 or higher.

Results

Participants

A total of 52 participants (IV cohorts, n = 36; SC cohorts, n = 16) received at least 1 dose of study medication (KPL-404 or placebo) and had at least 1 assessment. No participants discontinued the study, and all were included in the safety, PK, and PD analyses. Demographic and baseline characteristics of the study cohorts are presented in Table 1. In the IV cohorts, 50% (18/36) of participants were male, 69.4% (25/36) were White, mean age was 34.9 years, and mean body weight was 75.3 kg. In the SC cohorts, 68.8% (11/16) of participants were male, 56.3% (9/16) were White, mean age was 40.4 years, and mean body weight was 76.8 kg.

Safety

Single doses of KPL-404 given as IV infusion (dose range, 0.03–10 mg/kg) or SC injection (dose range, 1–5 mg/kg) were well tolerated, with no dose-limiting or dose-related safety findings. There was 1 serious AE (patellar fracture after a fall) in the KPL-404 IV 10 mg/kg cohort; this AE was considered unrelated to study treatment.

The incidence of treatment-emergent AEs (TEAEs) was low (Table 2). Headache was the only TEAE that occurred in more than 1 participant in either cohort (1
participant each in the 1 mg/kg and 10 mg/kg IV cohorts and 3 participants in the 5 mg/kg SC cohort). The majority of TEAEs were mild or moderate in severity, with the only severe TEAE being the unrelated patellar fracture. There was 1 nonserious TEAE reported on Day 22, a superficial thrombosis in a penile vein (1 mg/kg SC cohort) that was considered by the investigator as “possibly related” to study treatment. The participant’s D-dimer levels were always <2-fold upper limit of normal, and the coagulation panel and platelet counts were normal. This AE was managed with nonsteroidal anti-inflammatory drugs and warm compresses and resolved by Day 29.

Among all participants, there were no clinically meaningful changes from baseline in laboratory values, vital signs measurements, electrocardiogram parameters, or physical examination findings.

**Pharmacokinetics**

After IV administration, mean peak $C_{\text{max}}$, total AUC from time 0 to last measurable concentration ($\text{AUC}_{0-t}$), and total AUC from time 0 to infinity ($\text{AUC}_{0-\infty}$) of KPL-404 increased with increasing KPL-404 IV dose (Table 3). $C_{\text{max}}$ increased almost dose-proportionally, and AUC values increased more than dose-proportionally over the dose range of 0.03 to 10 mg/kg (see Supplemental Data, Appendix S3). Low to moderate interparticipant variability was observed for both $C_{\text{max}}$ and AUC parameters across IV cohorts, except for 0.03 mg/kg, which had slightly higher interparticipant variability because of the cohort’s small active sample size (n = 2). Median time to $C_{\text{max}}$ ($t_{\text{max}}$) was achieved within 3 hours post-dose across all IV cohorts. Mean apparent terminal elimination half-life ($t_{1/2}$) increased with increasing dose and ranged from 12.8 to 168 hours. As a consequence
of analytical sensitivity and the dose utilized, half-life determinations for the lower dose IV cohorts (0.03 and 0.3 mg/kg) are likely reflective primarily of the distribution phase and likely not representative of a true elimination half-life. Mean clearance and volume of distribution showed dose dependency, i.e., they decreased as KPL-404 IV dose increased. Given that the underlying assumption of linearity was absent across the range of doses explored, the accuracy and reliability of NCA derived parameters such as $t_{1/2}$, CL, and VD reported herein should be viewed in the context of the doses administered and the plasma concentrations achieved.

Similarly, after SC administration, mean $C_{max}$ and AUC serum exposure of KPL-404 increased with increasing KPL-404 dose. Median $t_{max}$ values were 72 and 143 hours for the 1 mg/kg and 5 mg/kg cohorts, respectively. Mean $t_{1/2}$ values were 83 and 122 hours, and mean apparent clearance values were 0.168 and 0.0206, for 1 mg/kg and 5 mg/kg, respectively. Prolonged exposure following SC (as well as IV) administration suggests that, at higher doses, less frequent dosing (e.g., every 2 to 4 weeks) may be clinically viable and worthy of exploration in Phase II/III studies.

Overall, inspection of the plasma concentration-time curves, which demonstrated both dose-dependent reductions in elimination rate (as judged by clearance) and concomitant increases in KPL-404 elimination $t_{1/2}$, suggests that KPL-404 pharmacokinetics are consistent with the presence of nonlinear process, such as saturable excretion, target-mediated drug disposition (TMDD), or another non-linear process. Inspection of the mean plasma concentration data (Fig. 1) reveals that the impact of this non-linear behavior appears more relevant at plasma KPL-404
concentrations in excess of 10 μg/mL across all doses and both routes of administration.

**Pharmacodynamics**

**CD40 Receptor Occupancy on B Cells.** Duration of full CD40 RO (≥90%) increased in a dose-related manner across the evaluated KPL-404 dose levels (Fig. 2). For the 0.3, 1, 3, and 10 mg/kg IV dose levels, full CD40 RO was maintained through Days 2, 9, 29, and 71, respectively. For the 1 and 5 mg/kg SC dose levels, full CD40 RO was maintained through Days 9 and 43, respectively. There was no evidence by flow cytometry of a clinically meaningful reduction of B-lymphocyte count from baseline. Full CD40 receptor occupancy by dose (Fig. 2) appears to coincide with plasma concentrations above ~ 10 μg/ml (Fig. 1). Further study in patients is necessary to determine if this observed plasma concentration is replicated or different in disease states, which could inform target trough plasma concentrations necessary for clinical efficacy.

**TDAR to KLH Antigen Challenge.** Magnitude and duration of inhibition of TDAR to KLH antigen challenge varied by KPL-404 dose level and route of administration (Fig. 3). A single dose of 10 mg/kg IV completely suppressed TDAR to the primary KLH challenge (Day 4) as well as the rechallenge on Day 29, with suppression sustained through Day 57 (last time point analyzed). A single dose of 3 mg/kg IV also resulted in full TDAR suppression to the primary KLH challenge on Day 4, but the recall response suppression following rechallenge on Day 29 was slightly attenuated 14 days later (Day 43). Following a single 1 mg/kg IV dose, TDAR was suppressed to levels below those
achieved with placebo but not completely abrogated. Following placebo IV administration, TDAR to the primary KLH challenge on Day 4 peaked at Day 15 and fell slightly by Day 29; TDAR to KLH rechallenge on Day 29 peaked on Day 36 with gradual fall-off in response through Day 57.

A single administration of KPL-404 5 mg/kg SC completely suppressed TDAR to the primary KLH challenge through Day 29 (last time point analyzed), while a single 1 mg/kg SC dose showed a pattern of TDAR attenuation similar to that seen with SC placebo. Recall response was not tested in patients in the SC dose arms.

The duration and magnitude of TDAR inhibition correlated with duration of full RO, except for the 3 mg/kg IV cohort in which the response lasted one additional week after the loss of RO.

**Immunogenicity**

ADAs to KPL-404 were completely suppressed while concentrations of KPL-404 were above approximately 0.2 µg/mL, or for at least 50 days at 5 mg/kg SC and at least 57 days at 10 mg/kg IV. Suppression of ADAs to KPL-404 is an independent indicator of target engagement and PD effect. ADA titers (evaluated in 6 patients) were detected at least once in 83.3% (n = 5) of participants in the 0.3 mg/kg IV cohort (Day 29); 16.7% (n = 1) of participants in the 1 mg/kg IV cohort (Day 29); and 33.3% (n = 2) of participants in the 3 mg/kg IV cohort (Days 50 and 57) (Fig. 4). No ADAs were detected in the 0.03 mg/kg and 10 mg/kg IV cohorts. In the SC cohorts, ADA titers were detected at least once at late time points in 66.7% (n = 4) of participants who received 1 mg/kg (Days 29, 50, and 65) and 50.0% (n = 3) of participants who received 5 mg/kg (Day 65). For ADA-
positive samples, titers ranged from 1:1 to 1:128; most of the positive samples had a titer of 1:8.

No differences in KPL-404 serum concentrations were observed between participants with negative versus positive ADA responses.

Discussion

The CD40/CD40L pathway is an essential co-stimulatory mediator of primary and secondary humoral immune responses to T-cell–dependent antigens. It is being actively targeted for treatment of autoimmune diseases in which abnormal B- and T-cell activation plays a role in pathogenesis and for prevention of allograft/xenograft rejection. This is the first-in-human (FIH) study of KPL-404, a unique, fully humanized IgG4 monoclonal antibody that targets CD40 and inhibits the interaction between CD40 receptor and CD40L (CD154) without depleting B cells.

Based on evaluations of AEs, clinical laboratory findings, and vital signs measurements in participants receiving KPL-404 versus participants receiving placebo, KPL-404 was well tolerated across a range of single IV (0.03 to 10 mg/kg) and SC (1 and 5 mg/kg) administrations. There were no serious AEs considered related to KPL-404, no dose-limiting safety findings, and no clear dose response for overall AE frequency or severity. Although the highest dose group (IV 10 mg/kg) had the greatest percentage of participants who reported an AE (83.3%, 5/6), percentage calculations based on very small numbers of participants should be interpreted with caution; also, given that this dose cohort was in Australia (prior IV cohorts were in the United States), the potential influence of geographic and cultural factors should not be discounted. No
event reported in the 10 mg/kg group occurred in >1 participant. Future studies with larger cohorts should provide more robust assessments of AE patterns.

The PK profile of KPL-404 showed dose-dependent increases in concentration and exposure and followed a decay profile consistent with saturable elimination or antigen-sink effect (i.e., TMDD), the identification and confirmation of which would require additional experimentation. Compared with lower dose cohorts, higher dose cohorts showed slower elimination of KPL-404 and longer duration of detectable concentrations with both IV and SC administration. Reasonably low to moderate PK variability between individuals was observed, with minimal discernable differences evident following SC administration versus that seen after IV infusion (3 and 10 mg/kg). Although the clinically efficacious dosing regimen remains to be confirmed by subsequent studies, the similarities in exposure following dose-adjusted IV and SC administration support the concept that either route of administration could ultimately be clinically useful, with dosing intervals potentially even as infrequent as every 2-4 weeks. There was no evidence of a clinically meaningful reduction in B-lymphocyte count from baseline, consistent with in vitro (Marken et al., 2021) and in vivo (Muralidharan et al., 2022) observations. There were no trends in observed serum KPL-404 PK parameters related to ADA status, suggesting no impact of ADA on the PK of KPL-404 after either IV or SC administration. However, given limited duration of PD follow-up, neutralizing effects cannot be ruled out based on these findings alone.

The inhibition of primary and recall (rechallenge) antibody responses to the test antigen KLH and RO pharmacodynamic assessments suggested that the extent and duration of TDAR suppression and full CD40 RO (≥90%) were dose-related regardless
of route of administration. The highest dose tested in this study, 10 mg/kg IV, provided complete suppression of TDAR to KLH challenge for at least 8 weeks; full RO was evident for at least 10 weeks in this dose group; thus it is likely that TDAR suppression would have been detected after 8 weeks had its evaluation been continued. In the 3 mg/kg IV group, despite RO being less than 90% after 4 weeks, only a slight breakthrough in TDAR response was evident after 5 to 8 weeks, indicating presence of efficacious concentrations of KPL-404 in tissues beyond 4 weeks to suppress the recall response to rechallenge. The suppression of TDAR to KLH challenge showed evidence of wearing off on Day 43, which was 2 weeks after the KLH rechallenge on Day 29. Similarly, a single administration of 5 mg/kg SC on Day 1 achieved compete TDAR suppression through at least 4 weeks (last evaluation), and suppression likely lasted even longer, given that full RO was evident for 6 weeks. In the 1 mg/kg IV or SC dose group, even though full RO and complete TDAR suppression were evident only through Day 9, the response to KLH rechallenge on Day 29 in the IV group was still markedly attenuated relative to placebo through 10 weeks; the magnitude of initial suppression was slightly greater with the IV dose, likely because of a differential systemic exposure at the time of initial antigen challenge. Considering the practical advantages of SC administration in chronic outpatient use, further clinical investigation is warranted to fully evaluate potential clinical dosing regimens.

Preclinical and clinical investigations suggested that other anti-human CD40 monoclonal antibodies required a mean trough concentration of approximately 40 µg/mL to achieve and maintain target engagement in tissue, which was higher than the concentration required for full RO in the periphery (Ulrich et al., 2018; Espié et al., 2020;
As the expression of CD40 in target tissues can vary in autoimmune diseases (Karnell et al., 2019b) or post-transplantation (Gaweco et al., 1998; Ma et al., 2014), careful analysis of actual or modeled PK in the serum or plasma and target engagement in the tissue will be required to identify the optimal dosing and schedule for maintaining clinical efficacy in autoimmune diseases and to prevent graft rejections. In the present study, ADAs were suppressed for at least 57 days after 10 mg/kg IV and for at least 50 days after 5 mg/kg SC. ADAs were detected only when KPL-404 serum concentrations fell to levels near or below the lower limit of quantitation (i.e., 0.08 µg/mL), suggesting that with regimens involving repeated administration, ADAs would likely remain suppressed between doses. In contrast, in studies with other compounds within this class (e.g., anti-CD40 monoclonal antibody BI 655064), efficacy failures have been reported along with the presence of ADAs, implying failure of full target engagement and suppression (Albach et al., 2018; Visvanathan et al., 2019; Jayne et al., 2021); such failures may suggest the combined effect of sub-optimal target engagement as well as an ADA “neutralization” phenomenon. Thus, suppression of antibody responses to the drug itself can be considered a reasonable surrogate marker of target engagement and PD.

Signaling through CD40/CD40L is implicated in a number of immune-mediated diseases and is emerging as an attractive strategic approach for managing autoimmune diseases such as systemic lupus erythematosus, lupus nephritis, rheumatoid arthritis, Graves’ disease, and Sjögren syndrome and for use in solid organ transplantation or xenotransplantation. Currently, several CD40/CD40L-targeted compounds are at various stages of clinical investigation, including iscalimab (CFZ533, anti-CD40) (Espié
et al., 2020; Fisher et al., 2020; Kahaly et al., 2020), ravaglimab (ABBV-323, anti-CD40) (Argiriadi et al., 2019), bleselumab (ASKP1240, anti-CD40) (Goldwater et al., 2013; Anil Kumar et al., 2018; Harland et al., 2020; Vincenti et al., 2020), BI 655064 (anti-CD40) (Visvanathan et al., 2019; Jayne et al., 2021), dazodilisep (HZN4920, VIB4920, MEDI4920; fusion protein targeting CD154) (Karnell et al., 2019a), and dapirolizumab pegol (anti-CD154 pegylated Fab) (Furie et al., 2021). Ongoing research in this rapidly advancing field of anti-CD40 or anti-CD154 therapies which will continue to provide both class- and agent-specific data that will be used to assess and refine the potential role of these types of therapies. While IV administration typically prevails for the majority of compounds within this class of agents, the prolonged full RO and PD observed with SC dosing of KPL-404 in this study could represent a clinical advantage as an optional route of administration for chronic SC dosing in patients with a broad range of autoimmune diseases or in transplantation, which is advantageous over in-hospital IV dosing of anti-CD40 or anti-CD40L monoclonal antibodies.

In conclusion, the PK profile, duration of full CD40 RO, and magnitude and duration of memory immune response suppression all support the design of next-phase studies of KPL-404 and suggest that chronic KPL-404 dosing regimens using not only IV but also SC administration could be practical.
Acknowledgments

The authors thank the patients for their participation, and for making this trial possible. The authors also thank Emily Plummer, Kasia Warchol, Sujatha Muralidharan, Alistair Wheeler, Guang-Liang Jiang, Moses Njenga, Madeline Spiers, Arian Pano, and MaryAnn Mascelli.

Bioanalytical data, including serum concentrations of KPL-404, anti–KPL-404 antibodies (ADAs), and responses to KLH (anti-KLH TDAR), were generated using methods developed and validated at Immunologix Laboratories (Tampa, FL, USA). Mean free CD40 receptors on B cells were analyzed using an RO assay developed and qualified at Caprion Biosciences (Montreal, Canada) and 360biolabs (Melbourne, Australia).
Authorship Contributions

*Participated in research design:* Paolini.

*Conducted experiments:* Ziemniak, Paolini.

*Contributed new reagents or analytic tools:* Samant, Ziemniak, Paolini.

*Performed data analysis:* Samant, Ziemniak, Paolini.

*Wrote or contributed to the writing of the manuscript:* Samant, Ziemniak, Paolini.
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FOOTNOTES

*Funding: The study was funded by Kiniksa Pharmaceuticals. Under the direction of the authors, medical writing and editorial assistance were provided by Sandra Westra, PharmD and Christopher Jaworski of Peloton Advantage, LLC, an OPEN Health company, and funded by Kiniksa Pharmaceuticals.

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Disclosures: M.S. was employed by and shareholder of Kiniksa Pharmaceuticals at the time the study was conducted. J.Z. is a consultant for Kiniksa Pharmaceuticals. J.F.P. is employed by, shareholder of, and inventor on patents for Kiniksa Pharmaceuticals.

Data Availability Statement: The individual anonymized data supporting the analyses contained in the manuscript will be made available upon reasonable written request to the senior author from researchers whose proposed use of the data for a specific purpose has been approved. Data will not be provided to requesters with potential or actual conflicts of interest, including individuals requesting access for commercial, competitive, or legal purposes. Data access may be precluded for studies in which clinical data were collected subject to legal, contractual, or consent provisions that prohibit transfer to third parties. All those receiving access to data will be required to enter into a Data Use Agreement (DUA), which shall contain terms and conditions that are customary for similar agreements and similar companies in the industry.
FIGURE LEGENDS

**Fig. 1.** Pharmacokinetic profiles for IV and SC KPL-404 dose groups. IV, intravenous; LLOQ, lower limit of quantification; SC, subcutaneous; SD, standard deviation (upward bars depicted).

**Fig. 2.** CD40 receptor occupancy (RO) on B cells (whole blood) compared with baseline. IV, intravenous; SC, subcutaneous; SE, standard error (upward bars depicted).

**Fig. 3.** T-cell–dependent antibody response (TDAR) to KLH antigen challenge. Only IV cohorts were rechallenged with KLH on Day 29. IgG, immunoglobulin G; IV, intravenous; KLH, keyhole limpet hemocyanin; SC, subcutaneous; SE, standard error (upward bars depicted).

**Fig. 4.** Antidrug antibody (ADA) titers over time in 15 participants (n=8 IV; n=7 SC) with detectable ADAs. ADAs were not detectable in 23 participants (n=18 IV; n=5 SC). ADA, antidrug antibody; IV, intravenous; SC, subcutaneous; Uns, unscheduled visit.
# TABLES

## TABLE 1
Demographic and baseline characteristics of study participants

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BMI, body mass index; IV, intravenous; SC, subcutaneous.
TABLE 2
Adverse events reported by ≥5% of healthy participants who received KPL-404 IV, KPL-404 SC, and placebo\textsuperscript{a}

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<th>KPL-404 IV</th>
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<td>2 (33.3)</td>
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<td>5 (83.3)</td>
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AE, adverse event; IV, intravenous; SC, subcutaneous.

<sup>a</sup>For table readability, dashes are used to represent 0.

<sup>b</sup>Determined by site Principal Investigator as worsened in intensity of frequency after study drug exposure until the end of the study.
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<th>AUC&lt;sub&gt;0-t&lt;/sub&gt;, h*µg/mL</th>
<th>AUC&lt;sub&gt;0-inf&lt;/sub&gt;, h*µg/mL</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt;, h</th>
<th>CL or CL/F, L/h</th>
<th>Vd or Vd/F, L</th>
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AUC₀-∞, area under concentration-time curve from time 0 to infinity (defined as AUC₀-₄ + (Clast/λz), where Clast is last measurable concentration and λz is apparent terminal elimination rate constant); AUC₀-₄, area under concentration-time curve from time 0 to last measurable concentration (calculated by linear trapezoidal method when concentrations are increasing and by logarithmic trapezoidal method when concentrations are decreasing [linear up/log down trapezoidal method]; CL, clearance, where CL = Dose/AUC₀-∞ (intravenous only); CL/F, apparent clearance where CL/F = dose/AUC₀-∞ (subcutaneous only); Cₘₐₓ, maximum concentration; CV, coefficient of variation; λz, apparent terminal elimination rate constant, where λz is magnitude of slope of linear regression of log concentration versus time profile during terminal phase; tₘₐₓ, time to maximum concentration; t₁/₂, apparent terminal elimination half-life where t₁/₂ = (ln2)/λz (see Supplemental Material, Appendix S3); Vd, volume of distribution, where Vd = CL/λz (intravenous only); Vd/F, apparent volume of distribution, estimated according to Vd/F = CL/F/λz (subcutaneous only).

Values are means (CV%), except for tₘₐₓ, where median (minimum, maximum) is reported.

n=1.

Mean tₘₐₓ is 3.52 h excluding the 49 h half-life of one subject.

n = 5
Figure 1

KPL-404 Serum Concentration (μg/mL) Geometric mean ± SD

Visit Day

0.03 mg/kg IV
0.3 mg/kg IV
1 mg/kg IV
3 mg/kg IV
10 mg/kg IV
1 mg/kg SC
5 mg/kg SC

LLQ
Figure 2

Free CD40 on B cells (Mean % vs Baseline)

Visit Day

0.3 mg/kg IV
1 mg/kg IV
3 mg/kg IV
10 mg/kg IV
1 mg/kg SC
5 mg/kg SC

Full receptor occupancy (≥ 90%)

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Figure 4

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