STATISTICAL ANALYSIS PLAN
STUDY KPL-301-C001

A Phase 2, randomized, double-blind placebo-controlled study to test the efficacy and safety of KPL-301 in giant cell arteritis

Sponsor:	Kiniksa Pharmaceuticals, Ltd. Hamilton, Bermuda c/o Kiniksa Pharmaceuticals Corp. 100 Hayden Ave Lexington, Massachusetts 02421
Study Drug:	KPL-301
Protocol Number:	KPL-301-C001
Version:	1.0
Date:	10SEP2020

HISTORY OF CHANGES

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	10 SEP 2020	Final SAP

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST (SGOT)	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
AUC_{0-24}	Area under the plasma concentration curve from 0 to 24 hours
CI	Confidence interval
C_{max}	Maximum concentration value
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Computed Tomography Angiography
DILI	Drug-induced liver injury
DLCO	Diffusing Capacity for Carbon monoxide
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOT	End of treatment
ESR	Erythrocyte sedimentation rate
[redacted]	
FDA	Food and Drug Administration
GCA	Giant cell arteritis
HR	Hazard ratio
[redacted]	
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-treat analysis set
MRI	Magnetic Resonance Imaging
NJS	NJS Associates Company
[redacted]	

Abbreviation	Full Term
[redacted]	
PET-CT	Positron Emission Tomography
PFT	Pulmonary Function Test
[redacted]	
POC	Proof of Concept
PP	Per-Protocol
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous
[redacted]	
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEAESI	TEAE of special interest
TESAE	Treatment emergent serious AEs
TIA	Transient ischemic attack
TLG	Table Listings and Graphs
ULN	Upper limit of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) described the statistical analyses and data presentations to be performed for study KPL-301-C001 (protocol amendement 4.0 dated 30 March 2020) 'a Phase 2, randomized, double-blind placebo-controlled study to test the efficacy and safety of KPL-301 in giant cell arteritis (GCA)'.

It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety. It is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

The SAP will be finalized and approved prior to the clinical database lock for the final primary endpoint and safety analysis when all randomized subjects have completed 26 weeks of treatment. The analyses of safety, efficacy will include all data collected in the database through the data cutoff date. A safety follows up analysis will be conducted at the end of a 12-week washout safety follow-up period for all subjects.

[redacted]

1.1. Objectives

1.1.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of KPL-301 versus placebo, coadminsitered with a 26-week steroid taper, for maintaining sustained remission for 26 weeks in subjects with new-onset or relapsing/refractory giant cell arteritis.

1.1.2. Secondary Objectives

The secondary objectives of the study, in subjects with new-onset and relapsing/refractory GCA, are:

- To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose
- [redacted]
- To evaluate the safety and tolerability of KPL-301
- [redacted]

[redacted]

- [redacted]
- [redacted]

1.2. Study Design

This Phase 2 randomized, placebo-controlled Proof of Concept (POC) study will evaluate the efficacy and safety of KPL-301 coadministered with a 26-week corticosteroid taper in subjects with GCA. The study will consist of an up to 6-week screening period, a 26-week double-blind placebo-controlled period during which subjects will receive blinded KPL-301 or placebo coadministered

with corticosteroid taper, and a 12-week washout safety follow-up period during which subjects will discontinue and wash off blinded KPL-301 or placebo.

Approximately 70 subjects with GCA will be randomized to receive KPL-301 or placebo at a 3:2 allocation ratio stratified by disease status (new-onset or relapsing/refractory). Subjects randomized to KPL-301 will receive the drug 150mg every other week by subcutaneous (SC) injection co-administered with a 26-week steroid taper.

Subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse must discontinue study drug (KPL-301 or placebo) and should receive escape therapy in accordance with local SoC per the Investigator. Escape therapy may include, for example, prednisone or similar > 60mg/day, IV corticosteroids, other immunomodulatory agents, and/or approved therapies (e.g., tocilizumab).

1.3. Sample Size Justification

The sample size calculation was based on the assumption that time to flare follows an exponential distribution and the proportion of subjects without a flare by week 26 will be 50% in placebo and 85% in KPL-301, the median time to flare would be approximately 26 weeks in placebo arm and 111 weeks in KPL-301 arm. The hazard ratio (KPL-301 vs. placebo) would be approximately 0.234. With a 2-sided significance level of 0.05 and a 3:2 randomization ratio for KPL-301 vs. placebo, it would require approximately 20 events to achieve 87% power using a two-sided log rank test.

Approximately 70 subjects will be randomized by disease stratum (new-onset or relapsing/ refractory) to receive KPL-301 or placebo at a 3:2 allocation ratio.

1.4. Randomization, Stratification, and Blinding

An Interactive Web Response System (IWRS) will be used for assignment of the Subject Identification Number at enrolment, randomization to a treatment arm (KPL-301 or placebo), and assignment of blinded investigational product.

The randomization is stratified by subjects' disease status (new-onset or relapsing/refractory). Permutated block randomization will be employed with the block size specified in the randomization request.

If a subject is randomized using incorrect baseline information from the stratification factor, that randomization will be accepted but the analysis will be based on the correct baseline information.

To control bias during the study conduct and analyses, and to ensure proper type I error control, subject treatment assignments are blinded to study team members. An unblinded team will conduct analyses by treatment until the final database lock, upon which the study team will be unblinded.

1.5. Data Cutoff

There will be two data cutoffs. The first data cutoff is for the primary efficacy and safety analyses. It will occur after all randomized subjects have completed 26 weeks of treatment. The second data cutoff will occur after all subjects have completed safety follow-up.

1.6. Analysis Software

Analyses will be performed using Statistical Analysis Software SAS® version 9.4 or higher.

2. DEFINITION OF ANALYSIS SETS

2.1. Safety Analysis Set (SAF)

All randomized subjects who take at least 1 dose of of study drug (KPL-301 or placebo) will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually administered to each subject.

2.2. Modified Intent-to-Treat (mITT) Analysis Set

All randomized subjects who receive at least 1 dose of study drug (KPL-301 or placebo) and have at least 1 assessment in the double-blind treatment period will be included in the mITT analysis set. Efficacy analyses will be primarly based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment.

2.3. Per Protocol (PP) Analysis Set

All mITT subjects without important protocol deviations deemed to impact efficacy or ethical conduct will be included in the PP analysis set and will be determined before unblinding. Subjects who had steriod therapy increase for at least 5 mg/day for at least 1 week or took prohibited GCA medication duing the treatment period before a protocol-defined flare or end of treatment, whichever occurred first, will be excluded from the PP analysis set.

In this study, subjects are at prednisone doses between 20 mg/day and 60 mg/day at time of randomization. For this dose range and under a tapering schedule of 6 months, which is shorter than what is considered standard of care (1 year or longer), a prednisone dose increase of 5mg or greater is considered a clinically significant change for the purposes of this SAP. Typical GCA corticosteroid taper protocols can be found in (Docken, 2020).

3. EFFICACY PARAMETERS / ENDPOINTS

3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the time to flare by week 26 defined as time from randomization to the first flare occurring within the treatment period.

3.2. Secondary Efficacy Endpoints

The hierarchical order of the secondary efficacy endpoints are as follows:

- Sustained remission rate at Week 26
- Time to elevated ESR by Week 26
- Time to elevated CRP by Week 26
- Time to signs/symptoms of GCA or new or worsening vasculitis on imaging by Week 26
- Cumulative steroid dose at Week 26
- Percentage of subjects who have completed the corticosteroid taper and who have a normal ESR by Week 26
- Percentage of subjects who have completed the corticosteroid taper and who have a normal CRP by Week 26

- Percentage of subjects who completed the corticosteroid taper and who have neither signs/symptoms of GCA nor new or worsening vasculitis on imaging by Week 26
- Cumulative steroid dose at the end of the Washout Safety Follow-up period

[redacted]

4. SAFETY PARAMETERS / ENDPOINTS

The following are safety endpoints:

- Incidence of treatment emergent adverse events
- Change in physical exam results
- Change in vital signs
- Change in clinical laboratory parameters
- Change in ECGs
- PFTs
- DLCO
- Dyspnea score
- O_2 saturation

5. GENERAL STATISTICAL CONSIDERATIONS

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. In case of $n<2$, where n indicates the number of evaluable subjects at the particular time point, the standard deviation will be empty. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the analysis set unless otherwise specified. The statistic "Missing" will also be presented as the number of missing entries/subjects, if any at that visit/timepoint, and presented as a summary statistic only when non-zero.

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

In by-visit summary tables, only scheduled visits/timepoints will be summarized. In listings all visits and timepoints with any data collected, including both scheduled and unscheduled visits, will be included.

The change from baseline values will be derived for each subject as the post-baseline evaluation minus the baseline evaluation.

Unless otherwise stated, any confidence interval computed will be derived using the SAS default method in the statistical procedure.

All statistical comparisons will be made using two sided tests at the alpha=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference.

For stratified analyses, if there is no event for both arms, or all responses are the same within a stratification group, unstratified analyses will be conducted. This principal will be analogously applied to subgroups, but only to those subgroups for which lack of events/responses require it.

Specifications for table, graphs, and data listing formats can be found in the TLF specifications for this study.

5.1. Data Analysis General Informaiton and Definition

5.1.1. Study Drug

Study drug or study treatment refers to SC KPL-301 or placebo.

5.1.2. Day 1 and Other Days

Date of first dose of study treatment (or Day 1) is defined as the day of the first administration of study treatment after enrollment. First dose refers to first dose in study unless otherwise specified.

Date of last dose of study drug is defined as the date of last administration of study treatment (last dose) in the study.

5.1.3. Baseline Values

For purpose of analyses, a baseline is defined as the last non-missing value obtained prior to the start of study treatment. For CRP and ESR, a baseline should be within 3 days of study treatment.

5.1.4. Last Contact

Last contact or last date known alive is defined as the last non-imputed date of any subject record prior to or on the data cutoff date in the clinical database.

Calculations using dates will adhere to the following conventions:

Study day for a date of interest (TARGET DATE) is calculated as

STUDY DAY = TARGET DATE – Day 1 + 1 if TARGET DATE is on or after Day 1;

STUDY DAY = TARGET DATE – Day 1 otherwise.

Note that negative study days are reflective of observations obtained during the screening period.

5.1.5. Duration Derivation

Unless otherwise specified for a specific panel or variable, duration variables will be derived according to the following rules. Duration variables expressed in units greater than day will be rounded to 1 decimal place.

Duration (in days) = [end date – start date +1]

Duration (in weeks) = [end date – start date +1] / 7

Duration (in months) = [end date – start date +1] / 30.4375

Duration (in years) = [end date – start date +1] / 365.25.

5.1.6. Randomization Strata

Randomization will be stratified by whether the disease is new or relapsing/refractory. The actual categorization of the randomization strata of disease status will be used in the analyses instead of what was entered in the IWRS. The new-onset disease cohort includes subjects who have been diagnosed within 6 weeks of the first dose date using the Acute Phase Reactants, Signs/Symptoms and Diagnostic Criteria specified in the protocol. That is, a subject is considered new-onset if Day 1 – first diagnosis date + 1 <= 42 days; and is relapsing/refractory otherwise.

5.1.7. Week 26

Week 26 in this document refers to the completion of the treatment period, which might not be exactly the 26th week, e.g. if due to treatment delay/use of + 3 days of out of window visit allowance more than 2 times. Efficacy assessments before the safety follow up will all be included in "at week 26", or "by week 26" analyses unless otherwise specified.

5.2. Methods for Handling Missing Data

Refer to Section 9 for detailed date imputation guidelines.

5.3. Windowing of Visits

Data will be summarized by visit week defined in the protocol when appropriate (e.g. lab parameters).

5.4. Protocol Deviations

All protocol deviations will be entered into eTMS by site staff. The study team will have a blinded review of protocol deviations to determine their classification (important, not important) periodically. Prior to the database lock, the study team will assess impact of all important protocol deviations on the efficacy or ethical conduct and whether they should be excluded from the per-protocol analysis set.

The number of important protocol deviations and the number of subjects with at least one important protocol deviation will be summarized by treatment group. Also, the number of subjects with at least one important protocol deviation with/without a potential impact on efficacy will be summarized by treatment group. The protocol deviation criteria types will also be summarized, with reference to the evaluabilitly document.

All protocol deviations will be presented in by-subject listings, and subjects with protocol deviations that lead to exclusion from the per-protocol analysis set will be flagged.

6. STATISTICAL METHODOLOGY

6.1. Study Populations

A summary of analysis sets by treatment and overall will be presented along with percentages relative to all randomized subjects.

- Subjects randomized
- Subjects in the safety analysis set
- Subjects in the mITT analysis set
- Subjects in the PP analysis set

6.2. Subject Disposition

The number and percentage of subjects will be tabulated for the treatment discontinuation status for the safety analysis set by treatment and overall:

- Subjects who completed study treatment
- Subjects who discontinued early from study treatment

Reasons for early treatment discontinuation will be summarized by the following categories collected on the electronic case report form (eCRF):

- adverse event (AE)
- death
- lack of efficacy
- lost to follow-up
- non-compliance with study drug
- physician decision
- pregnancy
- protocol deviations
- sponsor decision to terminate study
- withdrawal by subject and
- other

The number and percentage of subjects will be tabulated for the end of study status for the safety analysis set by treatment and overall:

- Subjects who completed study
- Subjects who are still on study
- Subjects who terminated study early

Reasons for early study termination will be summarized by the following categories collected on the eCRF:

- adverse event
- death

- lack of efficacy
- lost to follow-up
- non-compliance with study drug
- physician decision
- pregnancy
- protocol deviation
- study terminated by sponsor
- withdrawal by subject
- other

In addition, time from randomization to last study assessment (weeks) will be summarized descriptively.

By-subject listings will be provided for study disposition including days on study, eligibility, and discontinuation from treatment and study reasons.

6.3. Demographics and Baseline Disease Characteristics and History

Demographic and other baseline characteristics will be summarized by descriptive statistics for each treatment group and overall for the SAF. They will also be presented in by-subject listings.

Descriptive statistics will be provided for the following:

- age
- weight (kg)
- height (cm)
- body mass index (BMI) (kg/m^2)

Frequency tabulations will be presented as collected in the eCRF for:

- age (< 65 years or ≥ 65 years)
- sex
- race
- ethnicity
- substance use (tobacco) history (cigarettes, cigars, pipes, or chewing tobacco).

Disease history such as disease status (new-onset or relapsing/refractory), prior GCA (yes/no), biopsy (yes/no), imaging (yes/no), and prior treatment will be summarized using frequencies and percentages and presented in by-subject listings. Time since diagnosis to randomization (month), ESR value for eligibility and at baseline, and CRP value for eligibility and at baseline (local and central separately) will be summarized by descriptive statistics.

6.4. Medical History

Medical history data will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 before database lock. Medical history data will be summarized for the SAF

by treatment group and overall, by system organ class (SOC) and preferred term (PT) in descending frequency for overall. Subjects with multiple occurrences of the same medical condition will be counted once per each unique SOC and unique PT.

All medical history data will be listed by subject.

6.5. Prior and Concomitant Medications

Prior medication is defined as medication with at least one dose taken before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose date of study drug + 90 days (inclusive) of study drug.

Post-treatment medication will be defined as medications taken after the last dose of study drug.

Additionally, the medications will be considered concomitant if the start date of the medication is missing.

A medication that started prior to the first dose of the study drug and continued after last dose date will be considered as prior, concomitant, and post treatment.

Prior and concomitant medications will be coded using WHO Drug Dictionary WHODrug version Enhanced 01Mar2018 B3 and will be classified by Anatomical Therapeutic Class (ATC) level 2 and preferred term (PT) for the Safety Analysis Set. Frequencies and percentages of subjects using each concomitant medication will be presented by treatment group. Subjects taking the same medication multiple times will be counted once per medication. All medication use will be listed regardless of the timing of the start of the medication.

6.6. Study Treatments and Extent of Exposure

Study drug exposure, prednisone taper exposure, and escape therapy will be summarized descriptived for the SAF by treatment and for overall. Cumulative steroid dose combining information from both prednisone taper and escape therapy will be summarized as efficacy endpoints and be further discussed in Section 6.7.3.5.

6.6.1. Treatment Duration

Duration of treatment (weeks) = (last dose date of drug – first dose date of drug + 1) / 7.

It will be calculated for study drug and corticosteroid taper respectively.

6.6.2. Cumulative Dose

Cumulative dose (mg) is defined as sum of all doses taken. The dosage will be counted as 0 for days when the drug is not taken/injected. It will be calculated for study drug, prednisone taper, and steroid respectively. Cumulative study drug and prednisone taper will be calculated during treatment period. Cumulative steroid doses will be calculated at the end of week 26 and at the end of the safety follow up.

For the study drug, one partial injection is considered half of the full dosage.

6.6.3. Average Daily Dose

Average daily dose (mg) is defined as the cumulative dose divided by the number of days dosed. This will be summarized for cumulative steroid dose.

6.6.4. KPL-301/Placebo Exposure

KPL-301 or placebo study drug exposure data will be summarized with descriptive statistics by treatment, and by treatment by randomization strata.

Summary statistics of study drug for the treatment duration (weeks) and number of injections will be presented. Number of injections by category (<10, 10-13, 14, >14) will be summarized by frequency and percent of subjects.

All KPL-301 exposure data will be listed.

6.6.5. Prednisone Exposure

Prednisone taper data will be summarized descriptively by treatment, and by treatment by randomization strata.

Summary statistics of prednisone for the treatment duration (weeks) and cumulative dose by earlier of flare and week 26 will be presented. Categorical summaries for prednisone starting dose (20mg, 25mg, 30mg, 35mg, 40mg, 50mg, 60mg) will be presented by treatment group.

All prednisone exposure data will be listed.

6.6.6. Escape Therapy Exposure

The number and percent of subjects receiving escape therapy, type of escape therapy and initial dose received will be summarized by treatment, and by treatment by randomization strata.

6.6.7. Compliance

Compliance to KPL-301/Placebo = Actual total number of injections received / planned total number of injections.

Compliance to prednisone will be measured by percentage of days in compliance = number of days in compliance / number of days on treatment. Descriptive summary will be presented for overall period and by week.

6.7. Efficacy Analysis

All efficacy analyses will be conducted by treatment for the mITT analysis set. Selected analyses may be in the PP analysis set. Endpoints involving flare will be based on adjudication primarily. Investigator assessment will only be used supportively.

6.7.1. Multiplicity Adjustment

Multiplicity adjustment with respect to the primary efficacy and secondary efficacy endpoints will be adjusted using the gate-keeping hierarchical testing procedure. The hierarchy order of the secondary endpoints is presented in Section 3.2. For each endpoint, the null hypothesis is that there is no treatment difference between KPL-301 and placebo. The alternative hypothesis is that KPL-301 is superior to placebo. For each test, the 2-sided type I error rate is 0.05. The primary endpoint will be tested first. If the 2-sided p-value is $\leq$0.05, statistical significance of the primary endpoint will be claimed, and the next hierarchical endpoint will be tested. This process will continue until an endpoint is not statistically significant.

There is no adjustment for other endpoints.

6.7.2. Analysis of Primary Efficacy Endpoint

The primary endpoint of time to flare by Week 26, is defined as time from randomization to the first flare occurring within the treatment period. Flare/relapse is defined as a C-reactive protein (CRP) of 1 mg/dL or greater and/or erythrocyte sedimentation rate (ESR) of 30 mm/h or greater AND at least one of the following signs or symptoms attributed to GCA:

- Cranial symptoms
  - New-onset localized headache
  - Scalp or temporal artery tenderness
  - Ischemic-related vision loss
  - Unexplained mouth or jaw pain upon mastication (i.e. claudication of tongue)
  - Transient ischemic aattach or stroke related to GCA
- Extracranial symptoms
  - Claudication of the extremities
  - Symptoms of PMR (shoulder & hip girdle pain associated with inflammatory morning stiffness)
- New or worsening angiographic abnormalities detected via MRI, CT/CTA, or PET-CT of the aorta or other great vessels or via ultrasound of the temporal arteries.

Supportive findings could include other symptoms related to worsening GCA, such as sustained daily recurrent fever with a temperature over 38°C for more than 1week, chronic anemia, or unexplained weight loss.

Subjects who do not experience a flare during this period will be censored according to Table 1 End of treatment (EOT) in the table refers to early discontinuation of treatment.

Table 1: Censoring Rules for Time to Flare by Week 26

	Scenario	Event or Censoring	Censoring Reason	Date of Event or Censoring
1	Flare occurrence on or prior to week 26	Event	No censoring	Date of flare
2	No flare occurrence on or prior to week 26	Censored	No flare occurrence	Date of last assessment by week 26
3	No flare occurrence on or prior to EOT	Censored	No flare occurrence by EOT	Date of last assessment by EOT
4	No post baseline assessment	Censored	No assessment	Date of randomization

Time to flare by week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier (KM) method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will be calculated using a log-log transformation. Plots of survival curves by treatment using the KM method will be presented. Additional survival plots will be provided by treatment for the stratification factor.

A log-rank test stratified by the stratification factor (disease status) will be used as the primary treatment comparison between KPL-301 and placebo. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding Wald 95% CI will be

calculated based on a Cox proportional-hazards model with treatment as a covariate and stratified by the stratification factor.

If subjects were randomized based on incorrect stratum, then the corrected stratum will be used for stratified analyses rather than the incorrect stratum recorded at randomization.

The primary analysis of time to flare will be based on the adjudication outcome. Time to flare per investigator's assessment will be used a supportive analysis of the primary endpoint. A 2x2 table of concordance will be used to assess the agreement between adjudicated and investigator assessments.

As a sensitivity analysis, the stratified analyses of time to flare based on adjudication will be repeated for the per protocol analysis set defined in Section 2.3 .

The stratified analyses of time to flare based on adjudication will also be repeated for the mITT analysis set by censoring subjects without flare before EOT at the last assessment date by week 26. That is, the censoring does not take into consideration of the early treatment discontinuation. The scenario 3 in the censoring table follows scenario 2 rule.

Subgroup analyses of the primary efficacy endpoint may be performed with age group, sex, race, and stratification factor.

6.7.3. Analysis of Secondary Efficacy Endpoints

All analyses of secondary efficacy endpoints will use the mITT population. Sustained remission rate will be based on the adjudication outcome. Local assessments of ESR, CRP, and imaging will be used for other secondary efficacy endpoints.

6.7.3.1. *Sustained remission rate at Week 26*

Subjects who complete the treatment period without a flare by week 26 will be consideted to have sustained remission. The sustained remission rate at week 26 can be obtained from the estimates of time to flare at week 26 by using the Kaplan-Meier method, along with their standard errors using Greenwood's formula. Comparison with p-value will be conducted between the treatment groups. Two-sided p-value and 95% CI calculated using normal approximation.

6.7.3.2. *Time to elevated ESR by week 26*

Time to elevated ESR will be defined as the time from randomization to earliest date of an ESR value of ≥30 mm/hr. All subjects who do not have an elevated ESR by week 26/ EOT will be censored at last assessment date or the randomization date, whichever is later.

Table 2: Censoring Rules for Time to Elevated ESR by Week 26

	Scenario	Event or Censoring	Date of Event or Censoring
1	Elevated ESR on or prior to week 26	Event	Date of elevated ESR
2	No elevated ESR on or prior to week 26	Censored	Date of last assessment with no elevated ESR by week 26
3	No elevated ESR on or prior to EOT	Censored	Date of last assessment with no elevated ESR by EOT
4	No post baseline assessment	Censored	Date of randomization

Analysis and presentation will be the same as that of the primary efficacy endpoint. The KM method to estimate the survival functions for each treatment group (overall and by stratification factor). The treatment comparison will be based on a stratified log-rank test. The Hazard ratio (HR) and its 95%

CI will be estimated using a stratified Cox model with treatment as the explanatory variable and strata as the stratification factor.

6.7.3.3. *Time to elevated CRP by week 26*

Time to elevated CRP will be defined as the time from randomization to earliest date of a CRP value of ≥1.0 mg/dL. All subjects who do not have an elevated CRP by week 26/ EOT will be censored at last assessment date or the randomization date, whichever is later. Detailed censoring rule follows that for ESR. Subjects with elevated CRP at baseline will be excluded from the analysis.

Analysis and presentation will be the same as that of the primary efficacy endpoint. The KM method to estimate the survival functions for each treatment group (overall and by stratification factor). The treatment comparison will be based on a stratified log-rank test. The HR and its 95% CI will be estimated using a stratified Cox model with treatment as the explanatory variable and strata as the stratification factor.

6.7.3.4. *Time to signs/symptoms of GCA or new or worsening vasculitis by imaging by week 26*

Time to signs/symptoms of GCA or new or worsening vasculitis by imaging will be defined as the time from randomization to earliest date of subjects experiencing signs/symptoms of GCA, or new or worsening vasculitis by imaging. All subjects who do not have an event by week 26/ EOT will be censored at last assessment date and/or randomization date, whichever is later. Detailed censoring rule follows that for ESR.

Analysis and presentation will be the same as that of the primary efficacy endpoint. The KM method to estimate the survival functions for each treatment group (overall and by stratification factor). The treatment comparison will be based on a stratified log-rank test. The HR and its 95% CI will be estimated using a stratified Cox model with treatment as the explanatory variable and strata as the stratification factor.

6.7.3.5. *Cumulative steroid dose at Week 26 and at the End of the Washout Safety Follow-up Period*

The cumulative corticosteroid dose from first dose date of study drug to Week 26 will be compared between the treatment descriptively, and analytically using analysis of covariance (ANCOVA). The stratification factor and the corticosteroid starting dose will be the covariates in the model for treatment comparisons. The analyses will include 95% CIs for the difference of the mean cumulative steroid doses between the treatment groups.

Similar analysis will be conducted for cumulative steroid dose from first dose date to the end of the washout safety follow up period.

The average daily dose during the same periods will be summarized descriptively.

6.7.3.6. *Percentage of subjects who have completed the corticosteroid taper and who have a normal ESR by week 26*

The number and percentage of subjects who completed the corticosteroid taper per schedule and have normal ESR (<30 mm/hr) by week 26 will be presented by treatment. Subjects will be considered to have completed the corticosteroid taper if receiving 1 mg/day for those start at 60 mg/day starting dose, or 0 mg/day for those start with doses less than 60 mg/day by week 26 and maintain through week 26. Having normal ESR by week 26 requires all assessments of ESR from the completion of corticosteroid taper through week 26 being normal. If there is no assessment after completion of taper, the subject will not be counted in the numerator.

The percentage will be compared between the treatment groups using a Cochran-Mantel-Haenszel test controlling for the stratification factor; the 95% confidence interval for the difference of percentages will be displayed using the Mantel-Haenszel weight for the stratification factor.

6.7.3.7. *Percentage of subjects who have completed the corticosteroid taper and who have a normal CRP by week 26*

The number and percentage of subjects who complete the corticosteroid taper and have normal C-reactive protein (<1.0 mg/dL) by week 26 will be presented by treatment. Having normal CRP by week 26 requires all assessments of CRP from the completion of corticosteroid taper through week 26 being normal. If there is no assessment after completion of taper, the subject will not be counted in the numerator.

The percentage will be compared between the treatment groups using a Cochran-Mantel-Haenszel test controlling for the stratification factor; the 95% confidence interval for the difference of percentages will be displayed using the Mantel-Haenszel weight for the stratification factor.

6.7.3.8. *Percentage of subjects who completed the corticosteroid taper and who have no signs/symptoms of GCA or new or worsening vasculitis by imaging by week 26*

The number and percentage of subjects who complete the corticosteroid taper and who have no signs/symptoms of GCA by week 26 will be presented by treatment. Having no signs/symptoms of GCA by week 26 requires all assessments of from the completion of corticosteroid taper through week 26 showing no signs/symptoms of GCA or new or worsening vasculitis by imaging by week 26. If there is no assessment after completion of taper, the subject will not be counted in the numerator.

The percentage will be compared between the treatment groups using a Cochran-Mantel-Haenszel test controlling for the stratification factor; the 95% confidence interval for the difference of percentages will be displayed using the Mantel-Haenszel weight for the stratification factor.

[redacted]

[redacted]

6.8. Safety Analysis

All safety analyses will be conducted based on the Safety Analysis Set. All safety data including those collected during the Washout Safety Follow-up will be listed by subject.

6.8.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment. Drug-related AEs will be considered those to be at least possibly related to investigational product based on the investigator's assessment.

Treatment emergent AEs (TEAEs) is defined as AEs that begin after the first administration of investigational products or existing AEs that worsen after the first dose of study medication through the 90 days after the last dose date.

TEAEs will be coded using MedDRA version 21.0. A summary of the frequency (number and percentage of subjects) of TEAEs will be presented by system organ class (SOC) and preferred term (PT) by treatment, in descreasing frequency of SOC and PT in the KPL-301 arm. The TEAE will also be analyzed by their severity (mild, moderate or severe), relationship to study drug, leading to death, resulting in dose interruption, leading to withdrawal of study treatment. Treatment emergent serious AEs (TESAE), drug related TESAEs, TEAE of special interest (TEAESI) will also be tabulated.

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and requires close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. AESI are defined in Section 13.1.3 of the protocol.

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 event with highest severity or relationship will be counted.

Tables will include the following details:

- Overview of TEAEs (summary from all the subsequent tables)
- TEAEs by severity
- Drug related TEAEs
- TESAEs
- Drug related TESAEs
- Non-serious TEAEs
- TEAESI
- TEAEs leading to permanent discontinuation of study drug
- TEAEs leading to dose interruption
- TEAEs resulting in deaths.

All AEs and SAEs occurring throughout the conduct of the study, including all-cause deaths, will be displayed in listings.

6.8.2. Clinical Laboratory Parameters

Laboratory assessments should be collected as per the schedule of assessments, starting at Screening, Baseline, Week 4, Week 12, Week 20, Week 26/EOT, and Final Safety Follow-up/Week 38.

Unscheduled laboratory assessments for safety issues are permitted as deemed necessary by the Investigator. Local laboratory tests and values may be used by the Investigator as necessary to support clinical decisions.

Clinical laboratory assessments are listed in Table 3.

Table 3: Clinical Laboratory Assessments

Clinical chemistry:	**Hematology:**	**Urinalysis:**
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Apolipoprotein A Apolipoprotein B Aspartate aminotransferase (AST) C3 C4 Calcium Chloride Creatinine Creatinine phosphokinase Glucose HbA1c High-density lipoprotein Low-density lipoprotein Phosphorus Potassium Sodium Total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN) Total Cholesterol Total protein Triglycerides Urea Uric acid	Hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential (total and percentage): Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Creatinine Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen

Other:
Serum pregnancy test prior to randomization Urine pregnancy test at Day 0, Week 12, Week 26 and the Final Washout Safety Follow-up Visit.

Continuous laboratory data will be examined for trends using descriptive statistics of actual values and changes from baseline over time in each treatment group. These data will also be categorized as low, normal or high based on the reference ranges of the central laboratory. Shift tables from baseline to worst post baseline time point will be presented. In shift tables from baseline to worst

post-baseline value, the worst value post baseline within a subject will include both scheduled and unscheduled visits. In each shift table, the denominator of the percentage in a cell within a baseline category (e.g., normal) will be the total number of subjects in each treatment group in the category at baseline.

Biochemistry and hematology lab tests will be assessed relative to laboratory normal ranges (low, normal, high). Shift from baseline to the worst grade on study, and from baseline to by visit reference will be presented. Shifts from baseline to worst value on study will be presented for categorical or ordinal lab parameters. Incidence of subjects with laboratory values outside laboratory supplied normal range will also be presented.

All biochemistry and hematology results will be presented in by-subject listings. Urinalysis results will be summarized by categoricals and will also presented in the listing.

6.8.3. Vital Signs

Vital signs including measurements of weight, respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature will be measured at each scheduled study visit starting from Screening. Blood pressure measurements should be obtained after the subject has been seated for at least 5 minutes. Body weight and BMI will also be included.

Vital signs will be summarized using descriptive statistics of actual values and changes from baseline over time and by treatment group.

All vital signs assessments will be listed appropriately.

6.8.4. Electrocardiogram

ECG variables will be summarized using descriptive statistics for each treatment group at Screening and post-baseline visit (unscheduled) for the following:

- QT
- RR
- PR
- QRS
- Heart Rate

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 treatment group at Screening. ECG assessments will be performed only at Screening, with the exception of unscheduled assessments.

All ECG data will be listed in by-subject listings.

6.8.5. Physical Examination Findings

A complete physical examination includes at minimum evaluation of vital signs, head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Physical examination assessments will be measured at Screening and Week 26/EOT.

Physical examination findings will be summarized by visit. The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant findings will be presented for each body system.

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

All physical examination findings will be presented in by-subject listings.

6.8.6. Respiratory Evaluations

Pulmonary Function Test (PFT) and Diffusing Capacity for Carbon monoxide (DLCO) will be assessed at Screening, Week 12, Week 26/EOT, and Final Safety Follow-up /Week 38 with a window of ±14 days.

PFTs, DLCO, and oxygen saturation will be summarized using descriptive statistics of actual values, change from baseline, percent change from baseline over time and by treatment group.

Percent of subjects meeting certain threshold values will be summarized over time and by treatment group for PFTs (<20%, ≥20% reduction from a previous value), and DLCO (<20%, ≥20% reduction from a previous value).

Dyspnea score will be summarized using descriptive statistics of actual values and change from baseline over time, and by minimum and maximum post-baseline value. Percent of subjects meeting threshold values of <3, 3-4, ≥5 will be summarized over time by treatment group.

Boxplots of actual results and change from baseline will be produced for PFTs, DLCO, oxygen saturation, and dyspnea score at each scheduled study visit.

The modified Borg scale (Borg, 2010) is a validated patient reported outcome and will be used to assess subjects' perceived sensation of difficulty in breathing (dyspnea) while resting. This scale is a linear scale of numbers ranking the magnitude of difficulty in breathing, ranging from 0 (nothing at all) to 12 (absolute maximum/highest possible).

Oxygen saturation will be assessed as part of respiratory system assessment. Pulse oximetry must be performed before PFTs and should be done with the subject in a seated position after a 10-minute period of rest. Dypsnea and oxygen saturation assessments will be conducted at every study visit with the exception of Baseline.

All respiratory evaluation data will be presented in by-subject listings.

7. CHANGES TO PLANNED ANALYSES FROM THE PROTOCOL

7.1. Changes from Protocol

- The protocol stated the first administration of subcutaneous KPL-301/placebo and oral prednisone taper will take place at the study site on Day 0. In this SAP, we defined the first administration of subcutaneous KPL-301/placebo as Day 1. The start date of the oral prednisome taper is not included the definition of Day 1 since not all patients took the first dose of subcutaneous KPL-301/placebo and oral prednisone taper on the same day.
- TEAE definition was updated to include AE through last dose + 90 days.
- CM definition was updated to include medications through last dose + 90 days.
- Included PFTs, DLCO, Dyspnea score, O_2 saturation in safety endpoints.
- The protocol described the categories of cranial symptoms as follows. Section 6.7.2 of this SAP adopts the abbreviated categories from the eCRF.
  - New or recurrent headache or pain or tenderness of the scalp or the temporal artery

  - Visual signs/symptoms such as ischemic retinopathy, optic neuropathy, diplopia, amaurosis fugax, etc.
  - New or recurrent claudication of the tongue, masseter muscle, or worsening temporal artery signs and symptoms
  - Transient ischemic attack (TIA) or stroke related to GCA in the opinion of the Investigator
- The protocol described the categories of extracranial symptoms as follows. Section 6.7.2 of this SAP adopts the abbreviated categories from the eCRF.
  - Classic PMR-like symptoms, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness
  - New or recurrent claudication in the peripheral circulation (i.e., in one of the extremities)

7.2. Impact of Covid-19 pandemic

The impact of the pandemic to the study conduct is expected to be limited as assessed by the amount missing data due to lack of office visits or other COVID-19 related issues with the conduct of the trial. Therefore there are no special data handling rules and analyses implemented for COVID-19 related protocol deviations. A separate document will be prepared to summarize any protocol deviations which occurred as a result of the pandemic.

8. REFERENCES

Borg GAJ. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14:37781.

Docken WP. Treatment of Giant Cell Arteritis. UpToDate Aug 2020 https://www.uptodate.com/contents/treatment-of-giant-cell-arteritis

Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005 Jan;113(1-2):9-19.

[redacted]

Mannion AF, Balagué F, Pellisé F, Cedraschi C. Pain measurement in patients with low back pain. Nature Clinical Practice Rheumatology 2007;3(11):610-18.

SAS Institute Inc. (2001): The SAS System, Version 8.2. Cary, NC. SAS Institute Inc.

[redacted]

[redacted]

9. APPENDICES

9.1. Handling of Missing Safety Data

No imputation will be made for completely missing date unless otherwise specified. General imputation rules mentioned below apply to partially missing or impossible dates:

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date
- If the start date is not missing, and the imputed stop date is before the start date, then the imputed stop date will be equal to the start date
- Any imputed dates need to be logical. For example, last dose date should not be later than death date.

When imputation rules in subsequent sections contradicts the general rule, always follow the general rule.

9.1.1. Adverse Event Date Imputation

Follow the general rule specified in Section 9.1.

Incomplete Start Date:

Missing day, month, and year

No imputation will be made; the corresponding AE will be included.

Missing day and month

- If the year is the same as the year of the first dose date, then impute day and month as the day and month of the first dose
- If the year is prior to the year of the first dose date, then impute day and month as 31 Dec
- If the year is after the year of the first dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the same as those of the first dose date, then impute day as the day of the first dose date
- If either the year of partial date is before the year of the first dose date, or the years are the same, but the month of partial date is before the month of the first dose date then impute day as last day of the month
- If either the year of partial date is after the year of the first dose date, or the years are the same, but the month of partial date is after the month of the first dose date, then impute day as first day of the month.

Incomplete Stop Date:

Missing day, month, and year

- No imputation will be made.

Missing day and month

- If the year is the same as the year of the last dose date, then impute day and month as the day and month of the last dose date
- If the year is prior to the year of the last dose date, then impute day and month as 31 Dec
- If the year is after the year of last dose date, then impute day and month as 01 Jan.

Missing day only

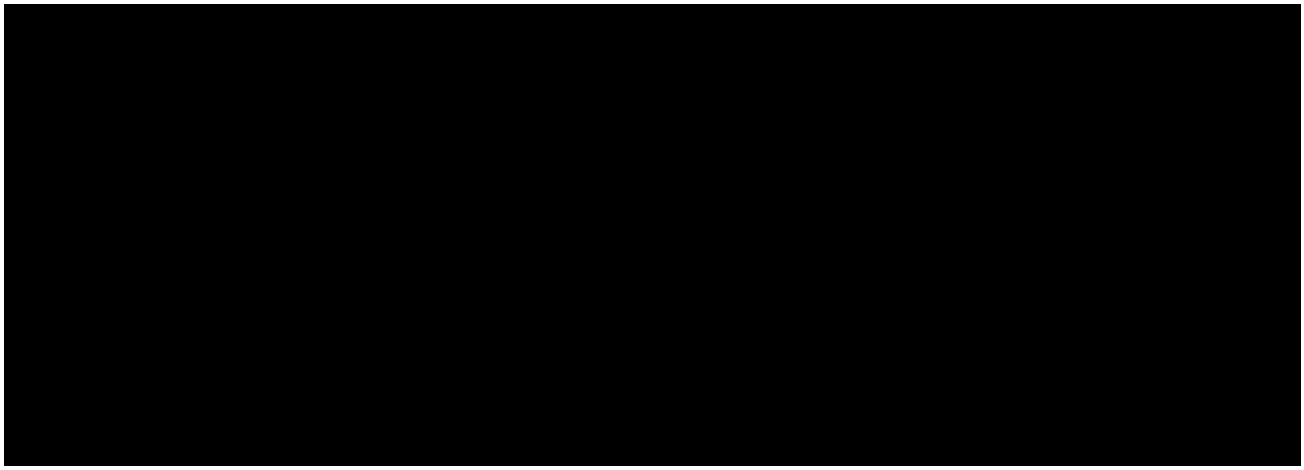
- If the month and year are the same as those of the last dose date, then impute day as the day of the last dose date;
- If either the year of partial date is not the same as the year of the last dose date, or the years are the same, but the month of partial date is not the same as the month of the last dose date, then impute day as last day of the month.

9.1.2. Concomitant Medication Date Imputation

Follow the general rules specified in Section 9.1 and rules in Section 9.1.1 .

[redacted]

[redacted]



Signature Page for RIM-CLIN-000608 v2.0

Approval	[redacted] 11-Sep-2020 02:14:52 GMT+0000

Approval	[redacted] 11-Sep-2020 02:21:19 GMT+0000

Approval	[redacted] 11-Sep-2020 11:24:56 GMT+0000

Approval	[redacted] 11-Sep-2020 11:38:01 GMT+0000

Signature Page for RIM-CLIN-000608 v2.0