KPL-404

KPL-404-C211

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of KPL-404 in Subjects with Moderate to Severe, Active Rheumatoid Arthritis with Inadequate Response or Intolerance to at Least One Biologic Disease-modifying Anti-rheumatic Drug or a Janus Kinase Inhibitor

Sponsor:	Kiniksa Pharmaceuticals, Ltd. Hamilton, Bermuda c/o Kiniksa Pharmaceuticals Corp. 100 Hayden Ave Lexington, MA 02421
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Protocol Number:	KPL-404-C211
Protocol Version:	Version 6.0
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SPONSOR APPROVAL SIGNATURE PAGE

Study Title:	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of KPL-404 in Subjects with Moderate to Severe, Active Rheumatoid Arthritis with Inadequate Response or Intolerance to at Least One Biologic Disease-modifying Anti-rheumatic Drug or a Janus Kinase Inhibitor
IND Number:	155,963
EudraCT Number:	2022-000169-42
Protocol Number:	KPL-404-C211
Protocol Version:	Version 6.0
Protocol Date:	28 Jun 2023

This study will be conducted in compliance with the clinical study protocol, International Council of Harmonisation (ICH) Good Clinical Practice and applicable regulatory requirements.

Sponsor's electronic signature appended to the end of this protocol.

Sponsor's Authorized Officer:

[redacted]

Kiniksa Pharmaceuticals, Ltd.
100 Hayden Ave
Lexington, MA 02421, USA

[redacted]

INVESTIGATOR'S AGREEMENT

Study Title:	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of KPL-404 in Subjects with Moderate to Severe, Active Rheumatoid Arthritis with Inadequate Response or Intolerance to at Least One Biologic Disease-modifying Anti-rheumatic Drug or a Janus Kinase Inhibitor
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I, the undersigned, am responsible for the conduct of the study at this site and affirm that:

I understand and will conduct the study according to the clinical study protocol, any approved protocol amendments, International Conference for Harmonisation (ICH) Good Clinical Practice (ICH Topic E6) and all applicable Health Authority requirements and national laws.

_____
Investigator's Name (Print)

_____ _____
Investigator's Signature Date

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role	Name	Address and Telephone Number
Responsible Physician	[redacted]	[redacted]
Drug Safety Physician	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company:
Kiniksa Pharmaceuticals, Ltd.

Name of Investigational Product: KPL-404

Name of Active Ingredient: KPL-404

Title of Study:
A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of KPL-404 in Subjects with Moderate to Severe, Active Rheumatoid Arthritis with Inadequate Response or Intolerance to at Least one Biologic Disease-modifying Anti-rheumatic Drug or a Janus Kinase Inhibitor

Study Centers: Approximately 100

Study Period:	**Phase of Development:** 2
Estimated date first subject enrolled: Q1 2022 Estimated date last subject completed: Q1 2024	

Objectives/Endpoints:

Primary Objectives:	**Primary Endpoints:**
• Cohorts 1 and 2: To evaluate the dose-response relationship as measured by safety, tolerability, and pharmacokinetics (PK) of multiple subcutaneous (SC) doses of KPL-404 versus placebo.	Cohorts 1 and 2: • Incidence of treatment-emergent adverse events (TEAEs) • Maximum serum concentration (C_{max}) • Area under the serum concentration time curve from 0 to the end of the dosing interval (AUC_{0-t})
• Cohorts 3 and 4: To evaluate the efficacy of KPL-404 versus placebo for the treatment of rheumatoid arthritis (RA).	• Cohorts 3 and 4: Change from baseline in disease activity score of 28 joints using C-reactive protein (DAS28-CRP) at Week 12
Secondary Objectives:	**Secondary Endpoints:**
• Cohorts 1 and 2: To evaluate the efficacy of multiple SC doses of KPL-404 versus placebo for the treatment of RA.	Cohorts 1 and 2: • Change from baseline in DAS28-CRP at Week 12
• Cohorts 3 and 4: To evaluate the safety, tolerability, and PK of KPL-404 versus placebo.	Cohorts 3 and 4: • Incidence of TEAEs • C_{max} • AUC_{0-t}
Other Objectives:	**Other Endpoints (All Cohorts):**
• [redacted]	[redacted]
[redacted]	[redacted]

	• Proportion of subjects achieving ACR20 responses at Week 12
	• [redacted]
	• [redacted]
	• [redacted]
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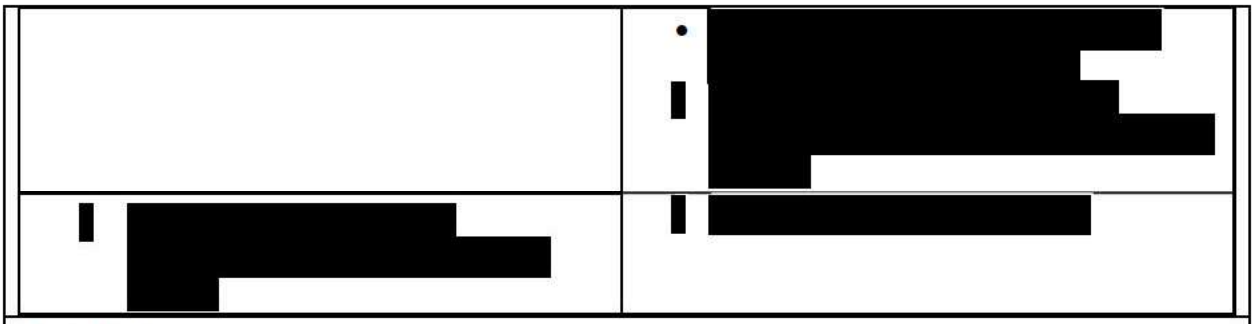

Study Design:

This is a 28-week (4-week screening period, 12-week treatment period, and 12-week safety follow-up period), multicenter, randomized, double-blind, placebo-controlled, multiple dose proof-of-concept study with PK lead-in designed to assess the safety, PK, efficacy and pharmacodynamics (PD) of KPL-404 in subjects with moderate to severe, active RA who have an inadequate response to or are intolerant to at least one biologic disease-modifying anti-rheumatic drug (bDMARD) and/or Janus kinase inhibitor (JAKi). The objectives of the study are to evaluate safety, efficacy, and PD compared with placebo across the estimated therapeutic range and to characterize PK across varying dose levels of KPL-404.

After signing the informed consent form (ICF), subjects will enter the study screening period (Day –28 up to –1), before returning for a baseline visit and administration of the first dose (Day 1). All subjects will receive SC injection of the investigational product on Day 1 at the study site. In the first 2 cohorts, subjects will be randomized in a 3:1 ratio to (Cohort 1) 2 mg/kg KPL-404 or placebo (n = 8) every 2 weeks (q2wk) or (Cohort 2) 5 mg/kg KPL-404 or placebo (n = 8) q2wk for 12 weeks.

Cohorts 1 and 2 will start sequentially, with each escalation approved after review by a Safety Review Committee (SRC), which will assess in an unblinded fashion the safety and tolerability data after all subjects complete through Week 12 and PK through Week 8 (anticipated steady state) and applicable data are available. The composition of the SRC, meeting frequency, and procedures for review and decision-making will be described in detail in the SRC Charter.

Following completion of Cohort 2, the study will enroll subjects into Cohort 3. Subjects will be randomized in a 1:1:1 ratio to receive one of the following:

- 5 mg/kg SC every week (qwk)
- 5 mg/kg SC every 2 weeks (q2wk; weekly dosing with alternating administration of KPL-404 q2wk or placebo q2wk)
- Placebo SC qwk

To maintain the blind, all subjects will return to the study site weekly. One group (5 mg/kg SC qwk) will receive active investigational product every week at each visit. One group (Placebo SC qwk) will receive placebo every week at each visit. One group (5 mg/kg SC q2wk) will alternate between receiving active investigational product and placebo.

At approximately the end of Cohort 3 enrollment, the study will enroll subjects into Cohort 4. Subjects will be randomized in a 3:2 ratio to receive one of the following:

- KPL-404 SC q4wk (600 mg loading dose at baseline followed by maintenance dosing 400 mg q4wk at Weeks 4 and 8)
- Matched Placebo (equivalent volume) SC q4wk (loading dose at baseline followed by maintenance doses at Weeks 4 and 8)

In Cohorts 3 and 4, SRC meetings will occur on a quarterly basis while enrollment is ongoing. The initial SRC meeting in Cohort 3 will occur within approximately 90 days of the start of enrollment or once 20 subjects are enrolled, whichever occurs first. All available safety and PK data will be

reviewed by the SRC at the initial meeting in Cohort 3. Subsequent meetings will prioritize review of safety data from all active cohorts. Additional details are specified in the SRC Charter.

Subjects will be observed for at least 60 minutes after the first administration and 30 minutes after subsequent administrations. If no safety concerns are identified during that time, subjects will be discharged from the study site after all study procedures have been completed. All subjects will return to the study site at all treatment and safety follow-up visits as per the Schedule of Activities for assessments of RA parameters as well as evaluations of safety, tolerability, PK, [redacted]

If a subject discontinues prematurely (i.e., before the end of treatment visit), the subject should be encouraged to complete the procedures for the end-of-treatment visit (Week 12) within approximately 2 weeks (for Cohorts 1, 2, and 3) or 4 weeks (for Cohort 4) from last dose of study drug, as well as visits thereafter through Week 24.

Number of Subjects (Planned):

- Cohorts 1–2: approximately 16 subjects
- Cohort 3: approximately 75 subjects
- Cohort 4: approximately 40 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects 18 to 80 years of age, body weight ≥ 40 kg to ≤ 140 kg, and diagnosis of RA for ≥ 3 months and fulfills the 2010 ACR/European Union League Against Rheumatism (EULAR) classification criteria for RA.

Investigational Product, Dosage, and Mode of Administration:

- Cohort 1: KPL-404, 2 mg/kg (or matching placebo) SC injection q2wk
- Cohort 2: KPL-404, 5 mg/kg (or matching placebo) SC injection q2wk
- Cohort 3:
  - 5 mg/kg SC every week (qwk)
  - 5 mg/kg SC every 2 weeks (q2wk; weekly dosing with alternating administration of KPL-404 q2wk or placebo q2wk)
  - Placebo SC qwk
- Cohort 4:
  - KPL-404 SC q4wk (600 mg loading dose at baseline followed by maintenance dosing 400 mg q4wk at Weeks 4 and 8)
  - Matched Placebo (equivalent volume) SC q4wk (loading dose at baseline followed by maintenance doses at Weeks 4 and 8)

Duration of Treatment:

Twelve weeks of double-blind, placebo-controlled study treatment.

Reference Therapy, Dosage, and Mode of Administration:

Placebo administered weekly, every other week, or monthly by SC injection.

Statistical Methods:

Randomization will be stratified by available documented evidence of prior inadequate response to ≤ 1 versus ≥ 2 classes of advanced targeted therapy (bDMARD or tsDMARD: e.g., TNF inhibitors, IL-6 receptor inhibitors, T-cell costimulatory inhibitors, anti-CD-20 antibodies, JAK inhibitors). For

efficacy analysis, a 2-sided type 1 error rate of 0.05 will be used if applicable. Details about all statistical analyses will be specified in the statistical analysis plan (SAP).

Sample size estimation:

The sample size for Cohorts 1 and 2 is based on safety and PK considerations. The sample size for Cohort 3 is based on a 2-sample t-test assuming an improvement in DAS28-CRP change from baseline for the KPL-404 being 1.2 points better than placebo (improvement for placebo = 1.0 point, standard deviation = 1.3). If 21 subjects in each of the 3 treatment arms (KPL-404 5 mg/kg qwk, KPL404 5 mg/kg q2wk, and placebo) complete 12 weeks of DAS28-CRP assessments, the study provides 83% power for the treatment comparison with 2-sided 0.05 type 1 error. In order to account for an anticipated discontinuation rate of 16%, approximately 25 subjects per arm (a total of approximately 75 subjects) are required to enroll in Cohort 3 for the study to achieve 21 completers per arm. The sample size for Cohort 4 is based on a 2-sample t-test assuming an improvement in DAS28-CRP change from baseline for the KPL-404 being 1.3 points better than placebo (improvement for placebo = 1.0 point, standard deviation = 1.3). Enrollment of 22 subjects into the KPL-404 arm and 14 subjects into the placebo arm (i.e., 3:2 randomization ratio) allows 80% power for the treatment comparison with 2-sided 0.05 type 1 error if all subjects complete 12 weeks of DAS28-CRP assessments. In order to account for an anticipated discontinuation rate of 10%, approximately 24 subjects (KPL-404) and 16 subjects (placebo) for a total of approximately 40 subjects are required to enroll under Cohort 4.

Analyses of efficacy:

For Cohorts 1 and 2, only descriptive statistics and listings will be produced for all efficacy parameters. No formal statistical testing for efficacy will be performed.

For Cohorts 3 and 4, an analysis of covariance (ANCOVA) model will be used to compare the change from baseline in DAS28-CRP at Week 12 for each of the KPL-404 dose groups and placebo. Baseline value and randomization stratification factor will be included as covariates in the ANCOVA model. No testing between the two KPL-404 dose groups in Cohort 3 will be conducted. ACR response rates at Week 12 between each of the KPL-404 dose groups and placebo will be compared using Cochran-Mantel- Haenszel (CMH) test adjusted by stratification factor. In addition, logistic regression models may be produced including key baseline characteristics as covariates in addition to treatment.

Interim analysis:

An interim analysis may be conducted to support internal decision-making, for example, when at least 50% of subjects in Cohort 3 have completed the 12-week treatment period. The Cohort 3 interim analysis may include cumulative safety, tolerability, PK, [redacted], clinical response (e.g., DAS28-CRP), and [redacted]. Selected Kiniksa personnel will be unblinded to the interim analysis. The data from the interim analysis will not be communicated to blinded study team personnel at the clinical research organization, investigational sites, or enrolled subjects until all subjects have completed the study and database lock has been achieved. Details of the individuals who will see group-level unblinded data will be provided in the Unblinding Plan. Further details regarding the interim analysis will be provided in the SAP.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AUC	Area under the curve
bDMARD	Biologic Disease-Modifying Anti-Rheumatic Drug
[redacted]	[redacted]
C_{max}	Maximum concentration
[redacted]	[redacted]
CRO	Clinical research organization
CRP	C-reactive protein
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
DAS28-CRP	Disease Activity Score of 28 Joints using C-Reactive Protein
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	End of study
EOT	End-of-Treatment
EULAR	European Union League Against Rheumatism
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	International Ethics Committee
IMP	Investigational medicinal product
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviation or Specialist Term	Explanation
JAKi	Janus kinase inhibitor
KLH	Keyhole limpet hemocyanin
[redacted]	[redacted]
MTX	Methotrexate
NOAEL	No-observed-adverse-effect level
PD	Pharmacodynamics
PGA	Patient global assessment
PhGA	Physician global assessment
PK	Pharmacokinetics
q2wk	Every 2 weeks
qwk	Once weekly
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RO	Receptor occupancy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
[redacted]	[redacted]
[redacted]	[redacted]
SJC	Swollen Joint Count
SRC	Safety Review Committee
TDAR	T-cell-dependent antibody response
TEAEs	Treatment-emergent adverse events
TJC	Tender Joint Count
TMDD	Target-mediated drug disposition
tsDMARDS	Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug
ULN	Upper Limit of Normal
VAS	Visual analog scale

4. INTRODUCTION

4.1. Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology. The hallmark of RA is an inflammatory process manifested by persistent symmetric polyarthritis of synovial joints, which can ultimately lead to bone erosions, deformity, and disability (McInnes et al, 2011). Left untreated, or inadequately treated, progressive functional impairment with increasing disability occurs, leading to decreased ability to perform activities of daily living resulting in a reduction in quality of life. The prevalence of RA in the general population is approximately 1% and increases with age in both sexes, with women being more prone to developing RA than men. Standard-of-care treatment includes early therapy with disease-modifying anti-rheumatic drug (DMARDs), including conventional synthetic DMARDs (csDMARDs) (e.g., methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide). In the last 2 decades, targeted biological DMARDs (bDMARDs) have revolutionized the treatment paradigm for RA, in which therapy is optimized until clinical remission or at minimum low disease activity is achieved. The bDMARDs have greatly improved the clinical, functional, and radiographic outcomes for patients with RA (Smolen et al, 2017). Despite a wide therapeutic armamentarium of bDMARDs, a blockade of any single cytokine or cellular subset has not shown control of disease in all RA patients. In randomized controlled studies and clinical practice, approximately 30% to 40% of treated patients show inadequate response to bDMARDs, fail to maintain good response over time, or experience adverse events (AEs) leading to treatment withdrawal (Favalli et al, 2016). These patients with inadequate response or intolerance to one or more bDMARDs, in many of whom multiple csDMARDs have previously failed, have few treatment options, and treatment of the disease in this population remains a crucial unmet need in the management of RA.

Studies have shown that patients refractory to specific bDMARDs might benefit from therapy with a different mechanism of action (Emery et al., 2008; Genovese et al, 2018). A recent study indicates that a switch in mechanism of action (from a Janus kinase inhibitor [JAKi] to a tumor necrosis factor inhibitor, or vice versa) in non-responders and incomplete responders leads to improvements in disease activity 3 to 6 months after randomization to study medication, with minimal risk of flare and without an increase in clinically meaningful adverse events (Fleischmann et al, 2020).

The CD40-CD40L costimulatory pathway is implicated in various autoimmune diseases. Numerous CD40-CD40L-mediated inflammatory reactions, such as induction of proinflammatory cytokines and upregulation of costimulatory activity of dendritic cells and monocytes/macrophages, are known to be important in the pathogenesis of RA (Berner et al, 2000). The pathway is thought to play a role in the pathogenesis of RA by stimulating autoantibody synthesis, resulting in profound inflammation. However, the role of the pathway in RA has yet to be fully elucidated (Guo et al, 2017).

Results in clinical studies have not yet confirmed the role of CD40/CD40L pathway inhibition in RA. Visvanathan, et al. (2019) reported a Phase 2 placebo-controlled, randomized clinical study of an anti-CD40 monoclonal antibody in which clinical improvements were observed relative to placebo, although the primary endpoint did not achieve statistical significance. However, a study

of an IV injectable CD40L (CD154 antagonist, (Albulescu, et al, 2018) reported decreased disease activity with at least low level of disease activity in 50% to 70% of patients.

Additional information is available in the Investigator's Brochure (IB).

4.2. Study Rationale

The safety, pharmacokinetics (PK), and pharmacodynamics (PD) of KPL-404 have been assessed in a single ascending-dose study in healthy subjects (KPL-404-C101). The clinical development plan is designed to focus next on assessing safety, tolerability, PK (primary objective), and efficacy (secondary objective) of KPL-404 with multiple-dose administration, initially with two ascending-dose cohorts: Cohort 1 (2 mg/kg dose level vs. placebo), administered subcutaneously (SC) on alternate weeks (q2wk), and Cohort 2 (5 mg/kg dose level vs. placebo SC q2wk). Cohort 3 is designed to assess the comparative efficacy (primary objective) as well as the safety, tolerability, and PK (secondary objectives) of KPL-404 using the weight-based 5 mg/kg SC dose level administered either weekly or biweekly versus placebo over 12 weeks. Cohort 4 is designed to assess the comparative efficacy, safety, tolerability, and PK of fixed-mg dose KPL-404 (400 mg) administered SC monthly versus placebo. Efficacy will be assessed using the primary endpoint, change from baseline in disease activity score of 28 joints using C-reactive protein (DAS28-CRP) at 12 weeks.

4.3. Dose Justification

4.3.1. Cohorts 1 and 2 Dose Justification

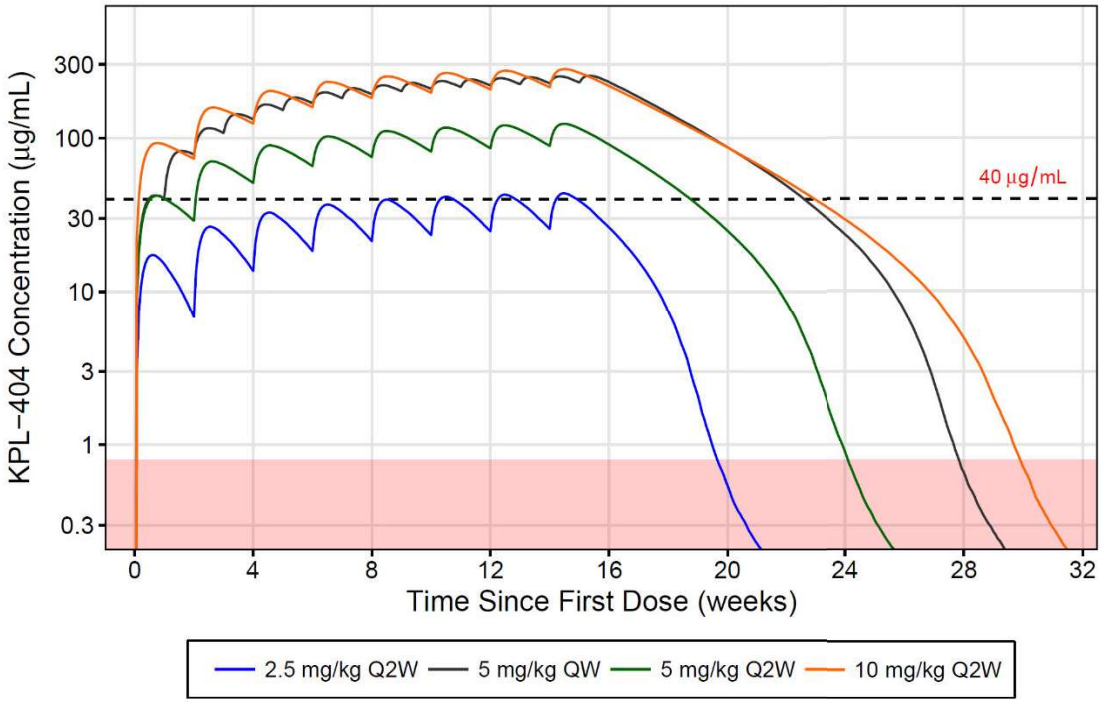
The Cohort 1 starting dose was selected based on the following factors.

1. Pharmacodynamics: Analysis of receptor occupancy (RO) data from study KPL-404-C101 demonstrated full CD40 RO (≥ 90%) saturation with varying durations across the evaluated dose levels. For IV doses (0.3, 1, 3, and 10 mg/kg), full CD40 RO was maintained through Days 2, 9, 29, and 71, respectively. For SC doses (1 and 5 mg/kg SC), full CD40 RO was maintained through Days 9 and 43, respectively. Analysis of the T-cell-dependent antibody response (TDAR) to keyhole limpet hemocyanin (KLH) demonstrated that single IV doses of 1, 3, and 10 mg/kg completely suppressed TDAR to primary KLH challenge through Days 9, 36, and 57 (last time point analyzed), respectively. Similarly, single SC doses of 1 and 5 mg/kg completely suppressed TDAR to primary KLH challenge through Days 9 and 29 (last time point analyzed), respectively, justifying a bi-weekly dosing frequency for all dose levels to be studied.
2. Safety Profile: The safety profile of the single ascending-dose study in healthy subjects (KPL-404-C101): single doses up to 10 mg/kg IV and 5 mg/kg SC were assessed. There were no deaths or related serious adverse events (SAEs), the only serious event being a patellar fracture related to a fall. There were no AEs observed that would limit dosing.
3. Pharmacokinetics: To evaluate optimal dosing regimens for Phase 2 clinical studies, a population PK model was developed using KPL-404 concentration-time data from healthy volunteers in Study KPL-404-C101. This population PK model simulated PK profiles for dose levels of 2.5, 5, and 10 mg/kg SC administered q2wk and for the dose level of 5 mg/kg SC administered every week (qwk) (Figure 1).

The model assumed a target mean trough concentration (C_{trough}) of 40 µg/mL as the preliminary estimate for a minimum efficacious plasma concentration (C_{eff}), consistent with the threshold established for similar assets in this class of anti-CD40 monoclonal antibody therapeutics (Ulrich 2018, Fisher 2020). Results from the simulations suggested that steady state concentrations would be achieved at/after approximately 8 weeks in all SC scenarios tested. Mean C_{trough} were predicted to be > 40 µg/mL for all SC dose levels examined when administered qwk. Mean C_{trough} were predicted to be > 40 µg/mL for KPL-404 dose levels ≥ 5 mg/kg SC when administered q2wk.
The simulated PK profiles for KPL-404 2.5 mg/kg q2wk had a mean maximum serum concentration (C_{max}) and an area under the serum concentration-time curve from time 0 to the end of first dosing interval ($AUC_{0-\tau}$) of 17.4 µg/mL and 3971.1 µg*h/mL, respectively, and increased to 44.2 µg/mL and 11748 µg*h/mL, respectively, at steady state. The mean accumulation ratio was approximately 3-fold following multiple dose administration and appeared to be consistent across all the dose range tested.

4. Safety Margin: KPL-404 was evaluated in 8-week and 26-week repeat-dose toxicity studies in Cynomolgus monkeys. The only adverse findings in the studies were an early termination on Day 143 of one female at 97 mg/kg SC after exhibiting clinical signs of poor health for several days, and another female administered 97 mg/kg SC that exhibited bilateral uveitis associated with a small blood clot in the anterior chamber of the eye. The no-observed-adverse-effect level (NOAEL) was 12-fold higher than the starting dose in this Phase 2 study, and the systemic exposure associated with the NOAEL by the SC route was approximately 10.6-fold higher. This provides an adequate safety margin between the proposed dose range for this study relative to the nonclinical safety findings.

Figure 1: Predicted Plasma Concentration of KPL-404 by Dose Level Following Weekly and Biweekly Subcutaneous Administration



Abbreviations: QW = qwk, every week; Q2W = q2wk, every 2 weeks.
Note: Shaded region represents lower limit of quantitation.

4.3.2. Cohort 3 Dose Justification

Cohorts 1 and 2 represent the ascending-dose portion of this study, and Cohort 3 represents the proof-of-concept portion, using the highest investigated dose level (5 mg/kg SC) from the ascending-dose investigation. Cohort 3 subjects will be randomized in a 1:1:1 ratio to receive KPL-404 5 mg/kg SC q2wk, KPL-404 5 mg/kg SC qwk, or placebo SC qwk. While the 5 mg/kg SC qwk administration frequency will not have been directly investigated in Cohorts 1 or 2, this dose level and exposure will have been investigated, and the weekly administration frequency will allow the Sponsor to understand increased KPL-404 exposure without administering larger dose levels all at once but rather by increasing dosing frequency from q2wk to qwk. To date, KPL-404 has been well tolerated. By maintaining the dose level and increasing the frequency, the injected volume and protein amounts will match those from Cohort 2 and are expected to represent known safety risks, such as injection site reactions. Additionally, pharmacokinetic modeling, using concentration-time data from study KPL-404-C101, demonstrated that expected exposures and C_{eff} are similar for 5 mg/mg SC qwk and 10 mg/kg SC q2wk (Figure 1).

4.3.3. Cohort 4 Dose Justification

Cohort 4 subjects will be randomized in a 3:2 ratio to receive fixed-mg dosing of KPL-404 SC q4wk (a 600 mg SC [or matching placebo] loading dose at the Baseline Visit followed by maintenance dosing of 400 mg SC [or matching placebo] at Week 4 and Week 8). The objective is to explore the efficacy of KPL-404 at lower trough concentrations than Cohort 3, approximating the minimum level required for T-cell-dependent antibody response suppression, as seen in Phase 1. This dosing regimen (i.e., a fixed-mg dose rather than weight-based dose) represents a different approach as compared to Cohort 3, and it does not represent a dose escalation. Rather, this fixed-mg (400 mg) administered dose provides a centered administered dose level, based upon early PK data showing a relatively neutral effect of weight on the PK of KPL-404, as would be expected given that monoclonal antibodies are large macromolecules with a volume of distribution restricted to the plasma. The 400 mg administered dose is 5 mg/kg for an average 80 kg subject. The 600 mg loading dose is intended to facilitate reaching steady state trough levels more rapidly, based on PK modeling. This regimen, based on the same modeling, is expected to provide peak plasma concentrations no greater than those projected in Cohorts 2 and 3 and trough plasma concentrations lower than the 5 mg/kg q2wk dose level in Cohort 2.

4.4. Benefit/Risk Assessment

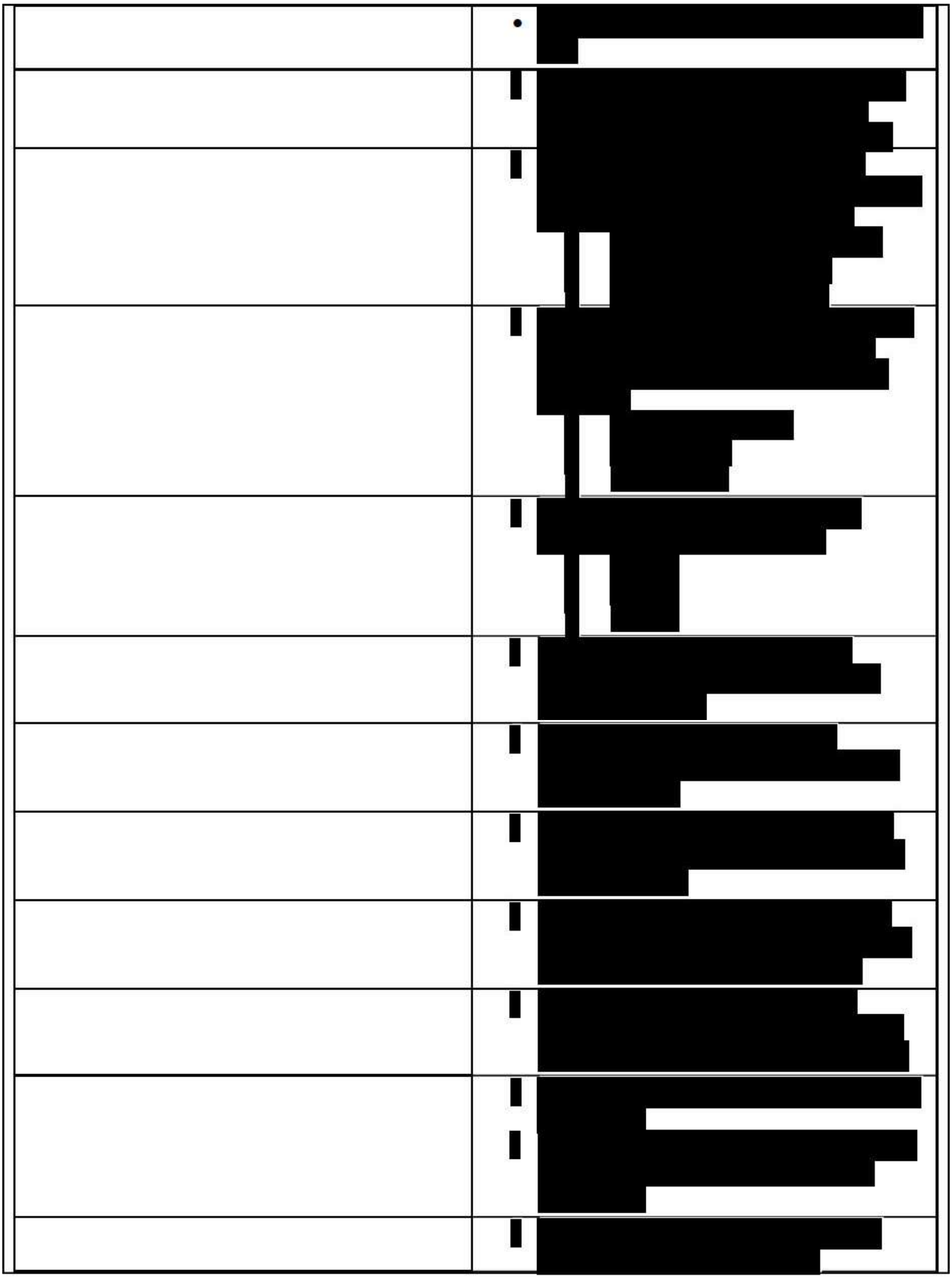
Nonclinical studies and the completed Phase 1 study have all provided safety information that support plasma concentrations and exposures up to those associated with the 5 mg/kg SC weekly dose level. Given the population of subjects who have failed to achieve an adequate response to existing biological products, PK, and safety data from the Phase 1 first-in-human study (KPL-404-C101), and nonclinical data, the Sponsor believes that KPL-404 has the potential to improve outcomes in this study population, with low risk of significant adverse events.

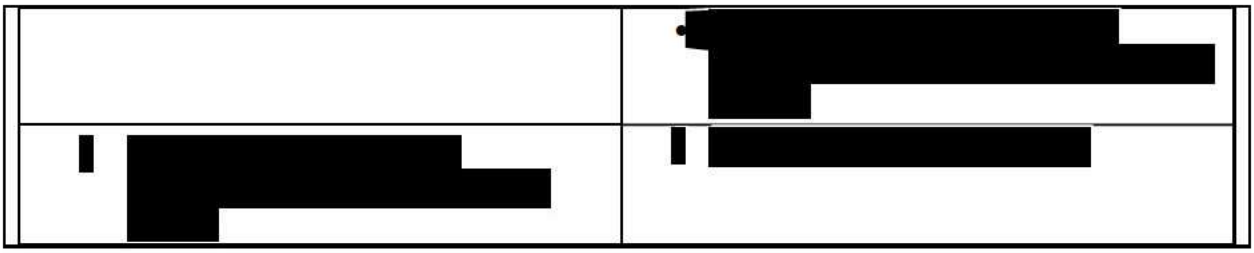
5. STUDY OBJECTIVES AND ENDPOINTS

See Section 10 and Section 11.4 for detailed explanations of assessments and efficacy endpoints, respectively.

Objectives/Endpoints:

Primary Objectives:	**Primary Endpoints:**
• Cohorts 1 and 2: To evaluate the dose-response relationship as measured by safety, tolerability, and pharmacokinetics of multiple subcutaneous (SC) doses of KPL-404 versus placebo.	Cohorts 1 and 2: • Incidence of treatment-emergent adverse events (TEAEs) • Maximum serum concentration (C_{max}) • Area under the serum concentration time curve from 0 to the end of the dosing interval (AUC_{0-t})
• Cohorts 3 and 4: To evaluate the efficacy of KPL-404 versus placebo for the treatment of rheumatoid arthritis (RA).	• Cohorts 3and 4: Change from baseline in disease activity score of 28 joints using C-reactive protein (DAS28-CRP) at Week 12
Secondary Objectives:	**Secondary Endpoints:**
• Cohorts 1 and 2: To evaluate the efficacy of multiple SC doses of KPL-404 versus placebo for the treatment of RA.	Cohorts 1 and 2: • Change from baseline in DAS28-CRP at Week 12
• Cohorts 3 and 4: To evaluate the safety, tolerability, and pharmacokinetics (PK) of KPL-404 versus placebo.	Cohorts 3 and 4: • Incidence of TEAEs • C_{max} • AUC_{0-t}
Other Objective:	**Other Endpoints (All Cohorts):**
• To [redacted]	[redacted]
	• [redacted]
	• Proportion of subjects achieving ACR20 responses at Week 12





6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

Figure 2 displays the overall schema for the study. A detailed outline of procedures and activities is provided in Appendix 1.

This is a 28-week (up to 4-week screening period, 12-week treatment period, and 12-week safety follow-up period), multicenter, randomized, double-blind, placebo-controlled, multiple dose proof-of-concept study with PK lead-in designed to assess the safety, PK, efficacy, and PD of KPL-404 in subjects with moderate to severe, active RA who have inadequate response to or are intolerant to at least one biologic disease-modifying anti-rheumatic drug (bDMARD) or JAKi. The objectives of the study are to evaluate safety, efficacy, and PD of KPL-404 compared with placebo across the estimated therapeutic range and to characterize PK across varying dose levels of KPL-404.

After signing the informed consent form (ICF), subjects will enter the screening period (Day –28 to –1), before returning for the baseline visit and administration of the first dose (Day 1). Subjects can be rescreened only once, at the discretion of the Investigator and with approval from the medical monitor. Abnormal laboratory values may in certain cases be repeated with the approval of the medical monitor without the need for rescreening. If a subject is rescreened, a new subject number will be provided, and laboratory assessments can be repeated once where appropriate.

All randomized subjects will receive a SC injection of the investigational product (IP) on Day 1 at the study site. In the first 2 cohorts, subjects will be randomized in a 3:1 ratio to escalating doses as follows:

- Cohort 1: 2 mg/kg KPL-404 or placebo every 2 weeks (q2wk) (n = 8)
- Cohort 2: 5 mg/kg KPL-404 or placebo q2wk (n = 8)

Cohorts 1 and 2 will start sequentially, with each escalation approved by a Safety Review Committee (SRC), which will assess in an unblinded fashion the safety, and tolerability data after all subjects complete through Week 12 and PK through Week 8 (anticipated steady state) and applicable data are available. The composition of the SRC, meeting frequency, and procedures for review and decision-making will be described in detail in the SRC Charter.

Following completion of Cohort 2, new subjects will enter Cohort 3. Subjects will be randomized in a 1:1:1 ratio to receive:

- 5 mg/kg SC every week (qwk)
- 5 mg/kg SC every 2 weeks (q2wk; weekly dosing with alternating administration of KPL 404 q2wk or placebo q2wk)
- Placebo SC qwk

To maintain the blind, all subjects will return to the study site weekly. One group (5 mg/kg SC qwk) will receive active investigational product every week at each visit. One group (Placebo SC qwk) will receive placebo every week at each visit. One group (5 mg/kg SC q2wk) will alternate between receiving active investigational product and placebo.

At approximately the end of Cohort 3 enrollment, the study will enroll subjects into Cohort 4. Subjects will be randomized in a 3:2 ratio to receive one of the following:

- KPL-404 SC q4wk (600 mg loading dose at baseline followed by maintenance dosing 400 mg q4wk at Weeks 4 and 8)
- Matched Placebo (equivalent volume) SC q4wk (loading dose at baseline followed by maintenance dose at Weeks 4 and 8)

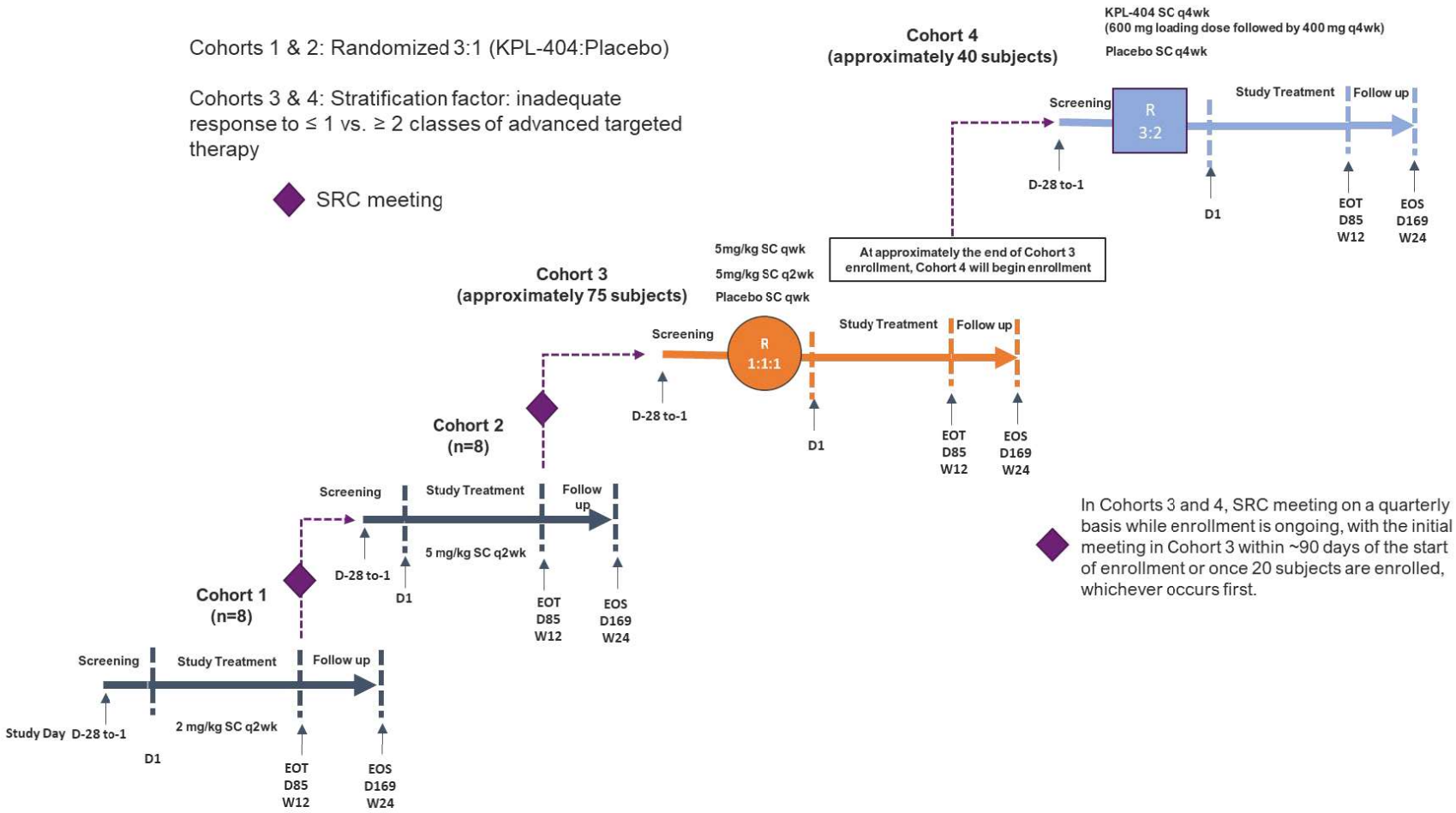
In Cohorts 3 and 4, SRC meetings will occur on a quarterly basis while enrollment is ongoing. The initial SRC meeting in Cohort 3 will occur within approximately 90 days of the start of enrollment or once 20 subjects are enrolled, whichever occurs first. All available safety and PK data will be reviewed by the SRC at the initial meeting. Subsequent meetings will prioritize review of safety data from all active cohorts. Additional details are specified in the SRC Charter.

Subjects will be observed for at least 60 minutes following the first administration and 30 minutes after subsequent administrations. If no safety concerns are identified during that time, subjects will be discharged from the study site after all study procedures have been completed. All subjects will return to the study site at all treatment and safety follow-up visits as per the Schedule of Activities (Appendix 1) for assessments of RA parameters as well as evaluations of safety, tolerability, PK, [redacted].

If a subject discontinues treatment prematurely (i.e., before the end-of-treatment visit), the subject should be encouraged to complete the procedures for the end-of-treatment visit (Week 12) within approximately 2 weeks (for Cohorts 1, 2, and 3) or 4 weeks (for Cohort 4) from last dose of study drug, as well as visits thereafter through the Week 24 visit, as per the Schedule of Activities.

At the end of the 12-week treatment period, all subjects will be followed up for safety and longevity of any treatment effect for an additional 12 weeks until the EOS visit (Week 24). An adverse event that occurs prior to study treatment administration should be recorded in the eCRF only if it is an SAE or is an AE related to a study procedure. All AEs/SAEs that occur after the first administration of study treatment through the EOS visit, whether or not they are related to the study, must be recorded in the eCRF. For subjects who terminate study participation early (i.e., before the Week 24 visit), the Investigator will report any SAEs that are reported to the Investigator within 30-day post-last dose administration.

Figure 2: Study Schema for KPL-404-C211



Abbreviations: D = day; EOS = end of study; EOT = end of treatment; PBO = placebo; qwk = every week; q2wk = every 2 weeks; SC = subcutaneous; SRC = Safety Review Committee; W = week.
NOTE: Advanced targeted therapies include bDMARDs and tsDMARDs, for example, TNF inhibitors, IL-6 receptor inhibitors, T-cell costimulatory inhibitor, anti-CD-20 antibody, and JAK inhibitors.

6.2. Number of Subjects

The study plans to enroll approximately 16 subjects in Cohorts 1 and 2, approximately 75 subjects in Cohort 3, and approximately 40 subjects in Cohort 4, across approximately 100 study sites.

6.3. Treatment Assignment

All subjects will be assigned to randomized study drug as per standard operating procedures defined by the Sponsor or designee.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. For further details on blinding, refer to Section 8.5. The date and reason that the blind was broken must be recorded.

6.4. Safety Review Committee

The SRC will consist of expert clinicians, pharmacologists, and/or statisticians. Any individual who has any affiliation with Kiniksa will be "firewalled" such that they take no part in operational activities and have no project-related communication with the study team. The SRC will review cumulative safety and PK data.

After all subjects in Cohorts 1 and 2 complete treatment through Week 12 and applicable data are available for review, an SRC meeting will be held to review unblinded safety and PK data to support dose escalation to the next cohort. Further details will be outlined in the SRC Charter.

In Cohorts 3 and 4, SRC meetings will occur on a quarterly basis while enrollment is ongoing. The initial SRC meeting in Cohort 3 will occur within approximately 90 days of the start of enrollment or once 20 subjects are enrolled, whichever occurs first. All available safety and PK data will be reviewed by the SRC at the initial meeting. Subsequent meetings will prioritize review of safety data from all active cohorts. Additional details are specified in the SRC Charter, and the charter may be amended as necessary for the SRC to review safety and PK data.

In the event of any concern regarding subject safety or risk mitigation, the SRC may contact the Sponsor Head of Global Medical Safety for additional discussion in order to finalize the decision. However, the Sponsor Head of Global Medical Safety will not be given access to subject-level unblinded data. Details of the review process will be defined in the SRC Charter.

6.5. Stopping Rules

A subject may be discontinued from treatment due to any Grade 3 (severe) or any Grade 4 (life-threatening) TEAE, regardless of causality.

For the study, enrollment in a cohort will be paused for review under any of the circumstances below:

- Two subjects develop the same Grade 3 TEAE
- One subject has a Grade 4 (life-threatening) or Grade 5 (fatal) TEAE

Any such review will be conducted by the SRC in conjunction with the Sponsor Head of Global Medical Safety and supported by additional clinical experts as appropriate. At the conclusion of the review, the study will resume (or otherwise) upon the approval of the Sponsor Head of Global Medical Safety.

6.6. Study Termination or Temporary Suspension

The Sponsor reserves the right to temporarily suspend or terminate this study, in part or whole, at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Noncompliance that might significantly jeopardize the validity or integrity of the study
- Recommendation to suspend or terminate the study by independent body such as a health authority
- Sponsor decision to terminate the study

Where required by applicable regulations, the Investigator or head of the medical institution must inform the Institutional Review Board (IRB)/International Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IECs when applicable) will be obtained prior to resuming the study.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

For inclusion in the study, subjects must fulfill all of the following criteria:

1. Voluntarily sign and date an informed consent form, approved by an Independent Ethics Committee/Institutional Review Board, prior to the initiation of any screening or study-specific procedures.
2. Adult male or female, age 18 to 80 years of age (inclusive) at the time of signing the informed consent form.
3. Body weight ≥ 40 to ≤ 140 kg for all cohorts.
4. Diagnosis of RA for ≥ 3 months fulfilling the 2010 American College of Rheumatology (ACR)/European Union League Against Rheumatism (EULAR) classification criteria for RA and that is categorized as ACR RA functional Class 1-3.
5. Treated with a biological disease-modifying anti-rheumatic drug (bDMARDs) AND/OR Janus kinase inhibitor (JAKi) therapy for RA for ≥ 3 months and had inadequate response or had to discontinue bDMARD AND/OR JAKi therapy due to intolerance or toxicity, regardless of treatment duration.
6. Currently receiving csDMARD therapy ≥ 3 months and on a stable dose for ≥ 4 weeks before the first dose of investigational product.
    a. The following csDMARDs are allowed: oral or parenteral methotrexate ([MTX]; 7.5 to 25 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and leflunomide (≤ 20 mg/day).
    b. A combination of up to 2 background csDMARDs is allowed, except the combination of MTX and leflunomide.
7. Meets all of the following disease activity criteria:
    a. Six or more swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at screening and baseline visits;
    b. Level of high-sensitivity C-reactive protein ≥ 3 mg/L (≥ 0.3 mg/dL) by central laboratory;
    c. Documented seropositivity for serum RF and/or ACPA (> ULN) at Screening or by prior laboratory evaluation.
8. Has completed a locally approved authorized COVID-19 vaccine regimen according to local guidance at least 3 weeks before the first dose of investigational product.
9. Must have discontinued all bDMARDs or JAKi prior to the first dose of investigational product. The washout period for bDMARDs or JAKi prior to the first dose of investigational product is specified below. For bDMARDs or JAKi not listed below, washout should be at least 5 times the mean elimination half-life of a drug:
    d. ≥ 4 weeks for etanercept;
    e. ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab, and sarilumab;

f. ≥ 1 year for rituximab;
g. ≥ 2 weeks for JAKi (either investigational or commercially available treatment).

10. For potential participants already receiving opiate analgesia, the dose must be limited to no greater than 50 mg oral-morphine-equivalents per day (50 MME/day). .
11. If female, must be either postmenopausal (defined as no menses for 12 months without other medical cause), permanently surgically sterile, or, for women of childbearing potential, must practice at least one highly effective method of contraception that is effective from study Day 1 through at least 30 days after the EOS visit (additional local requirements may apply). Sexually active female subjects must be:

- Nonpregnant, nonlactating, and having agreed to use a highly effective method of contraception from the screening visit until 30 days after EOS visit.
    - Note: highly effective methods of contraception include:
        - hormonal contraceptives associated with inhibition of ovulation (stable dose for at least 4 weeks prior to first dose of investigational product)
        - intrauterine device
        - intrauterine system
        - bilateral tubal occlusion
        - vasectomized male partner
        - abstinence from heterosexual intercourse

12. Sexually active male subjects must have documented vasectomy or must agree to use a condom or highly effective method of contraception as defined above with their partners of childbearing potential from first dose of investigational product until 30 days after EOS visit.
13. Male subjects must agree to refrain from donating sperm from first dose until 30 days after the last study drug administration. Female subjects must agree to refrain from donating eggs from first dose of investigational product until 30 days after EOS visit.
14. Female subjects of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) test at the screening visit and negative urine pregnancy test on Day 1.

7.2. Subject Exclusion Criteria

The subject may not enter the study if ANY of the following apply:

1. Prior exposure to any other anti-CD40/CD40L agent.
2. Inadequate response to 5 or more classes of advanced targeted therapies (bDMARD or tsDMARD; e.g., TNF inhibitors, IL-6 receptor inhibitors, T-cell costimulatory inhibitors, anti-CD-20 antibodies, JAK inhibitors). This does not include prior discontinuation due to drug intolerance.

3. Injectable corticosteroids (including intra-articular) or treatment with > 10 mg/day dose oral prednisone or equivalent within 8 weeks prior to randomization. (Note: Concomitant treatment with nonsteroidal anti-inflammatory drugs, acetaminophen, oral corticosteroids [equivalent to prednisone ≤ 10 mg/day], or inhaled corticosteroids at a stable dose ≥ 4 weeks prior to baseline for stable medical conditions is allowed and should be kept at a stable dose throughout the study.)
4. Has received any investigational product within 30 days or 5 half-lives, if the half-life is known, of the investigational product (whichever is longer) before the first dose of investigational product.
5. Concurrent enrollment in another clinical study, with the exception of observational studies.
6. Major surgery within 8 weeks prior to screening or planned major surgery within 6 months after baseline.
7. Transplanted organs (except corneal transplant performed more than 3 months prior to baseline).
8. Receipt of live (attenuated) vaccine within the 4 weeks before baseline or expected need of live vaccination during study participation including 4 weeks after the last dose of investigational product.
9. History of any arthritis with onset prior to age 16 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and nonradiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms]). Current diagnosis of secondary Sjogren's syndrome is permitted.
10. Clinically significant active infection, including signs/symptoms suggestive of infection, any significant recurrent or chronic infection (including positive hepatitis C virus antibody), or any episode of infection requiring hospitalization or treatment with IV antibiotics within 12 weeks before screening, or treatment with oral anti-infectives within 14 days prior to the first dose of investigational product. Subjects with any opportunistic infection within 6 months before screening will be excluded from the study.
11. Presence of symptoms indicative of COVID-19 infection (according to the opinion of the Principal Investigator) unless a PCR test for COVID-19 has been reported as negative within the previous 7 days or is acquired prior to randomization.
12. Subjects at a high risk of infection (e.g., history of hereditary or acquired immune deficiency disorder), a history of an infected joint prosthesis at any time with that prosthesis still in situ, leg ulcers, indwelling urinary catheter, or persistent or recurrent chest infections.
13. Subjects testing positive for human immunodeficiency virus infection. HIV test will not be required if a subject had a previously documented negative HIV result within 8 weeks screening.

14. Subjects with chronic active hepatitis B infection as defined below will be excluded from the study:
    a. Hepatitis B surface antigen positive.
    b. Hepatitis B anti-core antibody positive but anti-surface antibody negative.
15. Positive (or 2 indeterminate) QuantiFERON® test results unless confirmation of prior completion of appropriate treatment for latent TB and no evidence of active TB (when possible, test should be performed at least 4 weeks after receiving an mRNA COVID-19 vaccine).
16. History of thromboembolic event, a significant risk of future thromboembolic events (defined as a definitive diagnosis of thrombophilia OR an unstable condition associated with an increased incidence of thrombosis, such as atrial fibrillation or anti-phospholipid syndrome). All history of thrombosis should be approved by the medical monitor.
17. Laboratory values meeting the following criteria within the screening period (prior to randomization) of investigational product:
    a. Serum aspartate aminotransferase > 3 × upper limit of normal (ULN);
    b. Serum alanine aminotransferase > 3 × ULN;
    c. Total bilirubin > 2 × ULN;
    d. Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73 m^2;
    e. Absolute neutrophil count < 1,500/µL;
    f. Hemoglobin < 9 g/dL;
    g. Total white blood cell count < 2,500/µL;
    h. Platelet count < 150,000/µL;
    i. Absolute lymphocyte count < 800/µL.
18. Known history of allergy or reaction to any component of the KPL-404 or placebo formulation and/or other products in the same class.
19. History of cancer within the last 5 years from screening, except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured.
20. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
21. History of any of the following cardiovascular conditions:
    a. Moderate to severe congestive heart failure (New York Heart Association class III or IV);
    b. Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
    c. Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
22. Clinically relevant or significant electrocardiogram (ECG) abnormalities, including ECG with QT interval corrected for heart rate (QTc) > 500 msec.

23. Any condition that, in the opinion of the Investigator, could interfere with evaluation of the investigational product or interpretation of subject safety or confound the results of the study.

7.3. Treatment Discontinuation, Withdrawal of Consent, and Lost to Follow-Up Criteria

Subjects are free to discontinue study treatment or withdraw consent from the study at any time, without prejudice to their medical care.

Treatment Discontinuation

Subjects will be discontinued from study treatment if any of the following criteria are met.

- Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator
- Noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator
- Pregnancy
- Thromboembolic event
- Anaphylactic reaction related to investigational medicinal product (IMP)
- Severe infection (severe AE or SAE) or opportunistic infections (regardless of severity/seriousness)
- Any clinically relevant sign or symptom, including a RA flare requiring prohibited study medications(s), that in the opinion of the Investigator warrants subject discontinuation from study treatment.

Upon decision to discontinue treatment, the Sponsor should be notified immediately. If a subject is prematurely discontinued from IP (study treatment), he or she should complete the end of treatment (EOT) visit (Week 12) within approximately 2 weeks (for Cohorts 1, 2, and 3) or 4 weeks (for Cohort 4) from last dose of study drug, as well as visits thereafter through Week 24, as per the Schedule of Activities, for all safety and efficacy assessments. The Investigator may also request that the subject return for additional visits.

Withdrawal of Consent

Subjects are free to withdraw consent from the study at any time, without prejudice to their medical care. Only study subjects who withdraw consent will be considered discontinued from the study (as differentiated from treatment discontinuation).

If a subject is discontinued from the study (withdraws consent), the Sponsor will be notified, and the date and reasons for the study discontinuation / withdrawal of consent will be documented in the subject's electronic case report form (eCRF).

Lost to Follow-Up

Subjects will be defined as lost to follow-up if they have not responded to 3 phone calls and 1 registered post letter. Missing data due to lost to follow-up will be covered in the Statistical Analysis Plan (SAP).

In the event of an unscheduled visit, only the relevant assessments/activities pertaining to the visit need to be performed and entered. All discontinued subjects will be followed until resolution of all their AEs or until the EOS visit.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

Table 1: Investigational Product

	Investigational Product	
Product Name:	**KPL-404**	**Placebo**
Dosage Form:	KPL-404 drug product is manufactured at 200 mg/mL as a sterile preservative-free solution in a single-use vial for parenteral administration. [redacted]	KPL-404 placebo is a sterile preservative-free solution for parenteral administration with identical composition as the drug product, but without the protein. [redacted]
Unit Dose	**Cohort 1**: 2 mg/kg KPL-404 q2wk **Cohort 2**: 5 mg/kg KPL-404 q2wk **Cohort 3**: • 5 mg/kg SC qwk • 5 mg/kg SC q2w (weekly dosing with alternating administration of KPL 404 q2wk or placebo q2wk) **Cohort 4**: • KPL-404 SC q4wk (600 mg loading dose followed by maintenance dosing 400 mg q4wk at Weeks 4 and 8)	Placebo volume will be matched to KPL-404 at the corresponding dosage level. In Cohort 3 in the placebo group, placebo will be given qwk; in the q2wk group, placebo will be alternated with KPL-404 administration. In Cohort 4, placebo will be administered as a volume-equivalent of KPL-404: a loading dose (i.e., 3 mL) followed by maintenance dosing (i.e., 2 mL) q4wk
Route of Administration	SC	SC
Physical Description	KPL-404 drug product is manufactured at 200 mg/mL as a sterile, preservative-free solution for parenteral administration. It is supplied as a single-use vial with a 1.0 mL extractable volume.	Placebo is a sterile, preservative-free solution for parenteral administration with identical composition as the drug product, but without the protein. It is supplied as a single-use vial with 1.0 mL extractable volume.

q2wk = every 2 weeks.

8.2. Concomitant and Rescue Medications

Medication restrictions applicable during the treatment period are described in Section 7.2 (exclusion criteria). Prior medication will be recorded up to 60 days prior to screening and prior medication for RA will be recorded up to 1 year prior to screening. Any medicinal product prescribed or over-the-counter, taken by a subject other than the study drug, is considered concomitant medication from Baseline (Day 1) to EOS.

During the treatment period up to Day 85 (EOT), the dose of background csDMARDs and corticosteroids or a new additional csDMARD may not be increased. If a subject develops RA flares requiring increased doses and/or new RA medications (as rescue medication), the subject must discontinue IMP after informing the medical monitor.

If a subject is discontinued from IP (study treatment), he or she should complete the EOT visit and remaining scheduled study visits through Week 24, per the Schedule of Activities, for all safety and efficacy assessments. The Investigator may also request that the subject return for additional visits.

After Day 85 (EOT), the dose of background csDMARDs and corticosteroids may be adjusted or a new additional csDMARD may be added to an existing one (except for combining MTX and leflunomide) if this is clinically indicated to improve disease management, in consultation with the medical monitor.

8.2.1. COVID Vaccines

Subjects are required to have completed a COVID-19 vaccine regimen to be eligible for the study. Subjects who desire to receive any additional COVID vaccines during study must discontinue treatment and wait at least 4 months after last dose of study drug to receive the vaccine in order for KPL-404 to wash out completely.

8.2.2. Contraception

Nonpregnant, nonlactating sexually active women of childbearing potential must agree to use a highly effective method of contraception from the screening visit until 30 days after EOS visit. Highly effective methods of contraception include:

- hormonal contraceptives associated with inhibition of ovulation (stable dose for at least 4 weeks prior to first dose)
- intrauterine device
- intrauterine system
- bilateral tubal occlusion
- vasectomized male partner
- abstinence from heterosexual intercourse

Sexually active male subjects must have documented vasectomy or must agree to use a condom or highly effective method of contraception, as defined above, with their partners of childbearing potential from first dose until 30 days after the EOS visit.

8.3. Treatment Compliance

The following measures will be employed to ensure treatment adherence and study procedure compliance with standard operating procedures defined by the Sponsor or designee:

- Doses will be administered under the supervision of the Investigator or authorized designee.
- Study drug accountability will be performed at the study site.

8.4. Randomization

All subjects who are eligible for study participation will be randomized on Day 1 prior to study drug administration. Each subject will be randomized to receive KPL-404 or placebo as per the randomization schedule prepared before the study by the Sponsor or designee. Randomization will be stratified by available documented evidence of prior inadequate response to ≤ 1 versus ≥ 2 classes of advanced targeted therapy (bDMARD or tsDMARD; e.g., TNF inhibitors, IL-6 receptor inhibitors, T-cell costimulatory inhibitors, anti-CD-20 antibodies, JAK inhibitors).

For Cohorts 1 and 2, subjects will be randomized 3:1, KPL-404 to placebo.

The overall randomization ratio in Cohort 3 is 1:1:1 (5 mg/kg q2wk, 5 mg/kg qwk, placebo). To maintain blinding, the placebo volume will be matched to the corresponding 5 mg/kg volume, and all subjects will be required to attend weekly visits through the treatment period.

The overall randomization ratio in Cohort 4 is 3:2 KPL-404 (600 mg loading dose at baseline followed by maintenance dosing 400 mg q4wk at Week 4 and Week 8) to matched placebo (equivalent volume; SC q4wk; loading dose at baseline followed by maintenance dose at Week 4 and Week 8).

An Interactive Response Technology (IRT) system will issue a unique randomization code to each subject, which will assign the treatment to the subject. The study drug will be assigned, prepared, and administered according to instructions in the Pharmacy Manual.

8.5. Blinding

This will be a double-blind, placebo-controlled study. Investigators, the subjects, and remaining clinical site staff will be blinded to treatment throughout the course of the study. The Sponsor will also be blinded to subject treatment assignment while each cohort's enrollment and subject follow-up is ongoing. Specified Sponsor representatives (and designees) may be unblinded to subject treatment assignment in completed cohorts (i.e., all participants in the cohort having completed study participation [Week 24/EOS]), and this unblinding will be documented in the Unblinding Plan.

The unblinded treatment assignment for each individual subject may be made available to the Investigator through the IRT system only in the event of a medical emergency or an adverse reaction that necessitates identification of the study drug for the medical management or welfare of that subject. Except in a medical emergency, the Investigator and blinded clinical site staff will remain blinded during the conduct of the study. The process and requirements for unblinding will be detailed in an Unblinding Plan. The date and reason for breaking the study blind should be documented.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

KPL-404 drug product is a monoclonal antibody consisting of 2 heavy chains and 2 light chains covalently linked by disulfide bridges. It binds to CD40 with an affinity of 7.2 nM, and blocks CD154-mediated activation of B-cells.

[redacted]

Placebo includes the above excipients only, but without the active ingredient.

9.2. Study Drug Packaging and Labeling

KPL-404 drug product and placebo are supplied in single-use vials, each vial with a 1.0 mL extractable volume. Each vial will be labeled in accordance with local law and regulation.

9.3. Study Drug Storage

KPL-404 drug product and placebo should be stored at 2° to 8°C.

9.4. Study Drug Preparation

KPL-404 drug product and placebo must be prepared under aseptic conditions. Preparation instructions can be found in the Pharmacy Manual.

9.5. Administration

KPL-404 drug product and placebo will be administered by SC injection. There is no restriction on fasting, water intake, or postures pre-/post-dose. Additional details on administration can be found in the Pharmacy Manual.

Investigational product should be administered at a study visit scheduled within the protocol-specified time window. If the study visit occurs outside the protocol-specified time window, every effort should be made to complete the visit procedure, including assessments, sample collection, and investigational product administration, as close as possible to the protocol-specified study visit time interval. Provided that sequential administration of investigational product doses can be separated by at least 24 hours, study visits occurring outside the protocol-specified time window should include administration of investigational product. While an out-of-window administration of investigational product would be a protocol deviation, it is preferable to have the out-of-window administration rather than to have a missed dose.

9.6. Study Drug Accountability

The authorized designee must maintain an accurate record of the study drug administration including the exact volume, date, and time of dispensing. This drug accountability record will be available for review at any time by the study monitor. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

Complete details regarding study drug dispensing and accountability can be found in the Pharmacy Manual.

9.7. Study Drug Handling and Disposal

Additional details for study drug receipt, handling, and disposal can be found in the Pharmacy Manual.

10. STUDY ASSESSMENTS

Should it become necessary (e.g., due to COVID-19), at any point following randomization, home health nursing, telemedicine services, or other operational adjustments may be applied to in-person visits and dosing, in compliance with local requirements/regulations. Where permitted by local requirements/regulations, study drug administration by a qualified healthcare provider in the home setting requires written approval from the Sponsor for each subject and cannot be performed prior to Week 2 (i.e., after 2 completed study drug administrations at the clinical site).

10.1. Order of Assessments

The following assessments should be conducted in the order below, as required, at a pre-dose and post-dose time points. Assessments not listed below can be done in any order:

1. Patient-reported outcomes and clinician assessments
2. Vital signs
3. Blood sampling for safety, PK, efficacy, and [redacted] assessments
4. Study drug administration (if applicable) must follow all other assessments
5. Observational period: subjects will be observed for 60 minutes after dosing on Day 1 and 30 minutes after dosing through end of treatment.

10.2. General Assessments

10.2.1. Demographics

Demographic data including sex, age, race, and ethnicity will be collected at screening to study their possible association with subject safety and treatment effectiveness, as well as the impact of KPL-404 on PK.

10.2.2. Medical and Surgical History

A complete medical history will be compiled to include drug or alcohol abuse within the last 6 months, RA history, cancer within the last 5 years from screening, and surgical history.

10.2.3. Medication History

All prior medication will be recorded up to 60 days prior to screening. All prior medication for RA that were administered within the last year prior to the screening visit should be recorded. All documented prior advanced targeted therapies (bDMARD or tsDMARD; e.g., TNF

inhibitors, IL-6 receptor inhibitors, T-cell costimulatory inhibitors, anti-CD-20 antibodies, JAK ihibitors) for RA should be recorded along with response.

A COVID vaccine regimen consistent with local guidance must have been completed at least 3 weeks before the first dose of IP.

10.2.4. Vital Signs

Vital signs will be measured in a sitting position after 5 minutes rest in a quiet setting without distractions (e.g., television, mobile phones) and will include body temperature, systolic and diastolic blood pressure, and pulse rate per the Schedule of Assessments (Appendix 1).

Vital signs may also be measured at other times if judged to be clinically appropriate by the Investigator or if the ongoing review of the safety data suggests a more detailed assessment of vital signs is required. All measurements will be performed singly and may be repeated if outside the relevant clinical reference range. Additional vital sign assessments may be performed if clinically indicated, in the opinion of the Investigator.

10.2.5. Weight and Height

Height and weight will be measured and recorded per Schedule of Assessments in Appendix 1. Weight collected at Baseline will be used to calculate dose through all applicable dosing visits.

10.2.6. Physical Examination

A complete physical examination will be completed per Schedule of Assessments in Appendix 1. Complete exams exclude genitourinary/pelvic systems unless clinically indicated. An abbreviated physical examination may be performed at the discretion of the Investigator at any time during the study.

10.2.7. Electrocardiogram

Electrocardiogram (ECG) will be performed as per standard of care (e.g., after subject has been resting in supine position for 5 minutes). The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The ECG at screening will not be required if a subject had a previously documented normal ECG within 120 days of screening.

10.2.8. Chest X-ray

A chest X-ray, 2 views (posterior-anterior and lateral or oblique view), will be performed as part of a general baseline screen for underlying pulmonary disease. The chest x-ray will not be required if a subject had a previously documented normal chest x-ray within 120 days of screening.

10.3. Efficacy Assessments

10.3.1. Tender joint Count/Swollen Joint Count

The 68 joints will be examined and assessed as tender or not tender for Tender Joint Count (TJC) and 66 joints will be examined and assessed as swollen or not swollen for Swollen Joint Count (SJC) (Felson et al 1993; Smolen et al 1995). The 68 joints (34 joints on each side of the

subject's body) to be assessed and classified as tender or not tender include: 2 temporomandibular joints, 2 sternoclavicular joints, 2 acromioclavicular joints, 2 shoulder joints, 2 elbow joints, 2 wrist joints, 10 MCP joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 hip joints, 2 knee joints, 2 ankle joints, 2 tarsus, 10 metatarsophalangeal joints of the feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet. The 66 joints (33 joints on each side of the subject's body) to be assessed and classified as swollen or not swollen include all TJC68 joints except 2 hip joints.

The ACR20/50/70, DAS28-CRP, [redacted] are based on the TJC28/SJC28. The 28 joints will be examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC (Smolen et al 1995). The following 28 joints (14 joints on each side of the subject's body) will be assessed for tenderness and swelling: the 8 proximal interphalangeal joints of the fingers, the interphalangeal joints of the thumbs (n = 2), the 10 metacarpophalangeal joints plus the wrists (n = 2), elbows (n = 2), shoulders (n = 2), and knees (n = 2).

The TJC and SJC will be performed according to the Schedule of Activities in Appendix 1.

10.3.2. ACR20/50/70

The ACR20/50/70 is a composite measure defined as both improvement of 20%, 50%, or 70% in the number of tender and number of swollen joints, and a 20%, 50%, or 70% improvement in three of the following five criteria: patient global assessment (PGA), physician global assessment (PhGA), functional ability measure [Health Assessment Questionnaire (HAQ)], visual analog pain scale, and C-reactive protein (CRP). The components of the ACR20/50/70 will be performed according to the Schedule of Activities in Appendix 1. Please refer to Appendix 4 for a reference copy of the assessment.

10.3.3. DAS-28 CRP

The Disease Activity Score using C-reactive protein (DAS28 – CRP) considers 28 TJC and 28 SJC, patient global assessment of disease activity [collected via VAS, 1-100mm], and CRP. The components of the DAS28-CRP will be performed according to the Schedule of Activities in Appendix 1. Please refer to Appendix 4 for a reference copy of the assessment.

The DAS28-CRP will be calculated as follows:

$$DAS28\text{-}CRP = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*VAS + 0.96$$

10.3.4. [redacted]

[redacted]

10.3.5. Health Assessment Questionnaire-Disability Index

The Health Assessment Questionnaire-Disability Index (HAQ-DI) is composed of 8 categories, reviewing a total of 20 specific functions evaluating subject difficulty with activities of daily living over the past week. Categories include dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and errands and chores. Also identified are specific aids or devices utilized for assistance, as well as help needed from another person (aids/help).

10.3.6. [redacted]

[redacted]

10.4. Pharmacokinetic Assessments

Pharmacokinetic blood samples will be collected pre-dose by venipuncture or cannulation at the times indicated in the Schedule of Activities in Appendix 1. Procedures for collection and processing of PK blood samples will be detailed in the Laboratory Manual.

Serum concentrations of KPL-404 will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate report.

10.4.1. [redacted]

[redacted]

10.4.2. [redacted]

[redacted]

10.5. Safety Assessments

10.5.1. Clinical Laboratory Assessments

Laboratory assessments will be assessed at the time points indicated in the Schedule of Activities in Appendix 1, refer to Appendix 2 for the list of clinical laboratory tests to be performed.

The urine drug screen will include opioid antagonists or agonists.

10.6. Adverse and Serious Adverse Events

10.6.1. Definition of Adverse Events

10.6.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not caused by the medicinal (investigational) product.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- They induce clinical signs or symptoms
- They are considered clinically significant
- They require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered non-typical in subjects with the underlying disease.

10.6.1.2. Adverse Drug Reaction

An adverse drug reaction is defined as, “A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility” (see Annex IV, International Conference for Harmonisation [ICH]-E2A Guideline).

Information about adverse drug reactions for the investigational drug can be found in the IB.

10.6.1.3. Adverse Events of Special Interest

An AE of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and requires close monitoring and communication by the Investigator with the Sponsor or designee within 24 hours of knowledge of the event, regardless of seriousness criteria. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product. AESIs for the purposes of this study are as follows: thrombosis, serious infection, serious and non-serious bacterial infections, eye disorders, and anaphylaxis/hypersensitivity reactions. Anaphylaxis is defined below in Table 2 using Sampson’s criteria (Sampson 2006).

Table 2: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:		
1.	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)	
	AND AT LEAST ONE OF THE FOLLOWING:	
	a.	Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
	b.	Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2.	Two or more of the following that occur rapidly after exposure *to a <u>likely</u> allergen for that patient* (minutes to several hours):	
	a.	Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
	b.	Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
	c.	Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
	d.	Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3.	Reduced BP after exposure to *<u>known</u> allergen for that patient* (minutes to several hours):	
	a.	Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
	b.	Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year of age, less than (70 mm Hg 1 + [2 × age]) from 1 to 10 years or age, and less than 90 mm Hg from 11 to 17 years of age.

10.6.1.4. Serious Adverse Events

An SAE is an AE occurring during any study phase after the ICF is signed (ie, screening, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator, or placebo, that fulfills 1 or more of the following:

- Results in death
- It is immediately life-threatening
  - Life-threatening in the context of an SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (refer to the ICH-E2D Guidelines)
- It requires in-patient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious AE irrespective of whether a clinical event has occurred.

10.7. Relationship to Study Drug

The Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. The causal relationship between an AE and the study drug will be defined as below:

- Not related: when the AE is definitely caused by the subject's clinical state, or the study procedure/conditions
- Unlikely related: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE
- Possibly related: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- Definitely related: when the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced

If the relationship between the SAE and the investigational product is determined to be "possibly" or "definitely" related, the event will be considered related to the investigational product for the purposes of expedited regulatory reporting. If the relationship between the

SAE and investigational product is deemed to be "unlikely related," the case is considered not expedited in the USA or European Union.

10.8. Severity of Adverse Events

The severity of an AE will be recorded as one of the following:

- Mild = Grade 1: easily tolerated, does not interfere with normal daily activities, does not require intervention
- Moderate = Grade 2: causes some interference with daily activities; minimal, local, or non-invasive intervention indicated
- Severe = Grade 3: medically significant event; prevents daily activity and requires medical intervention; hospitalization or prolongation of hospitalization indicated
- Potentially life threatening = Grade 4: urgent intervention indicated; ER visit or hospitalization required
- Death = Grade 5

As appropriate, clinical judgment should be used to determine the severity of adverse events with further reference to the FDA Guidance for Industry: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). The guidance document should not supersede Investigator judgment, as adverse events should be evaluated in the context of the clinical situation.

10.9. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need to be reported as Aes. Abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE.

Adverse event collection will begin after the signing of the ICF. An adverse event that occurs prior to study treatment administration should be recorded in the eCRF only if it is an SAE or is an AE related to a study procedure. All Aes/SAEs that occur after the first administration of study treatment through the EOS visit, whether or not they are related to the study, must be recorded in the eCRF.

For subjects who terminate study participation early (i.e., before the Week 24 visit), the Investigator will report any SAEs that are reported to the Investigator within 30-day post-last dose administration.

Every reasonable effort will be made to follow subjects who have Aes/SAEs. Any subject who has an ongoing AE will be followed until resolution or the EOS visit.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

10.9.1. Pregnancy

Should a pregnancy occur, investigational product must be permanently discontinued, and the pregnancy must be reported and recorded on the Pregnancy Report Form. Pregnancy by itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as Aes.

Any AE considered serious by the Investigator, or which meets SAE criteria, or any other event or condition regardless of grade, which in their judgment represents a reportable event, must be reported to the medical monitor and the Sponsor as soon as the Investigator becomes aware of the event.

10.10. Reporting Adverse Events

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit, must be reported to the Sponsor or designee, within 24 hours of learning of its occurrence. Additionally, Investigator reporting of SAEs to IRB/EC and other regulatory health authorities may be required per local rules and regulations. The following contact information can be used for SAE reporting:

US 24 Hour Safety Hotline:

- [redacted]

[redacted]

Europe / Middle East / Africa (EMEA)/Asia Pacific 24 Hour Safety Hotline:

- [redacted]

[redacted]

Additional follow-up information, if required or available, should be sent to the above-mentioned Pharmacovigilance contact information as soon as possible and placed with the original SAE information.

The event must also be recorded on the clinical database. Preliminary reports of SAEs must be followed by detailed descriptions as soon as possible including clear and redacted photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested as applicable and if available.

If the SAE is not previously documented in the IB as reference safety information (RSI) and is thought to be related to the study treatment, then the event is considered a suspected unexpected serious adverse reaction (SUSAR), and Kiniksa or designee may need to issue an Investigator notification to inform all Investigators involved in any study with the same study treatment that

this SAE has been reported. The standard timelines for SUSAR reporting as per ICH E2A will be followed.

The Sponsor or designee will report all SUSARs to the applicable regulatory authorities no later than 15 calendar days after the Sponsor's initial receipt of this information. Fatal or life-threatening unexpected experiences for which there is a possibility that the experience may have been caused by the drug will be reported by the Sponsor or designee to the regulatory authorities by telephone or facsimile transmission no later than 7 calendar days after receipt of this information.

Any SAEs experienced after completion of the study should only be reported to the Sponsor/Investigator.

11. STATISTICAL ANALYSES

Statistics to be reported are outlined in this section. Analysis plans will be written and approved prior to performing the first interim analysis. All statistical analysis and reporting will be done using SAS 9.4 or higher.

Descriptive statistics and changes from baseline, as applicable, will be calculated for safety parameters. The details regarding analyses will be provided in the SAP. Additional exploratory and post hoc analyses of the data may be conducted as deemed appropriate.

11.1. Sample Size Justification

The sample size for Cohorts 1 and 2 are based on safety and PK considerations. The sample size for Cohort 3 is based on a 2-sample t-test assuming an improvement in DAS28-CRP change from baseline for the KPL-404 being 1.2 points better than placebo (improvement for placebo = 1.0 point, standard deviation = 1.3). Enrollment of 21 subjects in each of the 3 treatment arms (KPL-404 5 mg/kg qwk, KPL404 5 mg/kg q2k, and placebo) allows 83% power for the treatment comparison with 2-sided 0.05 type 1 error if all subjects complete 12 weeks of DAS28-CRP assessments. In order to account for an anticipated discontinuation rate of 16%, up to 25 subjects per arm and for a total of up to 75 subjects are required to enroll under Cohort 3.

The sample size for Cohort 4 is based on a 2-sample t-test assuming an improvement in DAS28-CRP change from baseline for the KPL-404 being 1.3 points better than placebo (improvement for placebo = 1.0 point, standard deviation = 1.3). Enrollment of 22 subjects into the KPL-404 arm and 14 subjects into the placebo arm (i.e., 3:2 randomization ratio) allows 80% power for the treatment comparison with 2-sided 0.05 type 1 error if all subjects complete 12 weeks of DAS28-CRP assessments. In order to account for an anticipated discontinuation rate of 10%, approximately 24 subjects (KPL-404) and 16 subjects (placebo) for a total of approximately 40 subjects are required to enroll under Cohort 4.

11.2. Interim Analysis

An interim analysis may be conducted to support internal decision-making, for example, when at least 50% of subjects in Cohort 3 have completed the 12-week treatment period. The Cohort 3 interim analysis may include cumulative safety, tolerability, PK, [redacted] clinical response (e.g., DAS28-CRP), and [redacted]. Should the Sponsor decide to conduct the Cohort 3

Interim Analysis, the Sponsor will provide the specifics of the interim analysis in the Statistical Analysis Plan (SAP) prior to such analysis as well as the list of unblinded individuals prior to unblinding of study data. The data from the interim analysis will not be communicated to blinded study team, personnel at the clinical research organization, investigational sites, or enrolled subjects until all subjects have completed the study and database lock has been achieved. Details of the individuals who will see group-level unblinded data will be provided in the Unblinding Plan. The SAP will be submitted sufficiently far in advance of any unblinding of study data to allow regulators to formulate and communicate any necessary feedback regarding the SAP prior to data unblinding.

11.3. Analysis Populations

Analysis populations are defined as follows:

- **Modified intent-to-treat (mITT) population**: All randomized subjects who receive at least one dose of study drug and have at least one post-baseline assessment for primary efficacy endpoint will be included in the mITT population. Efficacy analyses will be based on the mITT population.
- **Safety population**: All randomized subjects who receive at least one dose of study drug will be included in the safety population. Safety analyses will be based on the safety population.

11.4. Analysis of Efficacy

11.4.1. Efficacy Endpoints

11.4.1.1. DAS28-CRP

The primary endpoint for Cohorts 3 and 4 and a secondary endpoint for Cohorts 1–2 is change from baseline in DAS28-CRP at Week 12. The DAS28-CRP score is derived from the number of swollen joints (out of 28 assessed), number of tender joints (out of 28 assessed), CRP level, and PGA score.

11.4.1.2. [redacted]

[redacted]

11.4.1.3. ACR20/50/70

The ACR20/50/70 corresponds to at least a 20%, 50%, or 70% improvement in the number of tender (TJC28) and swollen joints (SJC28) from baseline and a corresponding improvement in 3 of the following 5 criteria:

- PGA
- Pain VAS
- PhGA
- HAQ (see Section 10.3.5)
- CRP level

11.4.2. Analysis Methods

For efficacy analysis, a 2-sided type 1 error rate of 0.05 will be used, if applicable.

For Cohorts 1 and 2, only descriptive statistics and listings will be produced for all efficacy parameters. No formal statistical testing for efficacy will be performed.

For Cohorts 3 and 4, an analysis of covariance (ANCOVA) model will be used to compare the change from baseline in DAS28-CRP at Week 12 for each of the KPL-404 dose groups and placebo. Baseline and randomization stratification factor will be included as covariates in the ANCOVA model. No testing between the two KPL-404 dose groups in Cohort 3 will be conducted. ACR response rates at Week 12 between each of the KPL-404 dose groups and placebo will be compared using Cochran-Mantel- Haenszel (CMH) test adjusted by stratification factor. In addition, logistic regression models may be used including key baseline characteristics as covariates in addition to the treatment. Details will be specified in the SAP.

Baseline is defined as the last non-missing value on or before Day 1.

11.5. Analysis of Pharmacokinetics

Descriptive statistics (arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and geometric coefficient of variation, as appropriate) will be listed and summarized for serum concentrations of KPL-404 and PK parameters. Where data are available, KPL-404 dose proportionality will be examined between the dose groups. The $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} estimates will be tested for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate. Where data are available, exposure of KPL-404 administered by SC injection will be compared across dose levels. Log-transformed $AUC_{0-\infty}$ and AUC_{0-t} estimates will be analyzed using an ANOVA model with group as a fixed effect. Other analytical tests may be employed depending on the characteristics of the dataset. Additional details regarding analyses will be provided in the SAP for PK analysis. Additional exploratory and post hoc analyses of the data may be conducted as deemed appropriate.

11.6. [redacted]

[redacted]

11.7. Analysis of Safety

Descriptive statistics and changes from baseline, as applicable, will be calculated for safety parameters. No inferential statistical analyses are planned. The details regarding analyses will be provided in the SAP. Additional exploratory and post hoc analyses of the data may be conducted as deemed appropriate.

Analysis of TEAEs, defined as AEs that start or increase in severity after the first dose of study drug during treatment period, will be coded to system organ class and preferred term using the latest version of MedDRA. Analysis of post-treatment AEs, defined as any AEs that occur during the off-treatment period, will also be summarized in a similar manner.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

Before the investigational site can enter a subject into the study, a representative study monitor of Kiniksa or designee will assess the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of the Sponsor or designee. This will be documented in a Clinical Trial Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or designee will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm that Aes and SAEs have been properly documented and reported, that those SAEs have been forwarded to Kiniksa, and that SAEs meeting criteria for reporting have been forwarded to the IRB/IEC.

Specific details will be outlined in the clinical monitoring plan.

12.2. Audits and Inspections

Authorized representatives of the Sponsor quality assurance unit, a regulatory authority, an IEC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Kiniksa may conduct a quality assurance audit. Please see Section 12.2 for more details regarding the audit process.

14. ETHICS

14.1. Ethics Review

Before initiating a trial, the Investigator/Institution must obtain approval/favorable opinion from the IRB or Independent Ethics Committee (IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures, and any other written information to be provided to subjects.

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. In addition, after study completion and finalization of the study report, the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results.

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case-by-case basis. Investigators will apply due diligence to avoid protocol deviations.

The IRB/EC will be informed by the Investigator of any changes to the approved protocol.

Any amendments to the protocol will require IRB/IEC approval. Any administrative amendments to the protocol will be provided to IRBs/IECs according to IRB/IEC procedures.

The IRB/IEC will be informed by the Investigator of serious and unexpected SAEs in accordance with the IRB/IEC reporting requirements. The Investigator will provide the IRB/IEC with progress reports per IRB/IEC procedures.

14.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented, executed, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations US CFR 21, and with the ethical principles laid down in the Declaration of Helsinki.

14.3. Informed Consent

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (eg, all procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that to participate, they must adhere to the contraception requirements specified in this protocol.

A copy of the approved version of all consent forms will be kept by the Investigator.

15. DATA HANDLING AND RECORD KEEPING

The Investigator is responsible for assuring that the data (recorded on CRFs and entered into the eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

15.1. Inspection of Records

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

15.2. Retention of Records

The principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Kiniksa or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

16. PUBLICATION POLICY

Publication of the study results shall be done in accordance with, and are subject to, the publication provision in the clinical trial agreement governing this study.

17. REFERENCES

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18. APPENDICES

APPENDIX 1. SCHEDULE OF ACTIVITIES

SCHEDULE OF ACTIVITIES – COHORTS 1 AND 2

Study Period	**Screening Period**	**Treatment Period**								**Safety Follow up Period**			
Week	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12/ EOT[a]**	**Wk 14**	**Wk 16**	**Wk 20**	**Wk 24/EOS**
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**
Visit Window			**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**
Informed consent	X												
Demographics	X												
Eligibility criteria	X	X											
Medical/surgical history[b]	X	X											
Randomization		X											
Safety assessments													
Adverse events[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[d]	X												
12-lead ECG	X[d]								X				
Physical examination[e]	X	X							X				
Vital signs[f]	X	X		X	X		X		X				
Height (screening only) and weight	X	X							X				

Study Period	**Screening Period**	**Treatment Period**								**Safety Follow up Period**			
Week	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12/ EOT[a]**	**Wk 14**	**Wk 16**	**Wk 20**	**Wk 24/EOS**
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**
Visit Window			**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**
Prior/concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X	X	X	X
RA assessments													
TJC68/SJC66	X	X		X	X		X		X	X	X	X	X
ACR20/50/70		X		X	X		X		X	X	X	X	X
DAS28-CRP		X		X	X		X		X	X	X	X	X
[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI[g]		X		X	X		X		X	X	X	X	X
[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood collection[n]:													
QuantiFERON test	X												
HBV/HCV	X												
HIV (local laboratory)[h]	X												
Serum β-hCG for WOCBP[i]	X												X
Central hs-CRP	X	X		X	X		X		X	X	X	X	X

Study Period	Screening Period	Treatment Period								Safety Follow up Period			
Week	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ EOT[a]	Wk 14	Wk 16	Wk 20	Wk 24/EOS
Day	-28 to -1	1	8	15	29	43	57	71	85	99	113	141	169
Visit Window			± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 4 days
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood chemistry[j]	X	X		X	X		X		X				
Hematology (CBC) with differential	X	X		X	X		X		X				
Coagulation panel	X	X		X	X		X		X				
[redacted]		[redacted]		[redacted]	[redacted]				[redacted]	[redacted]			[redacted]
Pharmacokinetic samples (serum)		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urine collection:													
Urinalysis[l]	X	X		X	X		X		X				
Urine β-hCG for WOCBP (local)[m]		X			X		X		X		X	X	X
IP administration[n]		X		X	X	X	X	X					

AE = adverse event; [redacted]; ACR = American College of Rheumatology; [redacted]; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; [redacted]; DAS28-CRP = disease activity core of 28 joints using C-reactive protein; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; HAQ-DI = Health Assessment Questionnaire Disability Index; HBV = hepatitis

B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IP = investigational product; [redacted] RA = rheumatoid arthritis; [redacted] SAE = serious adverse event; [redacted] SJC = swollen joint count; TJC = tender joint count; Wk = week; WOCBP = women of childbearing potential.

A If a subject prematurely discontinues prior to the completion of the treatment period (Week 12), the procedures for the EOT visit should be conducted within approximately 2 weeks after discontinuation, and the subject should be encouraged to complete the remaining visits, up to the Week 24 visit.

B Prior medication will be recorded up to 60 days prior to screening, prior medication for RA will be recorded up to 1 year prior to screening, and COVID-19 vaccine regimen at least 3 weeks before the first dose of IP. Medical history to include drug or alcohol abuse within the last 6 months, RA history, cancer within the last 5 years from screening, and surgical history.

C During the screening period, only SAEs and protocol-related nonserious Aes will be recorded.

D The chest x-ray and ECG will not be required if a subject had a previously documented normal chest x-ray/ECG within 120 days of screening.

E Complete physical examination (minus genitourinary/pelvic examination) at screening and EOT; abbreviated examination at baseline and other time points if deemed indicated by Investigator.

F Blood pressure, pulse rate, and body temperature should be measured before blood draws are performed.

G Patient-reported outcomes performed prior to other procedures.

H Subjects who have not had an HIV test within 8 weeks of screening will be tested. Subjects with tests results indicating positive HIV infection will not be eligible for study participation.

I If serum pregnancy test result is borderline, a repeat test is necessary to confirm eligibility. If still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result, and the subject can be enrolled into the study.

J Minimum 8-hour fast. If a subject is unable to fast when necessary, the non-fasting status will be recorded.

K [redacted].

L A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits.

M If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must permanently discontinue IP.

N All blood draws (including PK) must be done pre-dose at applicable visits.

SCHEDULE OF ACTIVITIES – COHORT 3

Study Period	**Screening Period**	**Treatment Period**												**Safety Follow up Period**			
Week	**Screening**	**Base-line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12/ EOT[a]**	**Wk 14**	**Wk 16**	**Wk 20**	**Wk 24/EOS**
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**99**	**113**	**141**	**169**
Visit Window			**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**
Informed consent	X																	
Demographics	X																	
Eligibility criteria	X	X																
Medical/surgical history[b]	X	X																
Randomization		X																
Safety assessments																		
Adverse events[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[d]	X																	
12-lead ECG	X[d]													X				
Physical examination[e]	X	X												X				
Vital signs[f]	X	X		X		X				X				X				
Height (screening only) and weight	X	X												X				
Prior/concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening Period	Treatment Period													Safety Follow up Period			
Week	**Screening**	**Base-line**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12/ EOT[a]**	**Wk 14**	**Wk 16**	**Wk 20**	**Wk 24/EOS**
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**99**	**113**	**141**	**169**
Visit Window			**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**
RA assessments																		
TJC68/SJC66	X	X		X		X				X				X	X	X	X	X
ACR20/50/70		X		X		X				X				X	X	X	X	X
DAS28-CRP		X		X		X				X				X	X	X	X	X
[redacted]		[redacted]		[redacted]		[redacted]				[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI[g]		X		X		X				X				X	X	X	X	X
[redacted]		[redacted]		[redacted]		[redacted]				[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood collection[n]:																		
QuantiFERON test	X																	
HBV/HCV	X																	
HIV (local laboratory)[h]	X																	
Serum β-hCG for WOCBP[i]	X																	X
Central hs-CRP	X	X		X		X				X				X	X	X	X	X
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]				[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood chemistry[j]	X	X		X		X				X				X				

Study Period	Screening Period	Treatment Period												Safety Follow up Period			
Week	Screening	Base-line	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12/ EOT[a]	Wk 14	Wk 16	Wk 20	Wk 24/EOS
Day	-28 to -1	1	8	15	22	29	36	43	50	57	64	71	78	85	99	113	141	169
Visit Window			± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 4 days	± 4 days	± 4 days	± 4 days
Hematology (CBC) with differential	X	X		X		X				X				X				
Coagulation panel	X	X		X		X				X				X				
[redacted]		[redacted]		[redacted]		[redacted]								[redacted]	[redacted]			[redacted]
Pharmacokinetic samples (serum)		X	X	X		X		X		X		X		X	X	X	X	X
[redacted]		[redacted]				[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urine collection:																		
Urinalysis[l]	X	X		X		X				X				X				
Urine β-hCG for WOCBP (local)[m]		X				X				X				X		X	X	X
Urine drug screen	X																	
IP administration[n]		X	X	X	X	X	X	X	X	X	X	X	X					

AE = adverse event; [redacted]; ACR = American College of Rheumatology; [redacted]; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; [redacted] DAS28-CRP = disease activity score of 28 joints using C-reactive protein; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; HAQ-DI = Health Assessment Questionnaire Disability Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IP = investigational product; [redacted]

[redacted] RA = rheumatoid arthritis; [redacted] SAE = serious adverse event; [redacted] SJC = swollen joint count; TJC = tender joint count; Wk = week; WOCBP = women of childbearing potential.

A If a subject prematurely discontinues prior to the completion of the treatment period (Week 12), the procedures for the EOT visit should be conducted within approximately 2 weeks after discontinuation, and the subject should be encouraged to complete the remaining visits at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24.

B Prior medication will be recorded up to 60 days prior to screening, prior medication for RA will be recorded up to 1 year prior to screening, and COVID-19 vaccine regimen at least 3 weeks before the first dose of IP. Medical history to include drug or alcohol abuse within the last 6 months, RA history, cancer within the last 5 years from screening, and surgical history.

C During the screening period, only SAEs and study procedure-related nonserious Aes will be recorded.

D The chest x-ray and ECG will not be required if a subject had a previously documented normal chest x-ray/ECG within 120 days of screening.

E Complete physical examination (minus genitourinary/pelvic examination) at screening and EOT; abbreviated examination at baseline and other time points if deemed indicated by Investigator.

F Blood pressure, pulse rate, and body temperature should be measured before blood draws are performed.

G Patient-reported outcomes performed prior to other procedures.

H Subjects who have not had an HIV test within 8 weeks of screening will be tested. Subjects with tests results indicating positive HIV infection will not be eligible for study participation.

I If serum pregnancy test result is borderline, a repeat test is necessary to confirm eligibility. If still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result, and the subject can be enrolled into the study.

J Minimum 8-hour fast. If a subject is unable to fast when necessary, the nonfasting status will be recorded.

K [redacted]

L A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits.

M If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must permanently discontinue IP.

N All blood draws (including PK) must be done pre-dose at applicable visits.

Schedule of Activities – Cohort 4

Study Period	Screening Period	Treatment Period						Safety Follow up Period			
Week	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12/ EOT[a]**	**Wk 14**	**Wk 16**	**Wk 20**	**Wk 24/EOS**
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**99**	**113**	**141**	**169**
Visit Window			**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**
Informed consent	X										
Demographics	X										
Eligibility criteria	X	X									
Medical/surgical history[b]	X	X									
Randomization		X									
Safety assessments											
Adverse events[c]	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[d]	X										
12-lead ECG	X[d]						X				
Physical examination[e]	X	X					X				
Vital signs[f]	X	X		X	X	X	X				
Height (screening only) and weight	X	X					X				
Prior/concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Screening Period**	**Treatment Period**						**Safety Follow up Period**			
Week	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12/ EOT[a]**	**Wk 14**	**Wk 16**	**Wk 20**	**Wk 24/EOS**
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**99**	**113**	**141**	**169**
Visit Window			**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**
RA assessments											
TJC68/SJC66	X	X		X	X	X	X	X	X	X	X
ACR20/50/70		X		X	X	X	X	X	X	X	X
DAS28-CRP		X		X	X	X	X	X	X	X	X
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI[g]		X		X	X	X	X	X	X	X	X
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood collection[n]:											
QuantiFERON test	X										
HBV/HCV	X										
HIV (local laboratory)[h]	X										
Serum β-hCG for WOCBP[i]	X										X
Central hs-CRP	X	X		X	X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood chemistry[j]	X	X		X	X	X	X				

Study Period	Screening Period	Treatment Period						Safety Follow up Period			
Week	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12/ EOT[a]**	**Wk 14**	**Wk 16**	**Wk 20**	**Wk 24/EOS**
Day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**99**	**113**	**141**	**169**
Visit Window			**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**
Hematology (CBC) with differential	X	X		X	X	X	X				
Coagulation panel	X	X		X	X	X	X				
[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]			[redacted]
Pharmacokinetic samples (serum)		X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urine collection:											
Urinalysis[l]	X	X		X	X	X	X				
Urine β-hCG for WOCBP (local)[m]		X			X	X	X		X	X	X
Urine drug screen	X										
IP administration[n]		X			X	X					

AE = adverse event; [redacted]; ACR = American College of Rheumatology; [redacted]; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; [redacted]DAS28-CRP = disease activity score of 28 joints using C-reactive protein; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; HAQ-DI = Health Assessment Questionnaire Disability Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IP = investigational product; [redacted]

[redacted] RA = rheumatoid arthritis; [redacted]; SAE = serious adverse event; [redacted] SJC = swollen joint count; TJC = tender joint count; Wk = week; WOCBP = women of childbearing potential.

A If a subject prematurely discontinues prior to the completion of the treatment period (Week 12), the procedures for the EOT visit should be conducted within approximately 2 weeks after discontinuation, and the subject should be encouraged to complete the remaining visits at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24.

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E Complete physical examination (minus genitourinary/pelvic examination) at screening and EOT; abbreviated examination at baseline and other time points if deemed indicated by Investigator.

F Blood pressure, pulse rate, and body temperature should be measured before blood draws are performed.

G Patient-reported outcomes performed prior to other procedures.

H Subjects who have not had an HIV test within 8 weeks of screening will be tested. Subjects with tests results indicating positive HIV infection will not be eligible for study participation.

I If serum pregnancy test result is borderline, a repeat test is necessary to confirm eligibility. If still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result, and the subject can be enrolled into the study.

J Minimum 8-hour fast. If a subject is unable to fast when necessary, the nonfasting status will be recorded.

K [redacted]

L A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits.

M If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must permanently discontinue IP.

N All blood draws (including PK) must be done pre-dose at applicable visits.

APPENDIX 2. CLINICAL LABORATORY EVALUATIONS

See Appendix 1 for timing of evaluations.

Blood chemistry	Albumin, alkaline phosphatase, anion gap, total bilirubin (indirect and direct), bicarbonate, calcium, chloride, total cholesterol, creatinine, gamma GT, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, total protein, AST, ALT, sodium, triglycerides, urea, and uric acid
Coagulation	d-Dimer, PT, INR, and PTT; anti-phospholipid antibodies (screening only)
Serology	HbsAg, HbsAb, HbcAb and HCVAb, HIV
Hematology	Absolute neutrophil count, differential, hematocrit, hemoglobin, MCH, MCHC, MCV, platelet count, erythrocytes, leukocytes (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Urinalysis	Bilirubin, blood, color, glucose, ketone, leukocytes, nitrite, pH, protein, specific gravity, turbidity, urobilinogen. If blood, leukocytes, nitrite, or protein are out of range, then microscopic exam (includes bacteria, cast, crystals, epithelial cells, red blood cell, white blood cell) will be automatically run.
Urine drug screen	Amphetamines (includes methamphetamines and ecstasy/MDMA), cocaine metabolites, opiates (includes heroin, codeine, and oxycodone) methadone, phencyclidine
Other	Serum pregnancy test

Note: All laboratory tests will be collected locally.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, GT = glutamyl transferase, HbsAg = hepatitis B surface antigen, HbsAb = hepatitis B surface antibody, HbcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus, INR = International Normalization Ratio, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MDMA = methylenedioxymethamphetamine, PT = prothrombin time; PTT = partial thromboplastin time

APPENDIX 3. SUMMARY OF CHANGES (VERSION 5.0 COMPARED TO VERSION 6.0)

The following table shows changes to the KPL-404-C211 protocol (Version 5.0 versus Version 6.0), which summarize the changes to the protocol. Additional minor changes were also made with respect to typos, minor edits for clarification, adding new abbreviations to the list of abbreviations, and updating the table of contents.

Protocol Section	Modification	Rationale
Throughout	Added/changed to Protocol Version 6.0, dated 28 Jun 2023. Administrative edits to correct typographical errors, minor edits for clarification, adding new abbreviations to the list of abbreviations, and updating the table of contents	Changes were made to identify the new protocol version and date and administrative changes for clarity, conciseness, and correctness.
Synopsis 5.0 Study Objectives and Endpoints	Primary and Secondary Objective and Endpoint were modified to include Cohort 4 alongside Cohort 3.	The objectives and endpoints for the new Cohort 4 were prespecified.
Synopsis 6.1 Overall Study Design	At approximately the end of Cohort 3 enrollment, the study will enroll subjects into Cohort 4. Subjects will be randomized in a 3:2 ratio to receive one of the following: • KPL-404 SC q4wk (600 mg loading dose at baseline followed by maintenance dosing 400 mg q4wk at Weeks 4 and 8) • Matched Placebo (equivalent volume) SC q4wk (loading dose at baseline followed by maintenance doses at Weeks 4 and 8)	Text was added to describe Cohort 4 dose levels and dose administration.
Synopsis 6.1 Overall Study Design 6.4 Safety Review Committee	In Cohorts 3 and 4, SRC meetings will occur on a quarterly basis while enrollment is ongoing. The initial SRC meeting in Cohort 3 will occur within approximately 90 days of the start of enrollment or once 20 subjects are enrolled, whichever occurs first. All available safety and PK data will be reviewed by the SRC at the initial meeting in Cohort 3. Subsequent meetings will prioritize review of safety data from all active cohorts.	Text was added to describe when SRC meeting will begin and how frequently they will occur for Cohorts 3 and 4.
Synopsis 6.1 Overall Study Design 7.3 Treatment Discontinuation, Withdrawal of Consent, and Lost to Follow-Up Criteria	If a subject discontinues prematurely (i.e., before the end of treatment visit), the subject should be encouraged to complete the procedures for the end-of-treatment visit (Week 12) within approximately 2 weeks (for Cohorts 1, 2, and 3) or 4 weeks (for Cohort 4) from last dose of study drug as well as visits thereafter through Week 24. Upon decision to discontinue treatment, the Sponsor should be notified immediately. If a subject is prematurely discontinued from IP (study treatment), he or she should complete the end of treatment (EOT) visit (Week 12) within approximately 2 weeks (for Cohorts 1, 2, and 3) or 4 weeks (for Cohort 4) from last dose of study drug as well as visits thereafter through Week 24, as per the Schedule of Activities, for all safety and efficacy assessments. The Investigator may also request that the subject return for additional visits.	These paragraphs were modified for clarity to describe when subjects should return for an end-of-treatment visit following premature discontinuation of treatment.

Protocol Section	Modification	Rationale
Synopsis 6.2 Number of Subjects	**Number of Subjects (Planned):** • Cohort 4: approximately 40 subjects The study plans to enroll approximately 16 subjects in Cohorts 1 and 2, approximately 75 subjects in Cohort 3, and approximately 40 subjects in Cohort 4, across approximately 100 study sites.	Text was revised to describe the Cohort 4 sample size.
Synopsis	**Reference Therapy, Dosage, and Mode of Administration:** Placebo administered weekly, every other week, or monthly by SC injection.	Text was revised to describe the dose administration frequency being evaluated in this clinical trial.
Synopsis 11.1 Sample Size Justification	The sample size for Cohort 4 is based on a 2-sample t-test assuming an improvement in DAS28-CRP change from baseline for the KPL-404 being 1.3 points better than placebo (improvement for placebo = 1.0 point, standard deviation = 1.3). Enrollment of 22 subjects into the KPL-404 arm and 14 subjects into the placebo arm (i.e., 3:2 randomization ratio) allows 80% power for the treatment comparison with 2-sided 0.05 type 1 error if all subjects complete 12 weeks of DAS28-CRP assessments. In order to account for an anticipated discontinuation rate of 10%, approximately 24 subjects (KPL-404) and 16 subjects (placebo) for a total of approximately 40 subjects are required to enroll under Cohort 4.	Text was revised to describe the Cohort 4 sample size.
4.2 Study Rationale	The safety, pharmacokinetics (PK), and pharmacodynamics (PD) of KPL-404 have been assessed in a single ascending-dose study in healthy subjects (KPL-404-C101). The clinical development plan is designed to focus next on assessing safety, tolerability, ~~and~~ PK (primary objective), and efficacy (secondary objective) of KPL-404 with multiple-dose administration, initially with two ascending-dose cohorts: Cohort 1 (2 mg/kg dose level vs. placebo), administered subcutaneously (SC) on alternate weeks (q2wk), and Cohort 2 (5 mg/kg dose level vs. placebo SC q2wk). Cohort 3 is designed to assess the comparative efficacy (primary objective) as well as the safety, tolerability, and PK (secondary objectives) of KPL-404 using the weight-based 5 mg/kg SC dose level administered either weekly or biweekly versus placebo over 12 weeks. Cohort 4 is designed to assess the comparative efficacy, safety, tolerability, and PK of fixed-mg dose KPL-404 (400 mg) administered SC monthly versus placebo. Efficacy will be assessed using the primary endpoint, change from baseline in disease activity score of 28 joints using C-reactive protein (DAS28-CRP) at 12 weeks.	Study Rationale was revised to describe the inclusion of Cohort 4.

Protocol Section	Modification	Rationale
4.3 Dose Justification	Subheadings are added to clarify dose justifications for Cohorts 1 and 2, Cohort 3, and Cohort 4. Cohort 4 subjects will be randomized in a 3:2 ratio to receive fixed-mg dosing of KPL-404 SC q4wk (a 600mg SC [or matching placebo] loading dose at the Baseline Visit followed by maintenance dosing of 400mg SC [or matching placebo] at Week 4 and Week 8). The objective is to explore the efficacy of KPL-404 at lower trough concentrations than Cohort 3, approximating the minimum level required for T-cell-dependent antibody response suppression, as seen in Phase 1. This dosing regimen (i.e., a fixed-mg dose rather than weight-based dose) represents a different approach as compared to Cohort 3, and it does not represent a dose escalation. Rather, this fixed-mg (400 mg) administered dose provides a centered administered dose level, based upon early PK data showing a relatively neutral effect of weight on the PK of KPL-404, as would be expected given that monoclonal antibodies are large macromolecules with a volume of distribution restricted to the plasma. The 400 mg administered dose is 5 mg/kg for an average 80 kg subject. The 600 mg loading dose is intended to facilitate reaching steady state trough levels more rapidly, based on PK modeling. This regimen based on the same modeling is expected to provide peak levels no greater than those projected in Cohorts 2 and 3 and trough plasma concentrations lower than the 5 mg/kg q2wk dose level in Cohort 2.	Text was added to explain and justify the KPL-404 dose level, administration, and frequency of the Cohort 4 dosing.
Figure 2: Study Schema for KPL-404-C211	Figure 2 was updated to include Cohort 4.	Figure was revised to include Cohort 4.

Protocol Section	Modification			Rationale
Table 1: Investigational Product	**Unit Dose**	**Cohort 1**: 2 mg/kg KPL-404 q2wk **Cohort 2**: 5 mg/kg KPL-404 q2wk **Cohort 3**: • 5 mg/kg SC qwk • 5 mg/kg SC q2w (weekly dosing with alternating administration of KPL 404 q2wk or placebo q2wk) **Cohort 4**: • KPL-404 SC q4wk (600 mg loading dose followed by 400 mg q4wk)	Placebo volume will be matched to KPL-404 at the corresponding dosage level. In Cohort 3 in the placebo group, placebo will be given qwk; in the q2wk group, placebo will be alternated with KPL-404 administration. In Cohort 4, placebo will be administered as a volume-equivalent of KPL-404: a loading dose (i.e., 3 mL) followed by maintenance dosing (i.e., 2 mL) q4wk	Text was added to describe the KPL-404 dose level, administration, and frequency of the Cohort 4 dosing and to describe placebo administration in Cohorts 3 and 4.
8.4 Randomization	The overall randomization ratio in Cohort 4 is 3:2 KPL-404 (600 mg loading dose at baseline followed by maintenance dosing 400 mg q4wk at Week 4 and Week 8) to matched placebo (equivalent volume; SC q4wk; loading dose at baseline followed by maintenance dose at Week 4 and Week 8).			Cohort 4 randomization was described.
11.3 Analysis Populations	• Modified intent-to-treat (mITT) population: All randomized subjects who receive at least one dose of study drug and have at least one post-baseline assessment for primary efficacy endpoint will be included in the mITT population. Efficacy analyses will be based on the mITT population.			Text was added to clarify the mITT population definition and to align this definition with the Statistical Analysis Plan.

Protocol Section	Modification	Rationale
11.4.1.1 DAS28-CRP	The primary endpoint for Cohorts 3 and 4 and a secondary endpoint for Cohorts 1–2 is change from baseline in DAS28-CRP at Week 12.	Text was added to clarify that DAS28-CRP will be the primary endpoint for Cohorts 3 and 4.
[redacted]	[redacted]	[redacted]
11.7 Analysis of Safety	Analysis of TEAEs, defined as AEs that start or increase in severity after the first dose of study drug ~~and~~ during treatment period ~~through the EOS visit last treatment~~, will be coded to system organ class and preferred term using the latest version of MedDRA. Analysis of post-treatment AEs, defined as any AEs that occur during the off-treatment period, will also be summarized in a similar manner.	Text was added to align with the Statistical Analysis Plan definitions of TEAEs and post-treatment AEs.
Appendix 1. Schedule of Activities	A new Schedule of Activities was created to describe the assessments and activities for Cohort 4.	A new SOA was added to describe the timing and extent of activities for subjects enrolled into Cohort 4.

APPENDIX 4 CLINICAL OUTCOME ASSESSMENTS AND PATIENT REPORTED OUTCOMES

This appendix provides paper depictions of the outcome measures employed in Study KPL-404-C211. These paper depictions are provided for conceptual clarity and are for REFERENCE ONLY. These clinical outcome assessments and patient reported outcomes will be administered, and the responses collected, electronically via a provisioned tablet device that will remain at the clinical study sites.

1. ARC20/50/70

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AMERICAN COLLEGE OF RHEUMATOLOGY

Patient Assessment

Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing:

Very Well ├──────────────────────────────┤ Very Poorly

How much pain have you had because of your condition over the past week? Place a mark on the line below to indicate how severe your pain has been:

No Pain ├──────────────────────────────┤ Pain as Bad as It Could Be

Please answer the following questions, even if you feel that they may not be related to you at this time. Answer exactly as you think or feel – there are no right or wrong answers. Check the one best answer for each question.

Activity Level <u>Right now, are you able to:</u>	**Without any difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
1. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
2. Get in and out of bed?	0	1	2	3
3. Lift a full cup or glass to your mouth?	0	1	2	3
4. Walk outdoors on flat ground?	0	1	2	3
5. Wash and dry your entire body?	0	1	2	3
6. Bend down to pick up clothing from the floor?	0	1	2	3
7. Turn regular faucets on and off?	0	1	2	3
8. Get in and out of a car, bus, train or airplane?	0	1	2	3
9. Walk two miles?	0	1	2	3
10. Participate in sports and games as you like?	0	1	2	3
11. Get a good night's sleep?	0	1.1	2.2	3.3
12. Deal with feelings of anxiety or being nervous?	0	1.1	2.2	3.3
13. Deal with feelings of depression or feeling blue?	0	1.1	2.2	3.3

Your Name_____ **Today's Date**_____ **Time of Day** _____

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GL ☐

PN ☐

FN ☐

1=0.33
2=0.67
3=1.0
4=1.33
5=1.67
6=2.0
7=2.33
8=2.67
9=3.0
10=3.33
11=3.67
12=4.0
13=4.33
14=4.67
15=5.0
16=5.33
17=5.67
18=6.0
19=6.33
20=6.67
21=7.0
22=7.33
23=7.67
24=8.0
25=8.33
26=8.67
27=9.0
28=9.33
29=9.67
30=10.0

Instructions for Office Staff

Activity Level Index Scoring: For FN (questions 1-10) add total points and convert using scale on right. For PS (questions 11-13), add total points.

Visual Analog Scales: measure with metric ruler. Line is exactly 10 cm long. Scores should be recorded in cm.mm format.

Adapted from
Pincus T, Swearingen C, Wolfe F. Toward a Multidimensional Health Assessment Questionnaire. Arthritis Rheum 1999; 42:2220-2230.

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AMERICAN COLLEGE OF RHEUMATOLOGY

Patient Assessment

Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing:

Very Well |——————————————————————| Very Poorly

How much pain have you had because of your condition over the past week? Place a mark on the line below to indicate how severe your pain has been:

No Pain |——————————————————————| Pain as Bad as It Could Be

Please answer the following questions, even if you feel that they may not be related to you at this time. Answer exactly as you think or feel – there are no right or wrong answers. Check the one best answer for each question.

Activity Level **Right now, are you able to:**	**Without any difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
1. Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
2. Get in and out of bed?	0	1	2	3
3. Lift a full cup or glass to your mouth?	0	1	2	3
4. Walk outdoors on flat ground?	0	1	2	3
5. Wash and dry your entire body?	0	1	2	3
6. Bend down to pick up clothing from the floor?	0	1	2	3
7. Turn regular faucets on and off?	0	1	2	3
8. Get in and out of a car, bus, train or airplane?	0	1	2	3
9. Walk two miles?	0	1	2	3
10. Participate in sports and games as you like?	0	1	2	3
11. Get a good night's sleep?	0	1.1	2.2	3.3
12. Deal with feelings of anxiety or being nervous?	0	1.1	2.2	3.3
13. Deal with feelings of depression or feeling blue?	0	1.1	2.2	3.3

For Office Use Only

GL ☐

PN ☐

FN ☐

1=0.33
2=0.67
3=1.0
4=1.33
5=1.67
6=2.0
7=2.33
8=2.67
9=3.0
10=3.33
11=3.67
12=4.0
13=4.33
14=4.67
15=5.0
16=5.33
17=5.67
18=6.0
19=6.33
20=6.67
21=7.0
22=7.33
23=7.67
24=8.0
25=8.33
26=8.67
27=9.0
28=9.33
29=9.67
30=10.0

Your Name_____ **Today's Date**_____ **Time of Day** _____

Instructions for Office Staff

Activity Level Index Scoring: For FN (questions 1-10) add total points and convert using scale on right. For PS (questions 11-13), add total points.

Visual Analog Scales: measure with metric ruler. Line is exactly 10 cm long. Scores should be recorded in cm.mm format.

Adapted from
Pincus T, Swearingen C, Wolfe F. Toward a Multidimensional Health Assessment Questionnaire. Arthritis Rheum 1999; 42:2220-2230.

AMERICAN COLLEGE OF RHEUMATOLOGY
Physician Assessment

0= Absent
1= Present

Patient Right			Patient Left		
Joint	Pain	Swelling	Joint	Pain	Swelling
Shoulder	0 1	0 1	Shoulder	0 1	0 1
Elbow	0 1	0 1	Elbow	0 1	0 1
Wrist	0 1	0 1	Wrist	0 1	0 1
MCP I	0 1	0 1	MCP I	0 1	0 1
MCP II	0 1	0 1	MCP II	0 1	0 1
MCP III	0 1	0 1	MCP III	0 1	0 1
MCP IV	0 1	0 1	MCP IV	0 1	0 1
MCP V	0 1	0 1	MCP V	0 1	0 1
PIP I	0 1	0 1	PIP I	0 1	0 1
PIP II	0 1	0 1	PIP II	0 1	0 1
PIP III	0 1	0 1	PIP III	0 1	0 1
PIP IV	0 1	0 1	PIP IV	0 1	0 1
PIP V	0 1	0 1	PIP V	0 1	0 1
Knee	0 1	0 1	Knee	0 1	0 1

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Physician's Global Assessment: Mark an X on the line below to indicate disease activity (independent of the patient's self assessment):

Very Good |——————————————————————| Very Bad

Today's Physician Global Assessment Score_____ Baseline score _____ Percent Change _____

Total Painful Joints Today _____ Total Painful Joints Baseline _____ Percent Change _____

Total Swollen Joints Today _____ Total Swollen Joints Baseline _____ Percent Change _____

Acute-Phase Reactant: ESR or CRP Today_____ ESR or CRP Baseline _____ Percent Change _____

Scores from Patient Assessment

Today's Function (FN) Index _____ Baseline Function (FN) Index _____ Percent Change _____

Today's Patient Pain (PN) Score _____ Baseline Patient Pain (PN) Score _____ Percent Change _____

Today's Patient Global (GL) Score _____ Baseline Patient Global (GL) Score _____ Percent Change _____

Criteria for ACR 20 Improvement

Required	Achieved
> 20% Improvement in painful joint count	_____
> 20% Improvement in swollen joint count	_____
+	
> 20% Improvement in 3 of the following 5 areas	
Patient Pain Assessment (PN)	_____
Patient Global Assessment (GL)	_____
Physician Global Assessment	_____
Patient Self-Assessed Disability (FN)	_____
Acute-Phase Reactant (ESR or CRP)	_____

Felson, DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R, Paulus H, Strand V, Tugwell P, Weinblatt M, Williams HJ, Wolfe F, Kieszak S. American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis. Arthritis Rheum 1995; 38:727-735.

Supported by a grant from G.D. Searle and Co.

Patient's Name_____ Date_____ Physician's Initials_____

2. DAS28-CRP

DAS28 CRP form

Patient name ..... Date of Birth ____-____-_____

Observer name ..... Date ____-____-_____

		Left		Right	
		Swollen	Tender	Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
Total		Swollen		Tender	

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How active was your arthritis during the past week?
(Please mark the degree of activity on the scale below by placing a vertical line |)

Not active at all ——————————— **Extremely active**

Swollen Joint Count (0-28)
Tender Joint Count (0-28)
CRP
VAS disease activity (0-100mm)

DAS28-CRP = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.36*ln(CRP+1) + 0.014*VAS + 0.96

For free online calculator visit www.das28.nl

DAS-28 © Piet Van Riel, 1995.
DAS-28_CRP_AU1.2_eng-GBorl

[redacted]

4. HAQ-DI

HEALTH ASSESSMENT QUESTIONNAIRE

Name_____ Date_____

PATKEY#_____
QUESTDAT

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	____	____	____	____
- Shampoo your hair?	____	____	____	____
ARISING				
Are you able to:				
- Stand up from a straight chair?	____	____	____	____
- Get in and out of bed?	____	____	____	____
EATING				
Are you able to:				
- Cut your meat?	____	____	____	____
- Lift a full cup or glass to your mouth?	____	____	____	____
- Open a new milk carton?	____	____	____	____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	____	____	____	____
- Climb up five steps?	____	____	____	____

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PMSVIS_____
RASTUDY
QUESTNUM_____

DRESSNEW____

RISENEW_____

EATNEW_____

WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane
_____ Walker
_____ Crutches
_____ Wheelchair
_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Built up or special utensils
_____ Special or built up chair
_____ Other (Specify:_____)

ORSGASST____
RISEASST_____
EATASST
WALKASST____

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

1

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HAQ-DI – United States/English
HAQ-DI_AU1.0-eng-USen.doc

FOR REFERENCE ONLY

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

TOOL IS ADMINISTERED ELECTRONICALLY

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	____	____	____	____	
- Take a tub bath?	____	____	____	____	
- Get on and off the toilet?	____	____	____	____	HYGNNEW____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	____	____	____	____	
- Bend down to pick up clothing from the floor?	____	____	____	____	REACHNEW____
GRIP					
Are you able to:					
- Open car doors?	____	____	____	____	
- Open jars which have been previously opened?	____	____	____	____	
- Turn faucets on and off?	____	____	____	____	GRIPNEW____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	____	____	____	____	
- Get in and out of a car?	____	____	____	____	
- Do chores such as vacuuming or yardwork?	____	____	____	____	ACTIVNEW____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

____Raised toilet seat ____Bathtub bar

____Bathtub seat ____Long-handled appliances for reach

____Jar opener (for jars previously opened) ____Long-handled appliances in bathroom

____Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

____Hygiene ____Gripping and opening things

____Reach ____Errands and chores

HYGNASST____
RCHASST____
GRIPASST____
ACTVASST____

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

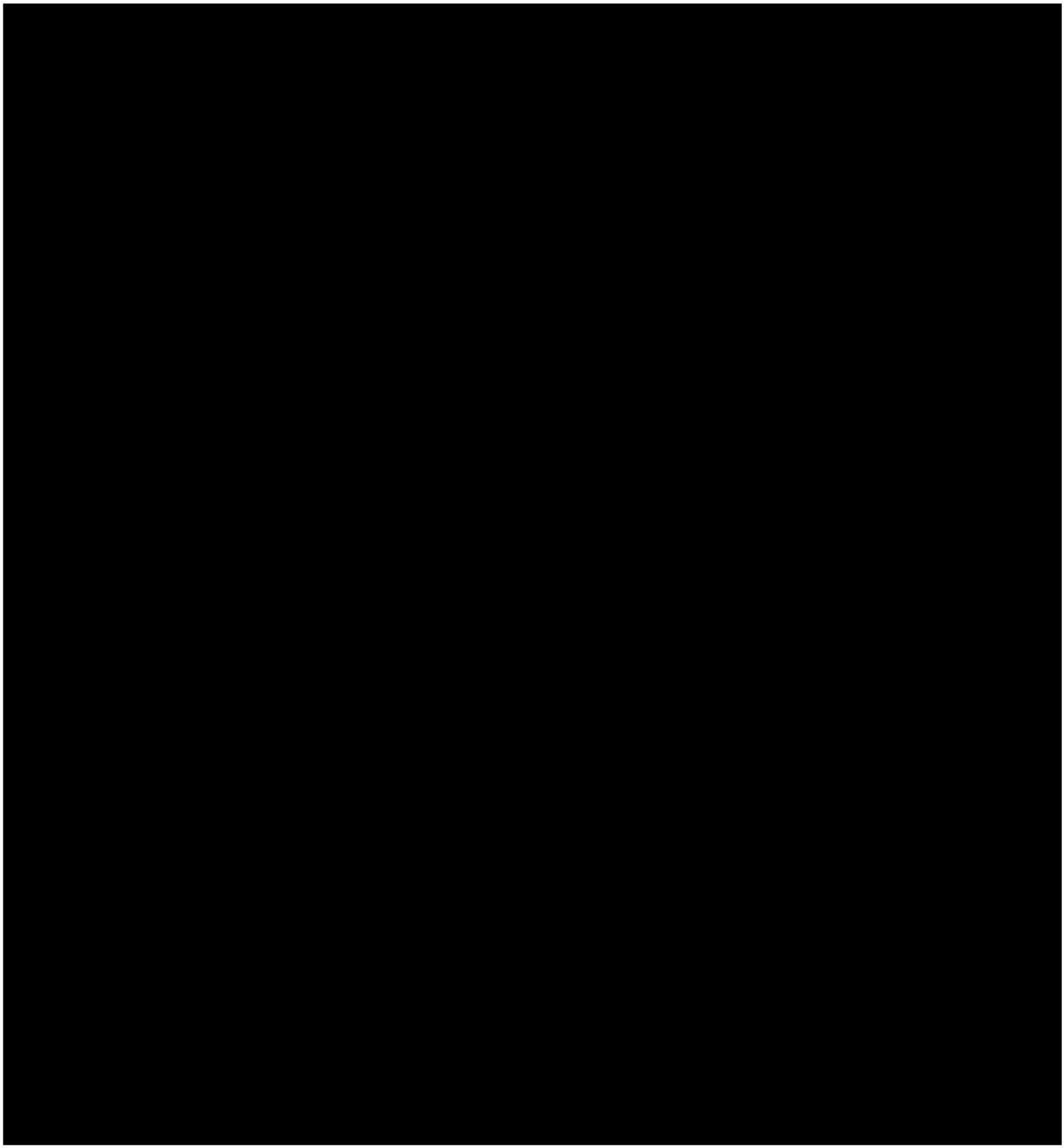
NO PAIN 0 _____ SEVERE PAIN 100

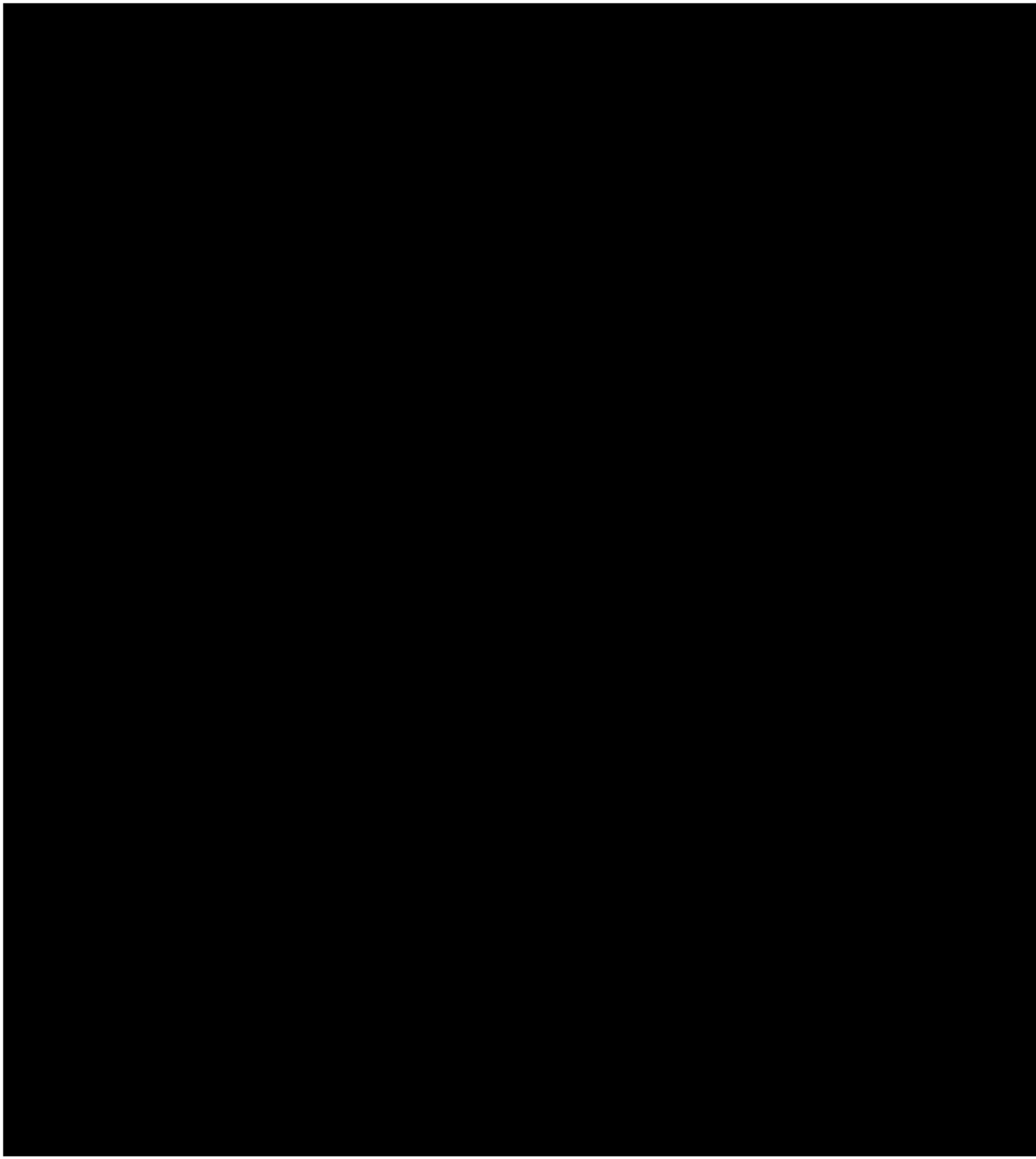
PAINSCAL____

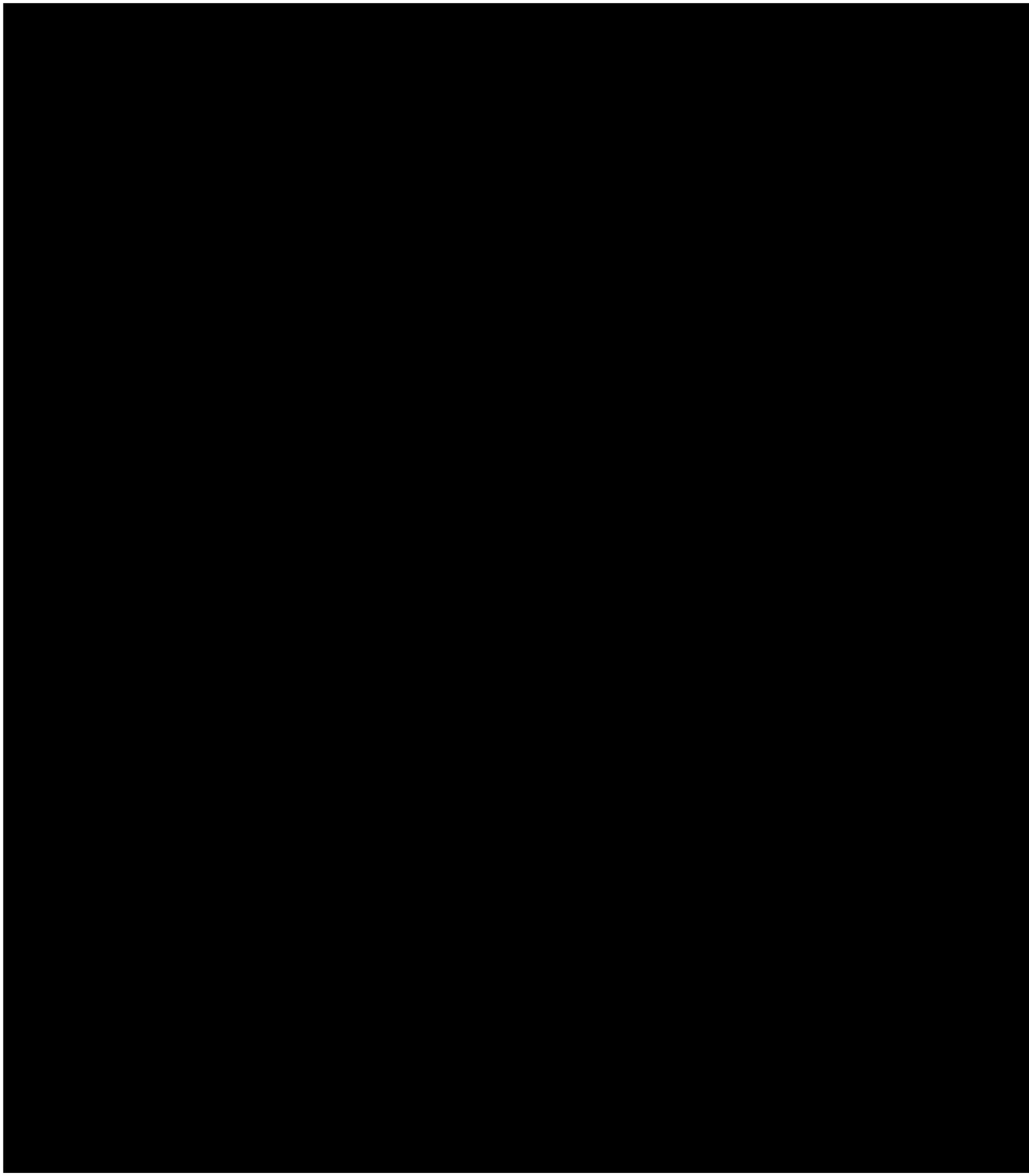
HAQ-DI – United States/English
HAQ-DI_AU1.0-eng-USorl.doc

[redacted]

[redacted]







Signature Page for RIM-CLIN-001081 v12.0

Task: Final Approval	[redacted]

Signature Page for RIM-CLIN-001081 v12.0