STATISTICAL ANALYSIS PLAN

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

Protocol Number:	KPL-404-C211
Study Phase:	Phase 2
Product Name:	KPL-404
Sponsor:	Kiniksa Pharmaceuticals, Ltd. Hamilton, Bermuda c/o Kiniksa Pharmaceuticals Corp. 100 Hayden Ave Lexington, MA 02421
Version:	Version 2.0
Date:	22Sep2023

HISTORY OF CHANGES

This current Statistical Analysis Plan (SAP) is based on Protocol Amendment 5 (Version 6.0) dated 28Jun2023 and Protocol Version 4 (Czech Republic) dated 13Jul2023. The previous version of the SAP was based on Protocol Amendment 4 (Version 5.0) dated 31Mar2023 and Protocol Version 3 (Czech Republic) dated 12Apr2023. This section summarizes major changes to the statistical analysis features in the SAP.

Version Number	Version Date	Description of Key Changes from Previous Version
1	08May2023	Original version
2	22Sep2023	Updated SAP per Protocol Amendment 5 and Protocol Version 4 (Czech Republic) as below. 1. Section 1.2 “Study Design” modification 2. Section 1.5 “Determination of Sample Size” modification 3. Added “baseline assessment” for mITT definition in Section 2.1 4. Section 3.5 “Analysis Timing” modification 5. “Prior inadequate response to number of classes of advanced targeted therapy (≤1 vs. ≥ 2)” instead of “Prior inadequate response to number of classes of advanced targeted therapy (1 vs. ≥ 2) ” in stratification factor for Cohorts 3 and 4 in Section 4.2.2 6. Added “The stratification will be derived per the information of prior inadequate response to RA medications for subjects who were randomized under Protocol Amendment 3, which will be reviewed in a blinded fashion before database lock” in Section 4.2.2 7. Corrected typos in the treatment duration calculation for Cohorts 1-3 and added treatment duration definition for Cohort 4 in Section 4.5 8. Add Cohort 4 schedule in Appendix 8.1

CONTENTS

LIST OF TABLES

LIST OF FIGURES

Listing of Abbreviations

Abbreviation	Full description
[redacted]	[redacted]
ACR	American College of Rheumatology
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
bDMARD	Biologic Disease-Modifying Anti-Rheumatic Drug
BMI	Body mass index
[redacted]	[redacted]
CI	Confidence interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CRO	Clinical research organization
CRP	High sensitivity C-reactive protein
CSR	Clinical study report
DAS28-CRP	Disease Activity Score of 28 Joints using C-Reactive Protein
DBL	Database lock
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EOS	End of study
ET	Early Termination
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HR	Heart rate
IPD	Important Protocol Deviation
IEC	International Ethics Committee
ICH	International Council for Harmonisation
IP	Investigational Product

Listing of Abbreviations

Abbreviation	Full description
[redacted]	[redacted]
ACR	American College of Rheumatology
[redacted]	[redacted]
AE	Adverse event
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ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
bDMARD	Biologic Disease-Modifying Anti-Rheumatic Drug
BMI	Body mass index
[redacted]	[redacted]
CI	Confidence interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CRO	Clinical research organization
CRP	High sensitivity C-reactive protein
CSR	Clinical study report
DAS28-CRP	Disease Activity Score of 28 Joints using C-Reactive Protein
DBL	Database lock
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EOS	End of study
ET	Early Termination
GCP	Good Clinical Practice
[redacted]	[redacted]
HR	Heart rate
IPD	Important Protocol Deviation
IEC	International Ethics Committee
ICH	International Council for Harmonisation
IP	Investigational Product

Abbreviation	Full description
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAKi	Janus kinase inhibitor
[redacted]	[redacted]
LOCF	Last observation carried forward
LS	Least squares
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
mITT	Modified intent-to-treat
[redacted]	[redacted]
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PT	Preferred term
qwk	Every week
q2wk	Every 2 weeks
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTcB	QT interval corrected for heart rate using Bazett's method
QTcF	QT interval corrected for heart rate using Fridericia's method
RA	Rheumatoid arthritis
[redacted]	[redacted]
SAE	Serious adverse experience/event
SAP	Statistical Analysis Plan
SC	Subcutaneous
[redacted]	[redacted]
SD	Standard deviation
SE	Standard error
[redacted]	[redacted]
SJC	Swollen joint count
SOC	System organ class
SRC	Safety Review Committee
[redacted]	[redacted]

Abbreviation	Full description
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
VAS	Visual Analog Scale
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains a detailed description of data presentations, statistical analysis methods, and data reporting specifications for the programming outputs and preparation of the Clinical Study Report (CSR) for study KPL-404-C211

The SAP is based on Protocol Amendment 5 (Version 6.0) dated 28Jun2023 and Protocol Version 4 (Czech Republic) dated 13Jul2023. The previous version of the SAP was based on Protocol Amendment 4 (Version 5.0) dated 31Mar2023 and Protocol Version 3 (Czech Republic) dated 12Apr2023.

A Safety Review Committee (SRC) SAP will be described in a separate document.

1.1. Study Objectives

1.1.1. Primary Objective(s)

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 3 and 4: To evaluate the efficacy of KPL-404 versus placebo for the treatment of rheumatoid arthritis (RA).

1.1.2. Secondary Objectives

Cohorts 1 and 2: To evaluate the efficacy of multiple SC doses of KPL-404 versus placebo for the treatment of RA.

Cohorts 3 and 4: To evaluate the safety, tolerability, and pharmacokinetics (PK) of KPL-404 versus placebo.

1.1.3. [redacted]

[redacted]

1.2. Study Design

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) 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 various 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 KPL-404: placebo 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 review 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)

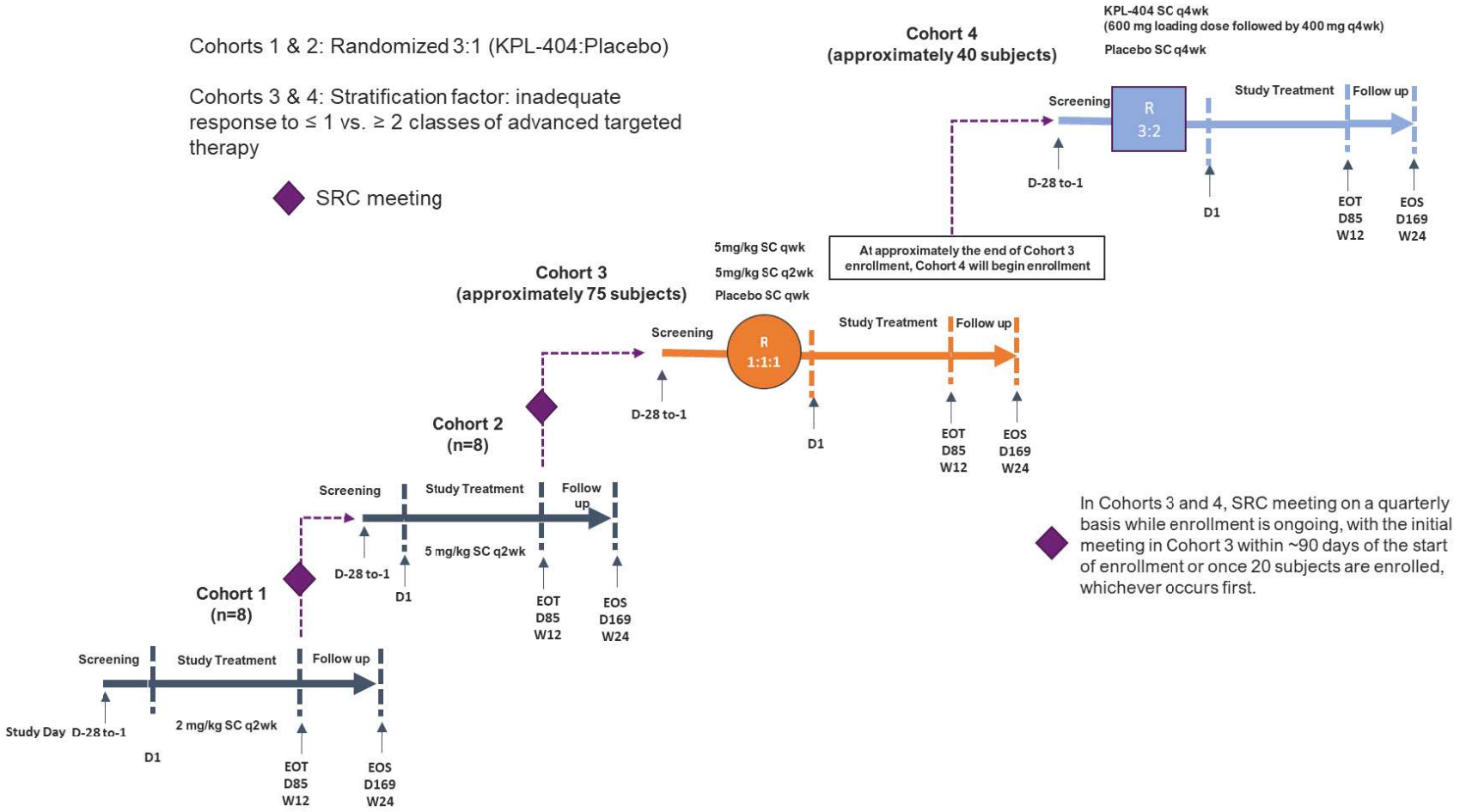
In Cohorts 3 and 4, SRC meetings will occur on a quarterly basis while enrollment is ongoing. The initial SRC meeting will occur within approximately 90 days of the start of enrollment or once 20 subjects are enrolled, whichever occurs first. All available safety and PK data will be reviewed by the SRC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

Subjects will be observed after IP administration on Day 1 and 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 (Section 8.1) 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 after study drug discontinuation) 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 first 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 1: Study Schema for KPL-404



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 inhibitor

1.3. Study Endpoints

1.3.1. Efficacy Endpoints

1.3.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in Disease Activity Score 28 with C-reactive protein (DAS28-CRP) at Week 12.

The definition of DAS28-CRP is in Appendix 8.3.

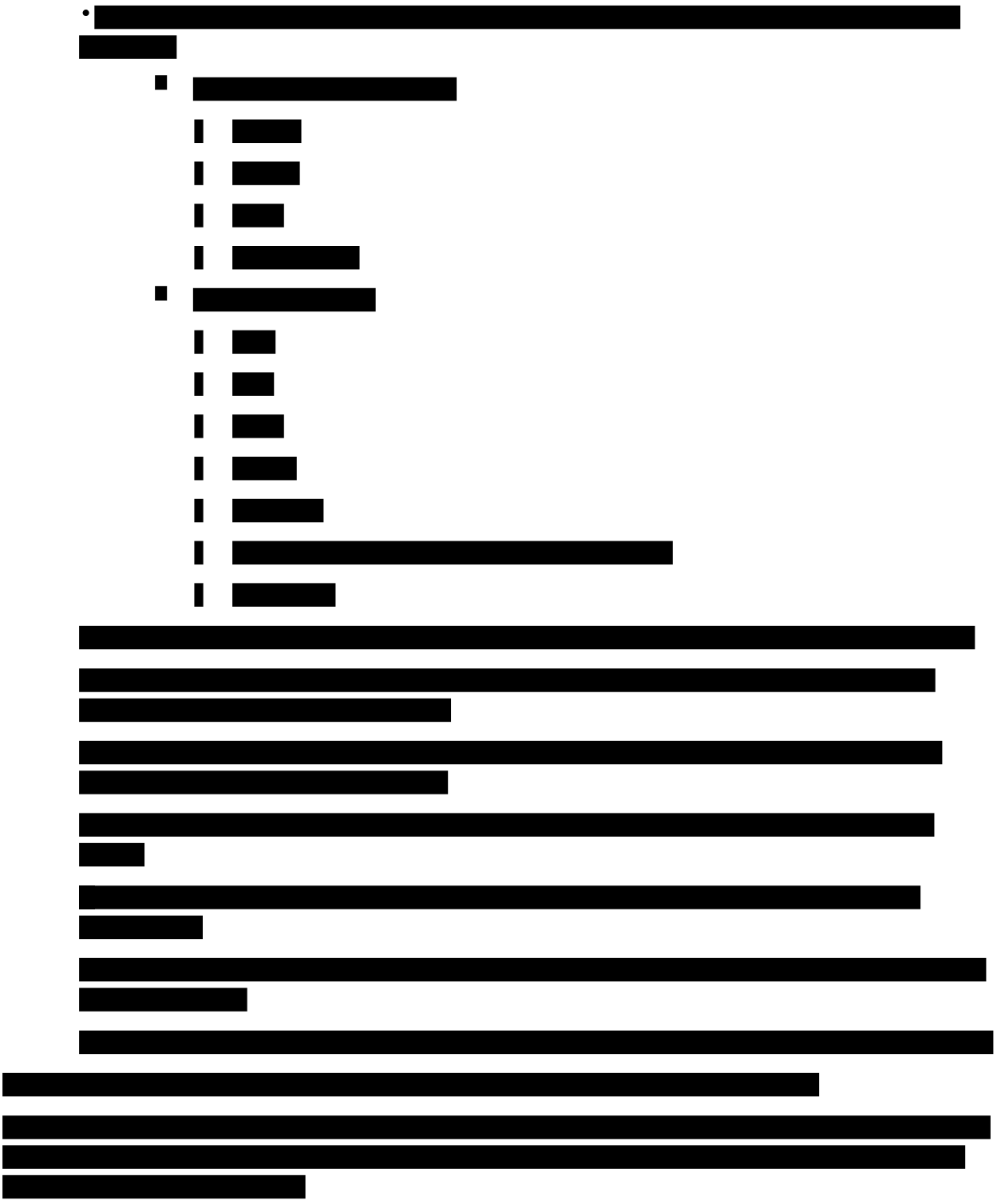
1.3.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as below.

- Proportion of subjects achieving an ACR20 response at Week 12
- Proportion of subjects achieving an ACR50 response at Week 12
- Proportion of subjects achieving an ACR70 response at Week 12

The definitions of ACR20, ACR50 and ACR70 are in Appendix 8.3.

1.3.1.3. [redacted]



1.3.2. Safety Endpoints

Safety endpoints include the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Vital signs and ECGs over time
- Changes from baseline in clinical laboratory test results

1.3.3. PK Endpoints

PK endpoints include the following:

- Maximum serum concentration (C_{max})
- Area under the serum concentration time curve from 0 to the end of the dosing interval (AUC_{0-t})

1.3.4. [redacted]

[redacted]

1.4. Estimands

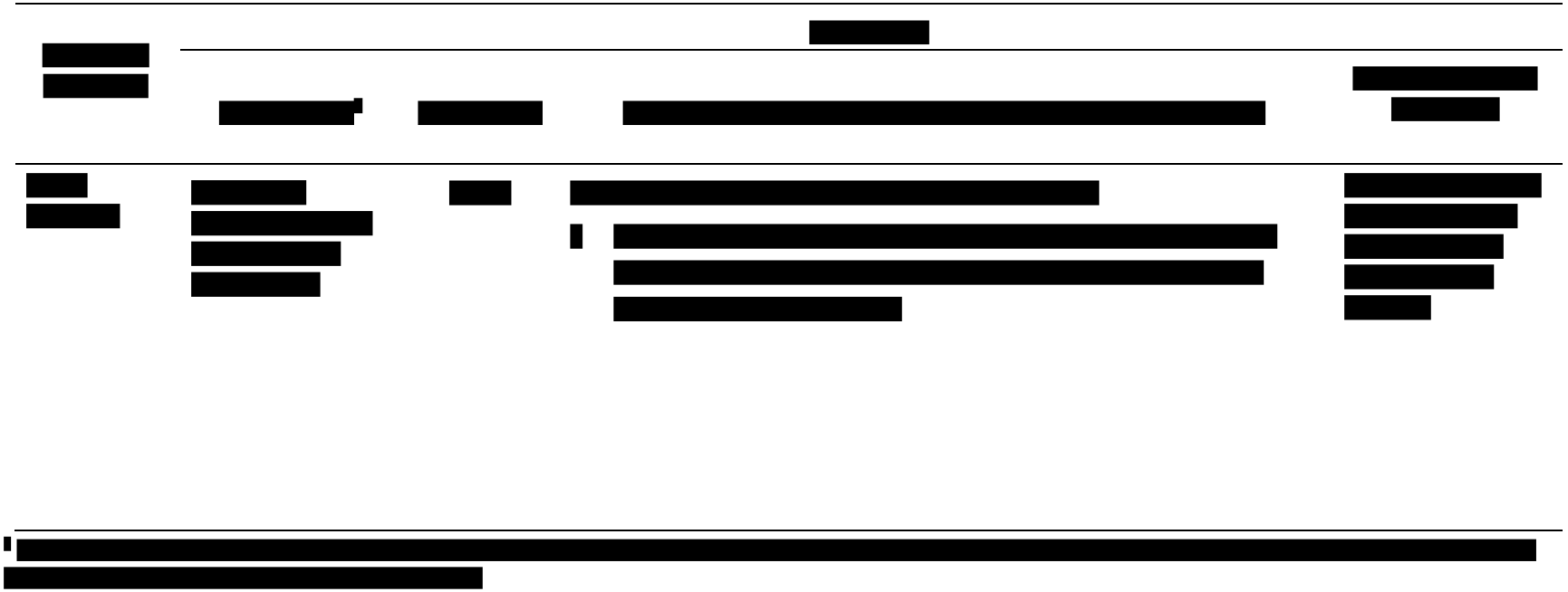
The primary estimands defined for main endpoints are summarized below in Table 1 . More details are provided in Section 4.6 .

Please note that subjects who miss at least one dose for any reason, without a clinical decision by the subject and investigator to discontinue study treatment, and then resume dosing before Week 12 are considered as having had dose interruption, not discontinuation, of study treatment. If a subject discontinues treatment prematurely, the subject is expected to complete the procedures for the end-of-treatment (EOT) visit (within approximately 2 weeks after last study drug administration). The EOT data will be considered as on-treatment.

Table 1: Summary of primary estimands for main endpoints

Endpoint Category	Estimands			
	Endpoint(s)[a]	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
Primary objective (for Cohort 3): To evaluate the efficacy of KPL-404 vs. placebo for the treatment of rheumatoid arthritis (RA).				
Primary endpoint	Change from baseline in DAS28-CRP at Week 12	mITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment or taking rescue medication before Week 12: data will be set to missing values after treatment discontinuation or rescue medication usage (whichever happens first), and the subject's last postbaseline observation before any intercurrent event will be carried forward (LOCF) to impute missing endpoint value (hypothetical strategy) In addition, the missing data imputation rules are as follows: • Missing data at Week 12 will also be imputed with LOCF method.	Analysis of Covariance (ANCOVA) model will be used with treatment, stratification factor and baseline as covariates.

Endpoint Category	Estimands			
	Endpoint(s)[a]	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
Secondary endpoint	Proportion of subjects achieving an ACR20/50/70 response at Week 12.	mITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment or taking rescue medication before Week 12: data will be set to missing values after treatment discontinuation or rescue medication usage, and the subject's last postbaseline observation before any intercurrent event will be carried forward (LOCF) to impute missing endpoint value for all seven ACR components. Responder status will be determined using the imputed components (hypothetical strategy). In addition, the missing data imputation rules are as follows: • Missing data at Week 12 will be imputed with LOCF method for all seven ACR components. Responder status will be determined using the imputed components. • Subjects who discontinue treatment due to lack of efficacy will be considered as non-responders for all time points beyond the time of discontinuation.	CMH test adjusted by stratification factor will be used.



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1.5. Determination of Sample Size

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 (CFB) for the KPL-404 being 1.2 points better than placebo (KPL-404 group CFB improvement = 2.2 points, placebo group CFB improvement = 1.0 point, standard deviation = 1.3). With 21 subjects in each of the 3 treatment groups (KPL-404 5 mg/kg qwk, KPL-404 5 mg/kg q2wk, and placebo) having completed 12 weeks of DAS28-CRP assessments, there is 83% power for the treatment comparison of active vs. placebo with 2-sided 0.05 type 1 error. In order to maintain this level of power after accounting for an anticipated discontinuation rate of 16%, up to 25 subjects per treatment group and up to a total of 75 subjects would need to be enrolled in 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.

2. STUDY ANALYSIS POPULATIONS

2.1. Modified Intent-to-Treat (mITT) Population

All randomized subjects who receive at least one dose of study drug and have a baseline assessment and 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.

2.2. Per Protocol (PP) Population

All mITT subjects who have no important protocol deviations that may potentially bias efficacy analyses of the study. These deviations will be pre-specified prior to study unblinding/database lock.

2.3. 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.

3. GENERAL STATISTICAL CONSIDERATIONS

All analyses and summaries will be produced using SAS® version 9.4 (or higher).

For inferential statistical analyses, each treatment group of KPL-404 will be compared to placebo. Unless otherwise specified, all tests will be at two-tailed using pre-specified level of significance 0.05.

Descriptive statistics (n, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) will be presented for continuous variables. For continuous efficacy endpoints, least square (LS) mean, LS mean difference, standard error (SE), and 95% confidence interval (CI) will be calculated.

For categorical variables (including binary variables), counts and percentages will be presented. For binary efficacy endpoints, 95% CI for difference in proportion and p-values will be presented.

Time to event data will be analyzed using the Kaplan-Meier (KM) method, which will include the estimated median with 95% confidence interval (CI) and the 25th and 75th percentiles.

Subject listings for all randomized subjects will be provided for all efficacy and safety data. In general, the subject listings will be sorted by cohort, treatment group, subject number and assessment date (and time, if applicable).

For Cohorts 1 and 2, pooled data will be analyzed by treatment group. Data from Cohorts 3 and 4 will be analyzed separately.

3.1. Baseline Value and Change from Baseline

The baseline value of efficacy parameters is defined as the last non-missing value before randomization and prior to the first dose of study medication otherwise specified.

For safety endpoints, baseline is defined as the last non-missing value obtained prior to the first dose unless otherwise specified.

Change from baseline, where applicable, will be calculated at each visit over time as the post-baseline evaluation minus the baseline evaluation.

3.2. Study Day

For efficacy endpoints analyses, study day is defined as the number of days from randomization date to the event/visit date. It is calculated as follows:

- If the event date falls on or after randomization date,

  Study day = Event or visit date – randomization date + 1

- If the event date falls before randomization date,

  Study day = Event or visit date – randomization date

For safety endpoints analyses, treatment day is defined as the number of days from first dose date to the event/visit date. It is calculated as follows:

- If the event date falls on or after first dose date,

  Treatment day = Event or visit date – first dose date + 1

- If the event date falls before first dose date,

  Treatment day = Event or visit date – first dose date

3.3. Analysis Visits

Efficacy assessments

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a subject receives treatment dose prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first treatment dose administration for that subject.

For efficacy variables, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 2. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same number of days away from the target day, the latest one will be used. Randomization day is used as the reference day (Day 1).

Table 2: Time window for efficacy variables

Visit	Target Day	Time windows for TJC68/SJC66	Time windows for ACR20/50/70, DAS28-CRP, [redacted] HAQ-DI, [redacted] P[redacted]
Screening (Days -28 to -1)	<1	≤-1	
Baseline (Week 0)	1	≤1	≤1
Week 2	15	2-22	2-22
Week 4	29	23-43	23-43
Week 8	57	44-71	44-71
Week 12	85	72-92	72-92
Week 14	99	93-106	93-106
Week 16	113	107-127	107-127
Week 20	141	128-155	128-155
Week 24	169	>155	>155

Safety assessment

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IP administration. Selected safety variables will be summarized by the analysis window defined in Table 3 for the by visit descriptive analysis. All available values will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same number of days away from the target day, the latest one will be used. First IP day is used as the reference day (Day 1).

Table 3: Time window for safety endpoints

		Time windows for							
Visit	**Target Day**	**Vital signs**	**CRP, [redacted]**	**Chemistry, Hematology, Coag. panel**	**Urinalysis**	**Urine pregnancy test**	**Height *, Weight**	**Physical examination**	**ECG**
Screening (Days -28 to -1)	<1	≤-1	≤-1	≤-1	≤-1	≤-1	≤-1	≤-1	≤-1
Baseline (Week 0)	1	<1-	<1-	<1-	<1-	<1-	≤1	≤1	
Week 2	15	2-22	2-22	2-22	2-22				
Week 4	29	23-43	23-43	23-43	23-43	2--43			
Week 8	57	44-71	44-71	44-71	44-71	44-71			
Week 12	85	>71	72-92	>71	>71	72-99	>1	>1	>1
Week 14	99		93-106						
Week 16	113		107-127			100-127			
Week 20	141		128-155			128-155			
Week 24	169		>155			>155			

* Height is collected at Screening visit only.

3.4. Missing Data Handling

Missing data handling for efficacy endpoints are specified in Section 4.6. No imputation will be performed for missing data for safety endpoints, unless otherwise specified. Incomplete AE start/end dates and incomplete medication start/end dates will be discussed in Section 8.2.

3.5. Analysis Timing

For Cohorts 1 and 2, the primary efficacy analysis will be performed after the last subject has completed the 12-week treatment period and data have been cleaned. While the follow-up period is ongoing, the study team with daily activities, investigational sites, or enrolled subjects will be kept blinded to the analysis results. The final analysis will be conducted after all subjects have completed the 24-week study and data have been cleaned for these two cohorts. The IP treatment for each subject in these two cohorts will still be kept blinded to the study team with daily activities, investigational sites, or enrolled subjects until the final database lock.

Please note that the analyses of Cohorts 1 and 2 at either Week 12 or at Week 24 should not be considered as an interim analysis, as Cohorts 1 and 2 are independent from Cohorts 3 and 4, which are the proof-of-concept portion of the study. In our primary efficacy analyses for Cohorts 3 and 4, data from Cohorts 1 and 2 will not be pooled with data from Cohorts 3 or 4. Hence there is no impact for Cohort 3 or Cohort 4 conduct and analyses.

For Cohort 3 and subsequently for Cohort 4, the primary analysis during the treatment period will be performed when all randomized subjects in a particular cohort have completed their 12-week treatment period and data have been cleaned. While the follow-up period is ongoing, the study team with daily activities, investigational sites, or enrolled subjects will be kept blinded to the individual results and IP treatment for each subject until the final database lock.

After all randomized subjects in Cohorts 3 and subsequently Cohort 4 have completed their 24-week study to include the post-treatment follow-up information and data have been cleaned, the database for each cohort will be locked sequentially. The final analysis for each cohort will be based on the individual final database lock.

4. STATISTICAL METHODOLOGY AND ANALYSES

4.1. Subject Disposition

The number and percentage of subjects will be tabulated for by Cohort, study drug, and overall:

- Screened Subjects (Signed Informed Consent)
- Randomized
- Randomized but not exposed to treatment
- Randomized and exposed to treatment

- Treatment Discontinuation
    - Subjects who completed treatment
    - Subjects who discontinued treatment early and the primary reasons for treatment discontinuation
- Study Discontinuation
    - Subjects who completed the study
    - Subjects who terminated the study early and the primary reasons for study discontinuation
    - Subjects with study ongoing at data cutoff

Subjects who were rescreened will be counted only once in the disposition summary based on the outcome of the last rescreening. If a subject failed multiple screenings, they will be counted only once as a screen failure. If a subject is randomized after multiple screenings they will be counted only once as a randomized subject.

4.2. Demographics and Baseline Characteristics

Demographic data and other baseline characteristics will be presented for all randomized subjects.

4.2.1. Demographics

The following demographic variables will be summarized by treatment group:

Age (years), calculated as the number of years between the date of birth and the date of signing the Informed Consent form.

- Age (years)
- Sex (Male or Female), Childbearing potential status for female.
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

4.2.2. Baseline Disease Characteristics

The following baseline characteristics will be summarized by treatment group.

- Duration of RA (Years)
- Rheumatoid factor (kIU/L)
- Anti-CCP (Positive, Negative)

- Stratification factor
  - Cohorts 1 and 2: Prior failure, inadequate response, or intolerance to RA medication category (bDMARD vs. JAKi)
  - Cohorts 3 and 4: Prior inadequate response to number of classes of advanced targeted therapy (≤1 vs. ≥ 2)
- ACR components
  - TJC
  - SJC
  - PGA
  - PhGA
  - HAQ-DI
  - CRP (mg/L)
  - Pain VAS
- DAS28-CRP

Please note that stratification factor (prior failure, inadequate response, or intolerance to RA medication category, bDMARD vs. JAKi) in Protocol Amendment 3 or earlier versions was changed to a new stratification factor (prior inadequate response to number of classes of advanced targeted therapy, ≤1 vs. ≥ 2) in Protocol Amendments 4 and 5 for Cohorts 3 and 4. The modified CRF will collect such information for subjects in Cohorts 3 and 4 who are randomized under either Protocol Amendment 3 or Protocol Amendments 4 and 5. The stratification will be derived per the information of prior inadequate response to RA medications for subjects who were randomized under Protocol Amendment 3, which will be reviewed in a blinded fashion before database lock.

4.2.3. Medical History

The medical history is coded using Medical Dictionary for Regulatory Activities (MedDRA) of the version at database lock. The summary of medical history will be presented with number (%) by System Organ Class (SOC) and Preferred Term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC in the KPL-404 combined column. Each subject will be counted only once for each PT within a SOC. Similarly, for determination of MedDRA SOC incidences, subjects who experience multiple medical conditions under the same SOC will be counted only once for that SOC.

Medical history details as collected on the electronic case report form (eCRF) such as body system, description, the date of onset, stop date and the current status of the condition will be presented in a by-subject data listing.

4.3. Prior, Concomitant and Rescue Medications

All medications will be coded using the World Health Organization (WHO) Drug Dictionary of the version at database lock.

Prior medications are defined as medications that started before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and continued into the treatment period, or (2) started on or after the date of the first dose of study drug. The number (%) of subjects who took prior and concomitant medications will be summarized on the anatomical class (ATC level 3) and PT.

The table for prior medications will be sorted by decreasing frequency of anatomic class followed by all PTs based on the overall incidence across treatment groups. In case of equal frequency regarding anatomical classes (respectively PTs), alphabetical order will be used.

The table for concomitant medications will be sorted by decreasing frequency of anatomic class followed by all PTs based on the incidence of the KPL-404 dose. In case of equal frequency regarding anatomical classes (respectively PTs), alphabetical order will be used.

If a subject develops RA flares requiring a rescue medication, the subject must discontinue IMP after informing the medical monitor. A table for these subjects taking RA rescue medications will be generated.

Similarly, a table of all prior RA therapies will be generated.

4.4. Protocol Deviations

A protocol deviation is defined as a change, divergence, or departure from the approved study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of study data or that may affect the subject's rights, safety, or well-being. All protocol deviations will be reviewed blindly before DBL.

Current ICH GCP guidelines request that the important protocol deviations must be listed in the clinical study report. These may include, but are not limited to:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria.
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn.
- Subjects that receive the wrong treatment or an incorrect dose.

A summary table will be provided as the number (%) of subjects with at least one important protocol deviation and the number (%) of subjects in each category. The protocol deviation data will also be presented as a by-subject data listing.

4.5. Treatment Exposure and Compliance

The study medication administration details including the administration date and time, dose, and comments will be presented in a by-subject listing.

The following parameters related to study drug administration will be summarized with descriptive statistics by treatment group for the safety population:

- Treatment duration in weeks is defined as [(minimum of (date of last study drug +13, EOS) - Day 1 + 1)/7] for Cohorts 1 and 2
- Treatment duration in weeks is defined as below for Cohort 3:

- 5 mg/kg SC qwk group: [(minimum of (date of last study drug +6, EOS) - Day 1 + 1)/7]
- 5 mg/kg SC q2wk group:
  - If the last dose is 5 mg/kg, then [(minimum of (date of last study drug +13, EOS) - Day 1 + 1)/7]
  - If the last dose is placebo, then [(minimum of (date of last study drug +6, EOS) - Day 1 + 1)/7]
- Placebo group: [(minimum of (date of last study drug +6, EOS) - Day 1 + 1)/7]

- Treatment duration in weeks is defined as [(minimum of (date of last study drug +27, EOS) - Day 1 + 1)/7] for Cohort 4
- Number of dose administrations (injections) received per subject will be summarized as 1 dose, 2 doses, 3 doses, 4 doses, 5 doses and 6 doses for Cohorts 1 and 2, up to 12 doses for Cohort 3, and up to 3 doses for Cohort 4. Treatment compliance is defined as the number of injections that the subject is actually received divided by the total number of injections that the subject is planned to take from the first injection of study medications up to the actual last injection of study medications. No imputation will be made for subjects with missing or incomplete data.

All study drug exposure data will be listed including reasons for dose not administered.

4.6. Analysis of Efficacy Endpoints

All efficacy analyses will be conducted by treatment group in the mITT population. The statistical analyses of the primary and secondary endpoints will be repeated in PP population. Analyses based on the mITT population will be the primary analyses and the analyses based on other populations will be considered as the supportive analyses.

Descriptive statistics will be provided for data in follow-up period by the treatment group, unless otherwise specified.

For Cohorts 1 and 2, descriptive statistics will be produced for all efficacy parameters. For the exploration of treatment effect, t-test and Fisher's exact test will be used for continuous endpoints and binary endpoints respectively.

For Cohorts 3 and 4, each endpoint will be analyzed following the details below.

4.6.1. Multiplicity Adjustment

As this is a phase 2 study, there is no multiplicity adjustment planned for the comparisons of multiple dose levels of KPL-404 versus placebo.

4.6.2. Analyses of Primary Efficacy Endpoint

The primary analysis for the efficacy endpoints will be based on the mITT population.

The following null hypothesis (H0) and alternative hypothesis (H1) will be tested for each KPL-404 dose against placebo:

- H0: No treatment difference between KPL-404 and placebo.
- H1: There is a treatment difference between KPL-404 and placebo.

The primary estimand for the primary endpoint is defined in Table 1, using the hypothetical strategy.

The intercurrent event that is deemed to have an impact on the interpretation of the variable of interest is treatment discontinuation or using any rescue medications. Data will be set to missing values after occurrence of any intercurrent event prior to Week 12, and the subject's last post baseline observation before the intercurrent event will be carried forward (LOCF) to impute missing endpoint value (for subjects whose postbaseline values are all missing, the baseline will be used to impute). Missing data at Week 12 will be imputed with LOCF method. Analysis of covariance (ANCOVA) models 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 stratification factor will be included as covariates in the ANCOVA model. The least square (LS) mean of each treatment group, LS mean differences (each KPL-404 group vs. placebo), their standard errors and two-sided 95% CIs, and the nominal p-values for treatment differences will be obtained from the model. No testing between the two KPL-404 dose groups will be conducted.

Sensitivity Analysis (As-Observed Analysis)

The data collected after the intercurrent event will be included in the sensitivity analysis to evaluate the robustness of the primary analysis results with respect to the method of handling data while treatment discontinuation or taking the rescue medications (treatment policy strategy). In addition, for subjects discontinuing the study treatment before Week 12, their off-study treatment values measured up to Week 12 will be included in the analysis. There is no imputation for missing data at Week 12.

For the sensitivity analysis of the primary efficacy endpoint, the observed data will be analyzed using a mixed model for repeated measures (MMRM) under the missing-at-random (MAR) assumption. Under this assumption, the efficacy outcome of subjects in each treatment group after early discontinuation will exhibit the same future evolution as subjects in the same group remaining in the study. The MMRM model will include fixed factors for treatment, visit, stratification factor, and treatment-by-visit interaction, and baseline DAS28-CRP as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. Kenward-Roger approximation will be used to calculate the denominator degrees of freedom. The LS mean, standard error, and LS mean treatment difference, along with the 95% CI and p-value will be provided.

4.6.3. Analyses of Secondary Efficacy Endpoints

The primary estimand for secondary efficacy endpoints is defined in Table 1, using the hypothetical strategy.

The intercurrent event is treatment discontinuation or using any rescue medications. Data will be set to missing values after occurrence of any intercurrent event prior to Week 12, and the subject's last post baseline observation before the intercurrent event will be carried forward

(LOCF) to impute missing endpoint value for all 7 ACR components (for subjects whose postbaseline values are all missing, the baseline will be used to impute). Missing data at Week 12 will be imputed with LOCF method. Responder status will be determined using the imputed components. However, subjects who discontinue treatment due to lack of efficacy will be considered as non-responders for all time points beyond the time of treatment discontinuation.

The analyses will use Cochran-Mantel- Haenszel (CMH) test adjusted by stratification factor. Response rate difference adjusted to stratification factors between each KPL-404 dose group and placebo will be derived. In addition, odds ratio and the corresponding 95% CI will be provided along with the p-values. If one or more expected cell frequencies are small (less than five), the CMH test may not be valid. In such cases, an exact CMH test will be performed instead.

In addition, logistic regression models may be used including key baseline characteristics as covariates along with the treatment groups.

4.6.4. [redacted]

[redacted]

4.7. Safety Analyses

All safety analyses will be conducted by treatment group in the Safety population for clinical and laboratory parameters, vital sign, and for adverse events (AEs). Adverse events will be coded using MedDRA of the version at database lock. Laboratory parameters, vital signs, and ECG data will be summarized as descriptive statistics by treatment, visit, and study period.

4.7.1. Adverse Events

Adverse events will be mapped to PT and SOC using the most up to date MedDRA of the version at database lock. A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug during treatment period. Furthermore, if an AE cannot be determined as treatment-emergent due to incomplete/missing date, conservatively, it will be considered as treatment emergent and included in the summary tables. A post-treatment AE is defined as any AE that occurs during the off-treatment period (see the definition of treatment duration in Section 4.5).

The following TEAE summaries will be summarized by treatment group.

- Any TEAEs
- Drug-related TEAEs
- TEAE by maximum severity (mild, moderate, severe)
- Serious TEAEs (SAEs)
- Drug related serious TEAEs
- TEAEs leading to dose interruption
- TEAEs leading to treatment discontinuation
- TEAEs leading to study discontinuation
- Death
- TEAEs of special interest (AESI)

A subject experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a subject experiences multiple AEs (preferred terms) within the same system organ class, then that subject will be counted only once for that system organ class. When summarizing by severity and relationship, only the event with highest severity or relationship will be counted. All AEs will be presented by SOC and preferred terms.

In addition, post-treatment AEs and SAEs will also be summarized.

All AEs will be displayed in by-subject listings.

4.7.2. Clinical Laboratory Tests

Hematology, chemistry, urinalysis, serology, and coagulation results will be summarized and listed.

Clinical laboratory assessments are listed in Table 4.

Table 4: Clinical Laboratory 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 = MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MDMA = methylenedioxymethamphetamine, PT = prothrombin time; PTT = partial thromboplastin time

The data collected in different units were converted to SI units (the International System of Units) for summary. The following summaries will be provided.

- Numeric laboratory values will be summarized as descriptive statistics for both actual value and change from baseline (post baseline minus baseline) by week. If lab values are recorded as <xx, the limits of xx will be used for summary.
- Shift table summarizing subject incidence of laboratory normal range (Low, Normal, High) at baseline contrasted with lowest or highest post baseline. Parameters with bidirectional abnormality (low and high) will be presented by post baseline lowest and highest. The shift table will include subjects without data so that all subjects in the SAF analysis set at baseline will be included.

Neutrophils

The incidence of neutropenia by maximal grade (lowest Neutrophils value reported) during the treatment period will be summarized. The 4 grades are defined as below:

- Grade 1: >=1.5 10^9/L – low limit of normal range
- Grade 2: >=1 – 1.5 10^9/L
- Grade 3: >=0.5 - 1 10^9/L
- Grade 4: < 0.5 10^9/L

For subjects with Grade 3 or 4 neutropenia, a listing with the individual neutropenia counts, WBC, platelet counts, lymphocytes and hemoglobin at each visit (including unscheduled visits for re-test) will be provided. In addition, the neutropenia counts at each scheduled visit during the study will be summarized by treatment group.

4.7.3. Vital Signs

All vital signs including weight, pulse rate, body temperature, respiration rate, and systolic and diastolic blood pressure will be summarized. Descriptive statistics will be presented for the observed value and the change from baseline by treatment and visit if applicable. For repeated assessments at a visit, the average of these values will be taken for the summary at the visit. A data listing of vital signs will also be provided.

4.7.4. Electrocardiogram

Numeric 12-lead ECG parameters will be presented for observed value and change from baseline at Week 12/EOT visit for each Cohort for the following parameters:

- Heart Rate
- QRS
- QT
- QTc
- PR

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results for the 12-lead ECG will be tabulated by Cohort. Incidence of a normal to abnormal shift for overall ECG interpretation from baseline to worst post baseline will also be summarized. For repeated assessment, if interpretations are the same, the last value will be taken for numerical assessment for summaries. If interpretations are different, the last value with the abnormal interpretation will be used for summary.

QT interval corrected for heart rate using Fridericia's method - Below incidence will be summarized:

- QTcF interval >500 msec
- QTcF change from the baseline (pre-dose) is >60 msec

All ECG data will be listed in a by-subject listing.

4.7.5. Physical Examination

Clinically significant new or worsened physical examination abnormalities following treatment will be recorded as AEs and will be reflected in the summary of AEs.

4.8. [redacted]

[redacted]

4.9. Pharmacokinetic (PK) Analysis

For all subjects, serum samples will be collected at time points indicated in the Schedule of Activities in Appendix 8.1.

Serum concentrations of KPL-404 and derived PK parameters (C_{max} and AUC_{0-t}) will be summarized using descriptive statistics by cohort and day/timepoint. Descriptive statistics will include arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and geometric coefficient of variation, as appropriate.

Individual listings of serum concentrations and PK parameters will be provided.

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. Scatter plots of PK parameters versus dose or log-dose will also be considered to assess dose proportionality. 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.

The PK analysis plan and report will be prepared separately.

4.10. [redacted]

[redacted]

5. INTERIM ANALYSIS

An interim analysis for Cohort 3 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 interim analysis may include cumulative safety, tolerability, PK, [redacted], clinical response (e.g., DAS28-CRP), and [redacted]. Should the Sponsor decide to conduct an Interim Analysis for Cohort 3, the Sponsor will provide the specifics of the interim analysis plan prior to such analysis as well as the list of individuals who received unblinded data prior to final database lock and formal unblinding of the study. The purpose of the interim analysis is to obtain early information for internal planning of subsequent KPL-404 development. The data from the interim analysis will not be communicated to the study team engaged in daily activities, to investigational sites, or to enrolled subjects until all subjects have completed the study and database lock has been achieved.

To maintain the overall probability of a type 1 error (i.e., alpha) at the specified 0.05 level, the Bonferroni-adjusted Haybittle-Peto method has been chosen as the alpha-spending function which assigns alpha=0.001 to the interim analysis, and 0.049 to the final analysis of the primary efficacy endpoint.

6. CHANGE FROM ANALYSES PLANNED IN PROTOCOL

The changes from the statistical analyses in Protocol Amendment 4 to SAP version 1.0 are summarized as below.

Analysis in the SAP	**Analysis planed in the protocol**	**Reason**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 2.1 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.	Section 11.3 Modified intent-to-treat (mITT) population: All randomized subjects who receive at least one dose of study drug will be included in the mITT population.	Updated definition in the SAP is more appropriate in the exploration of treatment effect in Phase 2 studies.

7. REFERENCES

1. Anderson, J et al (2012). Rheumatoid Arthritis Disease Activity Measures: American College of Rheumatology Recommendations for Use in Clinical Practice. *Arthritis Care Res (Hoboken)*. 2012 May; 64(5): 640–647. doi:10.1002/acr.21649.

[redacted]

8. APPENDICES

8.1. 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				

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**
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
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[p]:													
QuantiFERON test	X												
HBV/HCV	X												
HIV (local laboratory)[h]	X												
Serum β-hCG for WOCBP[i]	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**
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				
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]; [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 EOS; 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.

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[p]:																		
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]		■		■		■								■	■			■
Pharmacokinetic samples (serum)		X	X	X		X		X		X		X		X	X	X	X	X
[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; ACPA = anti-citrullinated protein antibody; 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]; [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 EOS; 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.

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; ACPA = anti-citrullinated protein antibody; 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.

8.2. Missing Data Imputation Rules

Handling of computation of treatment duration if investigational drug end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of investigational drug is equal to the date of last administration reported on the dosing CRF page. If this date is missing, the exposure duration should be kept as missing.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior and concomitant medication.

Handling of AEs with missing or partial date/time of onset

Missing or partial missing AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after, the AE will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of AE when date and time of first investigational drug date is missing

When the date and time of the first investigational drug is missing, all adverse events that occurred after or on the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

8.3. Definitions of DAS28-CRP, ACR20/50/70, [redacted]

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). 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 TJC and SJC will be performed according to the Schedule of Activities in Appendix 8.1.

DAS28-CRP

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 (mg/L) level, and patient global assessment of disease activity (PGA) score [collected via VAS, 0-100mm]. The components of the DAS28-CRP will be performed according to the Schedule of Activities in Appendix 8.1.

The DAS28-CRP is a measure of the disease activity and is calculated as follows:

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

A DAS28-CRP score above 5.1 means high disease activity, whereas a DAS28-CRP being ≥2.6 and < 3.2 indicates low disease activity, and below 2.6 represents remission.

ACR20/50/70

An ACR20 response is defined as at least a 20% improvement in both tender joint count (TJC) and swollen joint count (SJC), and at least a 20% improvement in three of the following five criteria: patient global assessment (PGA), physician global assessment (PhGA), functional ability measure [Health Assessment Questionnaire (HAQ)], patient's assessment of pain (visual analog scale; VAS) and C-reactive protein (CRP).

ACR50 and ACR70 are defined similarly, with 20% replaced by 50% and 70% respectively.

The components of the ACR20/50/70 will be performed according to the Schedule of Activities in Appendix 8.1.

HAQ-DI

The HAQ-DI is a standardized questionnaire developed for use in RA. The HAQ-DI, with the past week as the time frame, focuses on whether the respondent "is able to…" do the activity and

covers eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. The four responses for the HAQ-DI questions are graded as follows: without any difficulty = 0; with some difficulty = 1; with much difficulty = 2; and unable to do = 3. To calculate the Standard HAQ-DI Score (With Aids/Devices), there are three steps:

1. Sum the 8 category scores by using the highest sub-category score from each category.
   - For example, in the category ARISING there are two sub-category items. A subject responds with a 1 and 2, respectively; the category score is 2.
2. Adjust for use of aids/devices and/or help from another person when indicated.
   - Adjust the score for a category by increasing a zero or a one to a two.
   - If a subject's highest score for that sub-category is a two it remains a two, and if a three, it remains a three.
3. Divide the summed category scores by the number of categories answered (must be a minimum of 6) to obtain a HAQ-DI score of 0-3 (3=worst functioning).

A HAQ-DI score cannot be calculated validly when there are scores for less than six of the eight categories. HAQ-DI scoring ranges between 0 and 3. A high HAQ-DI score has been found to be a strong predictor of morbidity and mortality in RA.

Table 5: ACR components

ACR components	Range	Direction
TJC	0-68	Lower is better
SJC	0-66	Lower is better
Pain VAS	0-10	Lower is better
Patient global VAS	0-10	Lower is better
Physician global VAS	0-10	Lower is better
HAQ-DI	0-3	Lower is better
CRP (mg/L)	>0	Lower is better

CRP: C-reactive Protein, HAQ-DI: Health Assessment Questionnaire-Disability Index, TJC: Total Joint Counts, SJC: Swollen Joint Counts, VAS: Visual Analog Scale (cm).

[redacted]

[redacted]

Table 6: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]