Clinical Study Protocol

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

Protocol Number:	KPL-301-C001
EudraCT Number:	2018-001003-36
IND Number:	139,960
Investigational Medicinal Product:	KPL-301 (CAM-3001)
Phase:	Phase 2
Sponsor:	Kiniksa Pharmaceuticals, Ltd. Hamilton, Bermuda c/o Kiniksa Pharmaceuticals Corp. 100 Hayden Ave Lexington, Massachusetts 02421
Medical Monitor:	
Date of Protocol:	30 March 2020
Version of Protocol:	4.0

1 Protocol Approval

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

Protocol Number: KPL-301-C001

This study will be conducted in compliance with the clinical study protocol, ICH Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Senior Vice President
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100 Hayden Ave
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[redacted]
Signature

30 MAR 2020
Date

2 *Investigator and Administrative Structure*

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Responsible CRO:	[redacted]

3 Synopsis

Trial Number:

KPL-301-C001

Trial Title:

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

Trial Centers:

Multi-center Global Study

Development Phase: 2

Objective(s):

Primary:

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

Secondary:

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

a) To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose.

[redacted]).

c) To evaluate the safety and tolerability of KPL-301.

[redacted]

Efficacy Endpoints:

Primary Endpoint:

- Time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period

Secondary Endpoints:

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

[redacted]

Safety Endpoints:

- Incidence of treatment emergent adverse events
- Change in physical exam results
- Change in vital signs
- Change in clinical laboratory parameters
  - Serum chemistry
  - Hematology
  - Urinalysis

Methodology:

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 patients with GCA. The study will consist of a Screening Period (up to 6 weeks), a 26-week Double-Blind placebo-controlled Period during which subjects will receive blinded KPL-301 or placebo coadministered with a 26-week corticosteroid taper, and a 12-week Washout Safety Follow-up Period during which subjects will discontinue and wash off blinded KPL-301 or placebo.

Screening/Diagnostic Period:

Following signing of the informed consent form (ICF), potential subjects 50-85 years of age (inclusive) will be screened for meeting study-specified diagnostic criteria for GCA.

- Acute Phase Reactants - Westergren erythrocyte sedimentation rate (ESR) > 30 mm/hour or C-reactive protein (CRP) ≥ 1 mg/dL

  AND
- Signs/Symptoms - At least one of the following:
  i. Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp, or temporal artery pain or tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

ii. Unequivocal extra-cranial symptoms of GCA, such as claudication of the extremities

iii. Symptoms of polymyalgia rheumatica (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

AND

- Diagnostic Criteria - At least one of the following:
  i. Temporal artery biopsy (TAB) or ultrasound revealing features of GCA
  ii. Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as magnetic resonance imaging (MRI), computed tomography (CT)/computed tomography angiography (CTA) or positron emission tomography (PET)-CT of the aorta or other great vessels

Upon successful completion of the screening procedures, diagnosis criteria will be entered into an IWRS, and eligible subjects will be stratified for randomized study treatment into two cohorts according to whether subjects have new-onset disease or relapsing/refractory (hereafter, "relapsing" for brevity) disease.

- **New-onset** - The new-onset disease cohort includes subjects who have been diagnosed within 6 weeks of Day 0 using the above Acute Phase Reactants, Signs/Symptoms and Diagnostic Criteria.
- **Relapsing/refractory** – (either or)
  - The relapsing disease cohort includes subjects having prior documented diagnosis of GCA as per Diagnostic Criteria above > 6 weeks before Day 0 and who have active GCA disease defined by Acute Phase Reactants and Signs/Symptoms within 6 weeks of Day 0.
  - The refractory nonremitting disease subject has had no remission since the diagnosis of disease as per clinical expectations. Thus, the subject has documentation of prior diagnosis of GCA as per Diagnostic criteria above > 6 weeks before Day 0; however, presence of Acute Phase Reactants and Signs/Symptoms as per above persists within 6 weeks of Day 0.

Subjects who complete screening procedures and are not considered eligible (screen failures) may be rescreened one time provided there is reason to believe that eligibility criteria will be met.

Base Treatment Period:

Stratified eligible subjects will enter the double-blind treatment period after randomization 3:2 to blinded treatment with KPL-301 150 mg or placebo administered subcutaneously (SC) every other week (every 2 weeks). All subjects will also receive an unblinded 26-week oral prednisone taper according to a standardized tapering protocol.

Prior to first administration of KPL-301 or placebo, all subjects are required to have achieved remission (i.e., resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour). Should a subject in screening not achieve remission within the initial screening period they can be rescreened using their prior flare documentation following the relapsing/refractory non-remitting inclusion criteria.

The first administration of SC KPL-301/placebo and oral prednisone taper will take place at the study site on Day 0. Subsequent doses of KPL-301/placebo will be administered at the study site in conjunction with a scheduled study visit or administered by the subject on an outpatient basis in accordance with the dosing schedule. The oral steroid taper will be self-administered by study subjects on a daily basis.

Subjects will be followed at the study site at Weeks 1, 2, 3, 4, and approximately every 4 weeks thereafter (see Table 1). Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study site at any time.

If a flare/relapse is suspected during the treatment period, the Investigator must consult the Contract Research Organization (CRO)-designated Medical Expert to review and harmonize the elements of the diagnostic work-up. Flare/relapse is defined as a re-increase of CRP from normal to 1 mg/dL or greater and/or of ESR from less than 20 mm in the first hour to 30 mm or greater AND at least one of the following signs or symptoms attributed by the Investigator to new, worsening, or recurrent GCA:

- Cranial symptoms
  - 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
- Extracranial symptoms
  - 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)
- 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 in the opinion of the Investigator 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.

Although either acute phase reactant (CRP or ESR) may be used during the study for eligibility and to determine remission or flares, it is advisable that the same acute phase reactant used to determine remission at screening also be used to determine flares during the treatment period.

All elements of the diagnostic work-up pertinent to the Investigator diagnosis of a flare/relapse (i.e., the primary efficacy endpoint) should be reviewed with the CRO-designated Medical Expert and entered into the electronic Case Report Form (eCRF) promptly.

Flare/relapse is defined as major if cranial symptoms or ischemia-related visual loss are present or if there is clear evidence of new onset large vessel vasculitis (e.g., subclavian artery). In all other situations, flare/relapse attributed to PMR, vascular or other symptoms should be regarded as minor.

Subjects who experience a flare or subjects who cannot adhere to the protocol-defined steroid taper due to a flare should be managed to ensure the best possible care of the subject:

- The subject must discontinue the assigned study drug (KPL-301 or placebo) and should receive escape therapy in accordance with local SoC, as determined by the Investigator, which may include, for example, dose modifications of corticosteroids, other immunomodulatory agents, and/or approved therapies (e.g., tocilizumab). The dosages of all concomitant medications used to treat the GCA flare must be entered into the eCRF.
- Escape corticosteroid therapy can be escalated immediately. Due to possible safety and pharmacologic effects resulting from overlapping exposures to immunomodulatory agents on top of co-administered corticosteroids, the investigator should consider a washout period of at least 35

days (based on elimination half-lives) after the last dose of study drug if deemed clinically appropriate.

Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an End-of-Treatment (EOT) visit and will be followed for the intended duration of study treatment (i.e., through Week 26 and Washout Safety Follow-up) to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug administration) must complete at a minimum the Final Washout Safety Follow-up visit 84 ± 3 days from the last dose administered. Additional follow up using public records may be captured where possible.

Washout Safety Follow-up:

After subjects complete the 26-week double blind treatment period, they will discontinue and wash off of blinded KPL-301 or placebo during a 12-week Washout Period, which includes close safety follow-up and monitoring for potential GCA flares. During this time, it is recommended that subjects, regardless of remission status, receive SoC oral prednisone therapy, taking into consideration that they have just completed treatment with what may have been an efficacious therapy which supported the tapering off of standard of care concomitant oral corticosteroids. Clinicians may choose to observe subjects closely during the washout period without any change in concomitant medications or may choose (consistent with current SoC guidelines) to increase the daily corticosteroid dose prophylactically/empirically by approximately 10 mg above the prednisone dose administered at Week 26. The prednisone dose can then be tapered, increased or maintained throughout the remainder of the 12-week Washout Period as per Investigator discretion. After the Final Washout Safety Follow-up visit (Week 38) has been completed, the subjects will exit the trial and should be transitioned to SoC per investigator judgement. It is not required that the steroid taper have been completed (0 mg) prior to subjects exiting the trial at Week 38.

Number of Subjects:

Approximately 70 subjects will be randomized at a 3:2 allocation ratio. Approximately 42 subjects will be assigned to KPL-301, and approximately 28 subjects will be assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.

Eligibility Criteria:

Inclusion Criteria

1. Able and willing to provide written informed consent and to comply with the study protocol
2. Age of ≥ 50 to 85 inclusive
3. Diagnosis of new-onset or relapsing GCA classified according to the following criteria:

   New-onset: Initial diagnosis of GCA within 6 weeks of Day 0, defined as:

   a) Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/dL

   b) AND at least one of the following:

      i. Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery pain or tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

      ii. Unequivocal extracranial symptoms of GCA such as claudication of the extremities

      iii. Symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

   c) AND at least one of the following:

i. TAB or ultrasound revealing features of GCA

ii. Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRI, CT/CTA, or PET-CT of the aorta or other great vessels

Relapsing: Diagnosis of GCA > 6 weeks before Day 0 AND:

Active GCA within 6 weeks of Day 0 defined as clinical sign/symptom(s) as per above and Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/ dL

Refractory nonremitting: Diagnosis of GCA > 6 weeks before Day 0 AND:

No remission since the diagnosis of disease as per clinical expectations. i.e. Presence of sign/symptoms as per above and Westergren ESR>30mm/hour or CRP ≥ 1 mg/ dL within 6 weeks of Day 0.

4. Remission of GCA at or before Day 0 (resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour), such that the subject can safely participate in the study and follow the protocol-defined procedures, including initiation of the prednisone taper at the protocol-specified starting dose (i.e., ≤60 mg/day)
5. At Day 0, receiving or able to receive oral prednisone up to 60 mg/day for the treatment of GCA
6. If using methotrexate (MTX), oral or parenteral up to 25mg/week is permitted in screening if started more than 6 weeks prior to Day 0 and should be tapered to zero by Day 0
7. Willing to receive antiplatelet therapy depending on the Investigator's decision
8. Willing to receive treatment for prevention of corticosteroid-induced osteopenia/osteoporosis depending on the Investigator's decision
9. Female subjects must be:
   a) postmenopausal, defined as at least 12 months post cessation of menses (without an alternative medical cause), or
   b) permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation or having a male partner with vasectomy as affirmed by the subject, or
   c) nonpregnant, nonlactating, and if sexually active having agreed to use a highly effective method of contraception (i.e., hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Screening Visit until the Final Washout Safety Follow-up visit 84 ± 3 days from EOT Visit.
10. Male subjects must have documented vasectomy or if sexually active must agree to use a highly effective method of contraception with their partners of childbearing potential (i.e., hormonal contraceptives associated with the inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Day 0 until the Final Washout Safety Follow-up visit 84± 3 days from EOT Visit. Male subjects must agree to refrain from donating sperm during this time period.

Exclusion Criteria:

General Exclusion Criteria

1. Major surgery within 8 weeks prior to Screening or planned major surgery within 12 months after randomization
2. Transplanted organs (except corneal transplant performed more than 3 months prior to randomization)
3. Major ischemic event unrelated to GCA within 12 weeks of Screening

Exclusions Related to Prior or Concomitant Therapy

4. Concurrent enrollment in another clinical study, with the exception of observational studies
5. Previous treatment with KPL-301
6. Treatment with any non-biologic investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, prior to Screening
7. Any cell-depleting biological therapies (e.g., anti-CD20) within 12 months prior to Day 0; or previous treatment with noncell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-Interleukin [IL]-6 receptor [e.g. tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to Screening
8. Treatment with alkylating agents within 12 weeks prior to Screening
9. Intramuscular, Intra-articular or IV corticosteroids within 4 weeks prior to Screening
10. Receipt of live (attenuated) vaccine within the 4 weeks before Day 0
11. Treatment with hydroxychloroquine, cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil (MMF) within 4 weeks of Screening

Relating to Medical History

12. Female subjects who are pregnant, intending to become pregnant, or are breastfeeding
13. Any condition that, in the opinion of the Investigator, could interfere with evaluation of KPL-301 or interpretation of subject safety or confound the results of the study
14. Known history of allergy or reaction to any component of the KPL-301 or placebo formulation or to any other biologic therapy or prednisone or any of its excipients
15. Positive (or 2 indeterminate) QuantiFERON test results.
16. Clinically significant active infection including signs/symptoms suggestive of infection, any significant recurrent or chronic infection (including positive hepatitis C virus antibody [HCVAb]), or any episode of infection requiring hospitalization or treatment with IV antibiotics within 12 weeks before Screening. Subjects with any opportunistic infection within 6 months before Screening will be excluded from the study.
17. Subjects with chronic active hepatitis B infection as defined below will be excluded from the study:
    - Hepatitis B surface antigen (HbsAg) positive
    - Hepatitis B anti-core antibody positive but anti-surface antibody negative
18. Subjects at a high risk of infection (e.g., history of hereditary or acquired immune deficiency disorder including a history of known human immunodeficiency virus [HIV] infection), a history of an infected joint prosthesis at any time with that prosthesis still in situ, leg ulcers, indwelling urinary catheter, or persistent or recurrent chest infections
19. History of cancer within the last 10 years - except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured
20. Evidence of clinically uncontrolled respiratory disease. The Investigator should review the data from subjects' respiratory assessments including chest x-ray and pulmonary function tests (PFTs) including DLCO performed during the screening period or within 12 weeks prior to Day 0 if results of prior assessments are available. Available PFT and DLCO assessments must have had values ≥ 60% of predicted for measurements performed and no uncontrolled lung disease. A subject's medical regimen should not have been significantly intensified to control lung disease within 12 weeks prior to Day 0.
21. History of chronic respiratory tract infections
22. Congestive heart failure of New York Heart Association classification III or IV

23. At screening blood tests, any of the following:
    a) Aspartate transaminase (AST) > 2 × upper limit of normal (ULN)
    b) Alanine transaminase (ALT) > 2 × ULN
    c) Hemoglobin < 75 g/L
    d) Neutrophils < 1.5×10^9/L
    e) Creatinine clearance (CrCl) <30 mL/min

Test Products, Dosage, and Mode of Administration:

Subjects will be permitted to have received steroids (prednisone or equivalent) prior to inclusion in the study.

During the double-blind period, subjects will receive blinded KPL-301 150 mg or placebo, every 2 weeks, by SC injection, in addition to a protocol-specified oral corticosteroid taper.

Oral prednisone will be started at a dose between 20 mg/day to 60 mg/day (inclusive) at Day 0 depending on the subject's previous corticosteroid treatment, disease status, and Investigator discretion. The prednisone dose will then be tapered over the subsequent 26 weeks in accordance with the following tapering schedule shown in Table 3, with subjects entering the taper at different points, depending on their prednisone dose at Day 0.

After subjects have completed the 26-week double-blind treatment period, they will discontinue and wash off blinded KPL-301 or placebo during a 12-week Washout Period. During the Washout Safety Follow-up Period, patients may be closely observed with no additional therapeutic or may receive prophylactic prednisone and tapered as per Investigator discretion. After the Final Washout Safety Follow-up visit 84 ± 3 days from the EOT Visit has been completed, subjects will exit the trial and should be transitioned to SoC per investigator judgement, regardless of what dose of prednisone subjects are on.

Concomitant Medication:

Subjects should receive concomitant medications in line with current SoC practices for GCA. Such medications may include but not limited to the equivalent of the following examples: low-dose aspirin (dose allowed per SoC), pantoprazole (40 mg daily), calcium (1000 mg daily), cholecalciferol (800 U daily), and IV ibandronate 3 mg every 3 months, for the duration of the study.

Duration of Treatment:

Subjects will receive SC KPL-301 or placebo as well as coadministered study-supplied oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12-week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion. Thus, the total study duration will be up to approximately 38-44 weeks (including 6-week Screening Period).

Efficacy Measures:

- Clinical laboratory analyses (e.g., CRP, ESR, signs/symptoms)
- Clinical GCA assessments, including, signs/symptom(s), [redacted]
- Imaging studies (as applicable), including ultrasound, MRI, CT/CTA, PET-CT, TAB (if applicable)
- [redacted]

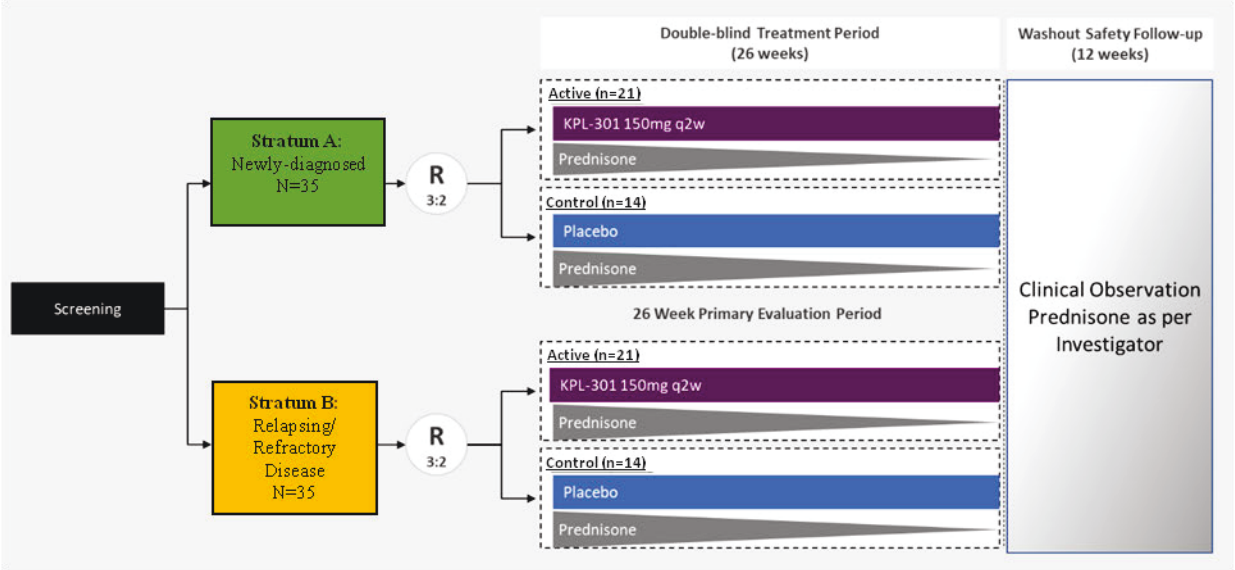
Safety Measure(s):

Safety measures include adverse events and clinical laboratory analyses (including chemistry, hematology, urinalysis, liver profiles, lipid panel, hemoglobin A1c [HbA1c], and anti-drug antibodies), vital sign measurements, electrocardiograms (ECGs), and physical examination findings.

[redacted]

[redacted].

Overview of Trial Design



Statistical Methods:

General Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding.

Modified Intent-to-Treat Analysis Set

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

Safety Analysis Set

All randomized subjects who take at least 1 dose of 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.

Per Protocol Analysis Set

All mITT subjects without important protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) analysis set.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period. Detailed censoring rules will be provided in the SAP.

The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the treatment period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare by Week 26. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as a covariate and stratified by the randomization strata.

The protocol definition of flare includes multiple components. Supportive analyses will be performed based on each individual component. The details will be described in the SAP. In addition, a sensitivity analysis will be performed using the same method described above for the per-protocol analysis set.

Secondary Efficacy Endpoint Analysis

Sustained remission rate at Week 26 will be estimated and compared using the Kaplan-Meier method

The following endpoints will be analysed using the Cochran-Mantel-Haenszel test, stratified by the randomized stratum:

- 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 have completed the corticosteroid taper and who have no signs/symptoms of GCA nor new or worsening vasculitis by imaging by Week 26

The following time to event endpoints will be analyzed using the same methods used for the primary efficacy endpoint:

- 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 by imaging by Week 26

The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate. Details will be described in the SAP:

- Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up period
- [redacted]
- [redacted]

[redacted]

- [redacted]

Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints, by treatment group and study visit. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed parameters such as incidence of adverse events (AEs), clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, PFT, and diffusing capacity for carbon monoxide (DLCO) parameters, and physical exam, where available.

[redacted]

[redacted]

Sample Size Estimation

Assuming 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 is estimated to be approximately 26 weeks in placebo and 111 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) is estimated to 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.

Table 1: **Schedule of Activities**

	Screening	Double – Blind Treatment Period (± 3 days)											Washout Safety Follow-up (± 3 days)		
Assessment	**Up to 6 weeks**	**Baseline/ Day 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26 / EOT[ac]**	**UNS[b]**	**Week 30**	**Week 34**	**Final Safety Follow-up[c] / Week 38**
Informed consent	X															
Demographics	X															
Medical history	X															
Eligibility	X	X														
Subject randomization		X														
Physical exam	X											X	X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X						X		X		X	X			X
Height	X															
Electrocardiogram	X												X			
Chest X-ray	X[g]												X			
Clinical GCA assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Temporal biopsy	X[f]											X[f]				
Imaging (ultrasound)	X[m]	X[n]						X[m]				X[m]	X[m]			X[m]
Imaging (MRI, CT/CTA, or PET-CT)	X[m]											X[m]	X[m]			
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local CRP	X[l]	X[l]											X[l]			
Pulmonary function tests	X[gh]							X[h]				X[h]	X			X[h]
DLCO	X[gh]							X[h]				X[h]	X			X[h]
Dyspnea score and O_2 saturation	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology	X															
TB screening	X															
Serum pregnancy test	X															
Urine pregnancy test		X						X				X	X			X
Hematology	X	X				X		X		X		X	X			X
Chemistry	X	X				X		X		X		X	X			X
Liver profile	X	X				X		X		X		X	X			X
Fasting lipid panel and HbA1c		X										X	X			X
Urinalysis		X										X	X			X

[redacted]

	Screening	Double – Blind Treatment Period (± 3 days)											UNS[b]	Washout Safety Follow-up (± 3 days)		
Assessment	**Up to 6 weeks**	**Baseline/ Day 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26 / EOT[ac]**		**Week 30**	**Week 34**	**Final Safety Follow-up[c] / Week 38**
[redacted]																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KPL-301 or PBO administration/dispensing		X[de]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]			
Prednisone dispensing[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

CRP=C-reactive protein; CT=computed tomography; CTA=computed tomography angiography; DLCO= diffusing capacity for carbon monoxide; EOT=end of treatment; ESR= erythrocyte sedimentation rate; GCA= giant cell arteritis; Hb1Ac= haemoglobin A1c (glycolysed haemoglobin); IMP = KPL-301 or placebo; MRI=magnetic resonance imaging; [redacted] O_2=oxygen; PBO=placebo; PET=positron emission tomography; [redacted]; TB=tuberculosis; UNS=unscheduled visit;

a. EOT visit must be conducted in the event the subject permanently discontinues KPL-301 or placebo. After the EOT visit, subjects who discontinue treatment should continue attending their remaining scheduled visits for the duration of the study.

b. In the event of an unscheduled visit, only the relevant assessments/activities pertaining to the visit need to be captured. Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study clinic at any time. This visit can be combined with the EOT visit in which all necessary EOT related assessments/activities should be completed.

c. All subjects, including subjects who prematurely discontinue the study (i.e., withdraw consent), must complete at a minimum the Final Safety Follow up visit 84 ± 3 days after the EOT Visit. Additional follow up using public records may be captured if possible.

d. At baseline, subject and/or caregiver should be trained on proper self-administration and handling and accountability of study drug. This training should be documented and can be repeated as necessary throughout the study.

e. If a study site or clinic visit coincides with the subject's scheduled dose, study treatment will be administered at the study site or clinic. Study drug treatment should be dispensed as necessary to the subject for home administration to ensure dosing compliance. Investigator staff may contact patients between visits to ensure compliance with protocol-specified treatment regimens.

f. New-onset subjects can have an optional temporal artery biopsy taken at Screening (or otherwise available from diagnostic workup) and Week 26 as part of the study. For relapsing/refractory patients, if the subject has not had a prior a temporal biopsy an optional biopsy can be done at Screening and Week 26. If the subject has an existing biopsy sample available this can be submitted as the screening/predose sample and an optional biopsy can be performed at Week 26.

g. Chest X-ray (or high res CT), DLCO, and PFTs should be obtained at Screening, or existing documentation (if available) within 12 weeks of Day 0 can be used and reviewed by the Investigator or designee.

h. PFTs and DLCO should be performed at Screening within 6 weeks prior to Day 0 (or documented report available from PFT &/or DLCO from within 12 weeks prior to Day 0). They should also be performed at Weeks 12 and 26 and 38 with a window of ±14 days.

[redacted]

k. Subjects will be given prednisone as necessary and instructed to dose in alignment with their prednisone taper. Investigator staff may contact patients between visits to ensure compliance with protocol specified treatment regimens.

l. Clinical decisions for determination of inclusion and flare will be based upon local laboratory values either ESR and/or CRP.

m. The imaging technique used during screening to diagnose GCA should be repeated at week 26 for the study. If ultrasound is available at screening for diagnosis of GCA this should be conducted again at weeks 12, 26 and 38, or in case of a suspected flare of GCA with no other imaging (MRI, CT/CTA or PET-CT) required. If MRI, CT/CTA or PET-CT was used at screening for diagnosis of GCA and no ultrasound is available, the same imaging technique used at screening should be repeated at week 26 or as necessary for diagnosis in case a suspected flare.

n. Ultrasound imaging if clinically relevant should be performed at or before Day 0 to support clinical remission decision making unless there is no evidence of temporal artery inflammation and diagnosis of GCA is confined to large vessels (By MRI or CT).

4 Table of Contents

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List of Tables

List of Figures

5 List of Abbreviations and Definition of Terms

ACR20	American College of Rheumatology definition of improvement by 20%
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDUS	color Doppler ultrasound
CI	confidence interval
CrCl	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
CTA	computed tomography angiography
DLCO	diffusing capacity for carbon monoxide
DMARD	disease modifying anti-rheumatic drug
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of Treatment
ESR	erythrocyte sedimentation rate
[redacted]	
GCA	giant cell arteritis
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony growth factor
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
HbsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
[redacted]	
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IWRS	Interactive Web Response System
KPL-301	Study Drug; nomenclature of mavrilimumab in this protocol
mITT	modified intent to treat
MMF	mycophenolate mofetil
MoDC	monocyte-derived dendritic cell
MRI	magnetic resonance imaging
MTX	methotrexate
[redacted]	
OLE	open-label extension

PD	pharmacodynamic
PET	positron emission tomography
PFT	pulmonary function test
PK	pharmacokinetics
PMR	polymyalgia rheumatica
POC	proof of concept
PP	per protocol
Q1	first quartile
Q3	third quartile
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
[redacted]	
SoC	standard of care
TAB	temporal artery biopsy
TB	tuberculosis
TIA	transient ischemic attack
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States of America

6 Introduction

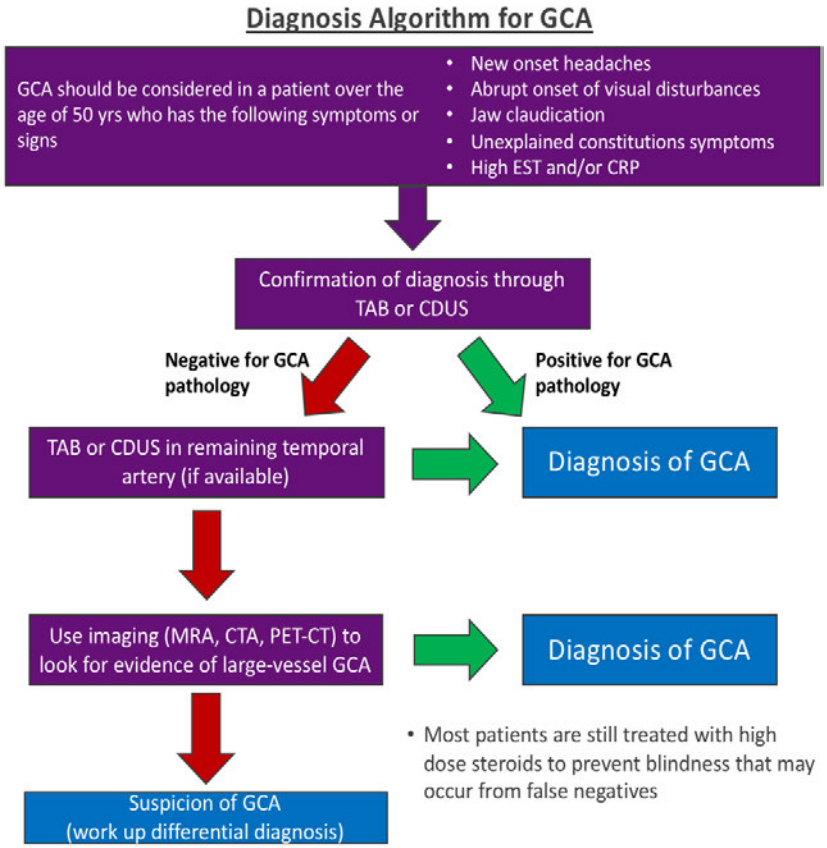
6.1 Overview

Giant cell arteritis (GCA) is a disease characterized by blood vessel inflammation and infiltration of monocytes, macrophages and the accumulation of giant cells (i.e., multinucleated fusions of macrophages) and has high unmet medical need (Dejaco et al, 2017; Roberts and Clifford, 2017). GCA, unless treated (either with long-term systemic corticosteroid treatment or tocilizumab with corticosteroid treatment), can lead to blindness, aortic aneurysm and/or death (Weyand and Goronzy, 2014). Granulocyte-macrophage colony growth factor (GM-CSF) is a key growth factor for many of the key inflammatory cell types at the site of the vascular lesion (i.e., macrophages, monocytes and giant cells; Wicks and Roberts, 2016), and additionally, GM-CSF is found in high concentrations at the site of damage in the vessel wall (Weyand et al, 1994). These data provide solid rationale for antagonizing this signaling pathway in GCA.

Mavrilimumab (also known as KPL-301 for this development program, or previously as CAM-3001) is a fully human monoclonal antibody that antagonizes GM-CSF biological activity by binding to its receptor alpha subunit (GM-CSFRα) and thereby preventing downstream signalling. KPL-301 has been studied in over 500 patients with rheumatoid arthritis (RA) and recently achieved its primary endpoint in a Phase 2b trial in this indication with a well-tolerated safety profile. KPL-301 may provide a treatment option in high unmet need indications where there is a strong mechanistic rationale for modulating key cell types in diseases in which GM-CSF signalling is critical for proper functioning (e.g., monocytes, macrophages, and granulocytes). Refer to the current version of the Investigator Brochure for further details.

GCA is an inflammatory disease of large- and medium-sized arteries that causes headaches, ischemic visual loss, and jaw and other muscle claudication (Dejaco et al, 2017). If left untreated, GCA can lead to monocular or binocular blindness, aortic aneurysm, myocardial infarction, and, rarely, stroke and death (Weyand and Goronzy, 2014). GCA presents with a wide and variable spectrum of signs and symptoms (Weyand and Goronzy, 2014). Diagnosis is usually made provisionally on the basis of clinical signs and symptoms and then confirmed by color Doppler ultrasound or by temporal artery biopsy (TAB) (Dejaco et al, 2018) (Figure 1). In the United States (US), the lifetime risk of developing GCA has been estimated at approximately one percent in women and 0.5 percent in men (Crowson et al, 2011). GCA generally affects adults over 50 years of age, with a 3:1 imbalance of women to men (Weyand and Goronzy, 2014). The reported prevalence of proven GCA in populations aged over 50 years varies significantly geographically and ranges between 24 to 200 per 100,000 individuals in the European Union and 24 to 278 per 100,000 individuals in the US (Salvarani et al, 2004; Lawrence et al, 2008; Lee et al, 2008).

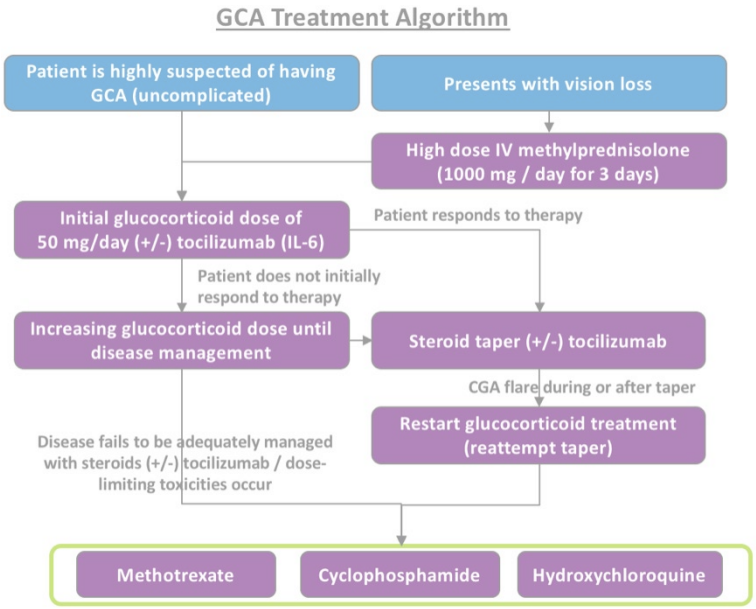
Figure 1: Diagnosis Algorithm for GCA



Abbreviations: TAB, temporal artery biopsy; CDUS: color Doppler ultrasound; MRA: magnetic resonance angiography; CTA: computed tomography angiography; PET-CT: positron emission tomography-computed tomography.

Glucocorticoids are the mainstay of treatment (Figure 2) because they normalize inflammatory markers; however, many patients receive long courses of this therapy to prevent disease flare-up, and long-term use is associated with significant and serious side effects, including glaucoma, fluid retention, hypertension, mood changes, memory changes, other psychological effects, weight gain, and diabetes (Roberts and Clifford, 2017).

Figure 2: GCA Treatment Algorithm



While corticosteroids are effective for some patients, many times patients are unable to wean from corticosteroids because they continue to experience disease flares as the dose is reduced (Dejaco et al, 2017; Salvarani et al, 2012). In one study cohort published in the literature that followed 106 patients with GCS over 4.5 to 10.1 years, 68 patients (64%) experienced at least one relapse, and 38 (36%) experienced two or more relapses during or after corticosteroid weaning (Alba et al, 2014).

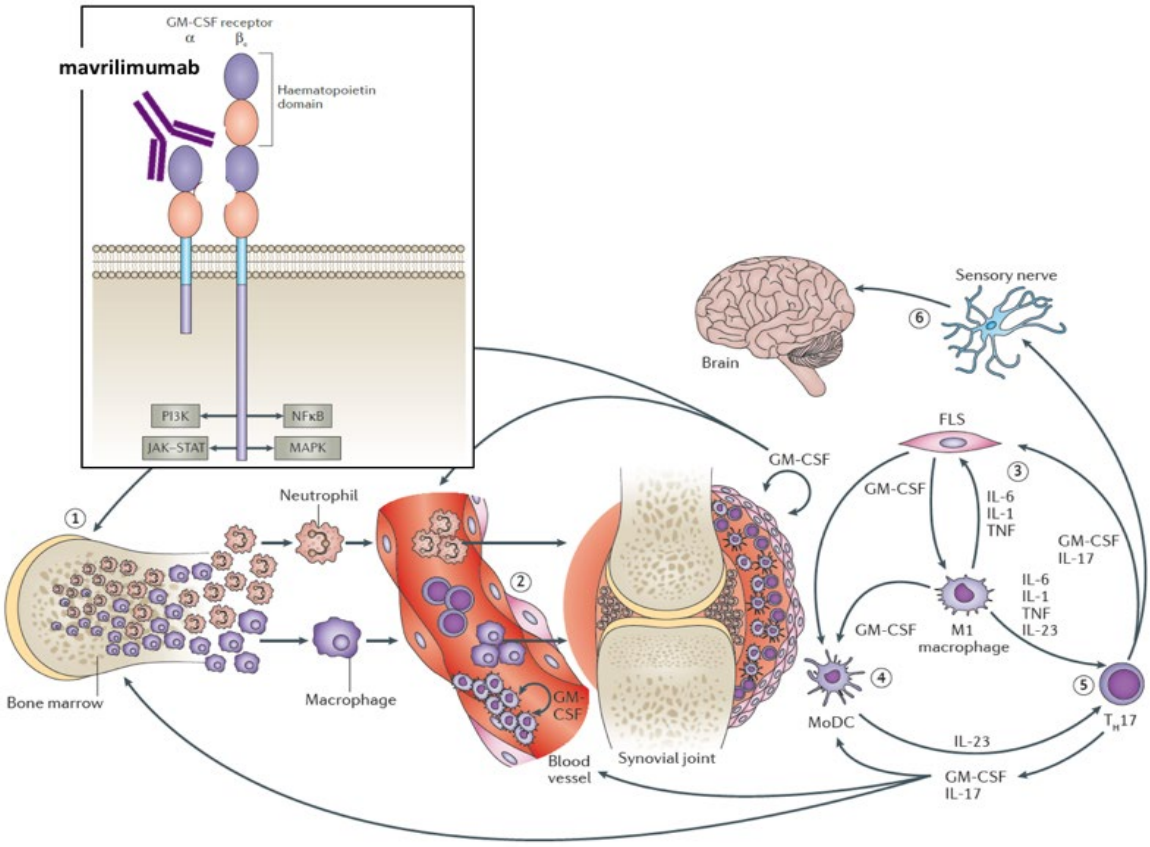
Experimental evidence in SCID mice (severe combined immunodeficiency model) suggests that glucocorticoid treatment inhibits the T-cell mediated pathology but does not adequately suppress tissue-infiltrating macrophage function—a key cell type generated and maintained by GM-CSF signaling, the target of KPL-301—and may explain why many patients require long-term chronic treatment and are unable to wean off corticosteroids (Brack et al, 1997). By blocking GM-CSF signaling at the receptor, KPL-301 may provide additional benefit to these patients by reducing long-term sequelae that result from chronic vessel inflammation and reducing steroid dependency.

ACTEMRA® (tocilizumab), an IL-6 receptor inhibitor, recently received marketing approval in the US and certain Europe countries in GCA for use concomitantly with a corticosteroid taper; however, an unmet need still remains for improved therapeutic options, as just under 50% of patients did not achieve sustained remission over 52 weeks on tocilizumab after a 26-week corticosteroid taper (Stone et al, 2017).

6.2 GM-CSF Biology

GM-CSF is a growth factor first identified as an inducer of differentiation and proliferation of myeloid cells (e.g., neutrophils, basophils, eosinophils, monocytes, and macrophages) (Wicks and Roberts, 2016). Studies using different approaches have demonstrated that with GM-CSF overexpression, pathological changes almost always follow (Hamilton and Anderson, 2004). Figure 3 illustrates an overview of the mechanism of action of KPL-301 and of key pathways involving GM-CSF.

Figure 3: GM-CSF Biology and KPL -301 Mechanism of Action



The following reported data suggest GM-CSF is a key mediator of inflammation and autoimmunity (Wicks and Roberts, 2016):

- GM-CSF enhances trafficking of myeloid cells through activated endothelium of blood vessels and can also contribute to monocyte and macrophage accumulation in blood vessels during inflammation.
- GM-CSF promotes activation, differentiation, survival, and proliferation of monocytes and macrophages as well as resident tissue macrophages in inflamed tissues.
- Local GM-CSF production leads to activation of the vasculature and bone marrow and also promotes the differentiation of effector T cells at inflamed sites and draining lymph nodes.
- GM-CSF also regulates the phenotype of antigen-presenting cells in inflamed tissues by promoting the differentiation of infiltrating monocytes into M1 macrophages and monocyte-derived dendritic cells (MoDCs).
- The production of IL-23 by macrophages and MoDCs, in combination with other cytokines such as IL-6 and IL-1, modulates T-cell differentiation.
- Locally-produced GM-CSF acts on sensory neurons expressing the GM-CSF receptor, transmitting painful stimuli to ascending nociceptive pathways in the spinal cord and brain.

Additionally, GM-CSF is a confirmed key mediator of at least one autoimmune disease, as demonstrated by the successful, clinically relevant, and statistically significant effect KPL-301 had on primary and secondary efficacy measures in multiple Phase 2 trials in patients with RA.

6.3 Non-Clinical and Clinical Experience with KPL-301

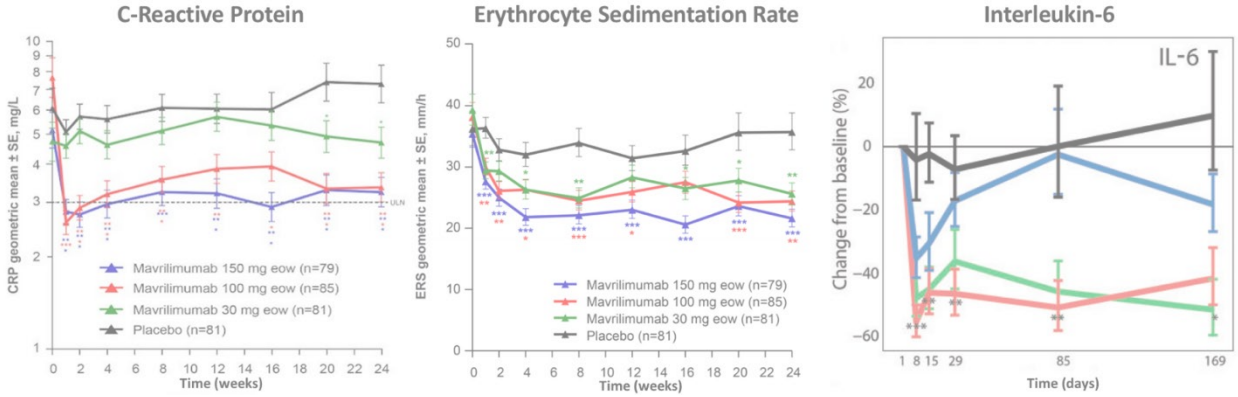
MedImmune studied KPL-301 in over 550 patients with RA through Phase 2b development. A summary of clinical trials conducted in RA is provided in Table 2. These studies provide proof-of-efficacy in an autoimmune disease and are an accurate representation of the safety profile of KPL-301 to-date. More detailed information on the safety profile and pulmonary test threshold values can be found in the IB.

Table 2: **Overview of KPL-301 Clinical Trials in RA**

Trial Name	Phase	Identifiers	Patient Segment	Results
Dose-Escalation Study to Evaluate The Safety and Tolerability of Single Doses of CAM-3001 (KPL-301) in Patients with RA	Phase 1	CAM-3001-0702; NCT00771420	Mild rheumatoid arthritis patients (remission/inactive) controlled on methotrexate	Achieved primary endpoint
EARTH: Study to Evaluate the Efficacy and Safety of CAM-3001 (KPL-301) in Subjects With Rheumatoid Arthritis	Phase 2a	NCT01050998; MI-CP219	Active rheumatoid despite stable methotrexate dose	Achieved primary endpoint
A Double-blind, Placebo-controlled, Single-dose Study to Evaluate the PK, IM and Safety in Japanese Subjects	Phase 1	NCT02213315; D2190C00016	Healthy Japanese Adults	Achieved primary endpoint
EARTH EXPLORER 1	Phase 2b	CP1071; NCT01706926	Moderate to severe rheumatoid arthritis patients with inadequate responders to disease modifying anti-rheumatic drugs	Achieved primary endpoint
EARTH EXPLORER 2	Phase 2b	CD1107; NCT01715896	Moderate to severe rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor alpha	Achieved primary endpoint
EXPLORER X	Phase 2b LTE	CP1109; NCT01712399	Patients from EARTH EXPLORER 1and 2	Achieved primary endpoint

In addition to the reductions to the primary endpoint demonstrated in the Phase 2b trials, other markers of inflammation (e.g., CRP, ESR, and IL-6) were similarly reduced and may provide evidence for KPL-301's utility across a broad range of indications with a similar biomarker profile, including GCA (Figure 4).

Figure 4: Reduction of Inflammatory Markers in RA Patients Treated with KPL-301



6.3.1 Clinical Development Plan for KPL-301 in GCA

Results from Phase 2b studies in RA have provided important information about the safety and efficacy profile of KPL-301. GCA is an appropriate indication for the study of KPL-301 due to the mechanistic rationale of inhibiting GM-CSF, a key growth factor for the cell types involved in the pathology of GCA (e.g., monocytes, macrophages and giant cells). Additionally, administration of KPL-301 in patients with RA markedly reduced key markers of disease activity that are also seen in GCA (i.e., CRP, ESR, and IL-6 receptor the target of tocilizumab). This patient population has a high level of unmet need owing to the number of patients who continue to experience relapsing disease despite currently existing therapies.

7 Study Objectives

7.1 Objectives

7.1.1 Primary Objective

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

7.1.2 Secondary Objective(s)

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

a) To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose.

[redacted]

c) To evaluate the safety and tolerability of KPL-301.

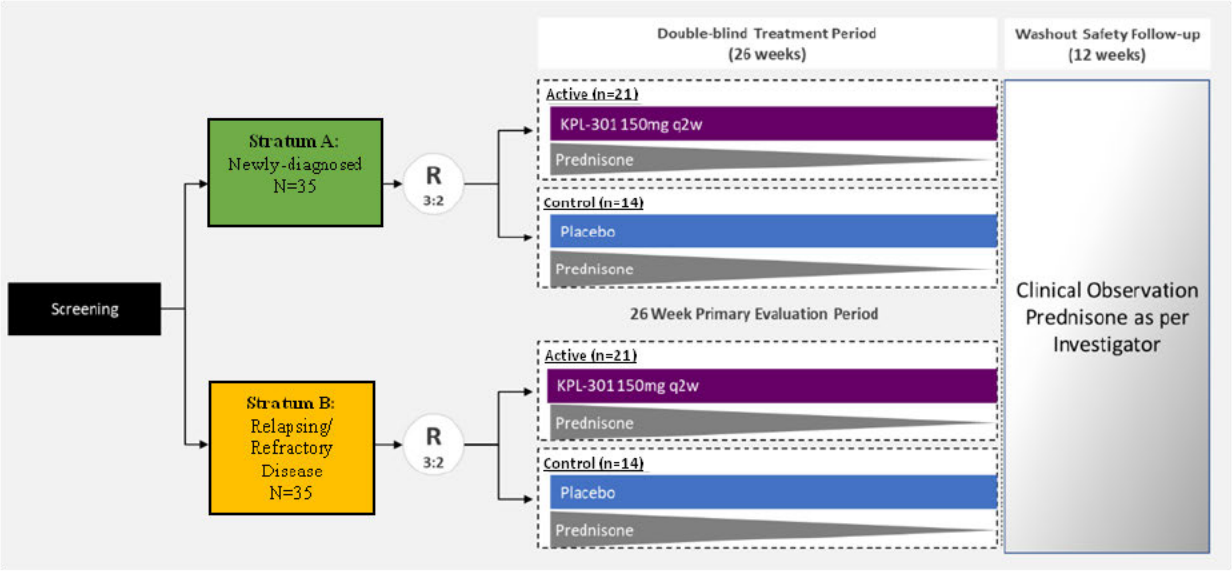
[redacted]

[redacted]

8 Study Design

This Phase 2 randomized, placebo-controlled POC study will evaluate the efficacy and safety of KPL-301 coadministered with a 26-week corticosteroid taper in patients with GCA. The study will consist of a screening period (up to 6 weeks), a 26-week double-blind placebo-controlled period during which subjects will receive blinded KPL-301 or placebo coadministered with a 26-week corticosteroid taper and a 12-week Washout Safety Follow-up Period during which subjects will discontinue and wash off blinded KPL-301 or placebo.

Figure 5: Overview of Trial Design



8.1 Rationale of Study Design

As this is the first study of KPL-301 in GCA, a double-blind placebo-controlled POC study is planned to investigate efficacy and safety of KPL-301 compared with placebo when coadministered with a 26-week steroid taper. The primary efficacy endpoint is time to flare.

The study will include patients with both new-onset and relapsing disease, and randomization will be stratified according to this criterion. The rationale for inclusion of both disease states is based on the following: in patients with GCA, arterial biopsy signatures demarcate two predominant disease clusters, which are IL-6/IL-17 T helper 17 (T_H17)-driven initial disease (responsive to glucocorticoid therapy) and IL-12/interferon gamma (IFNγ) T_H1-driven chronic disease (resistant to glucocorticoid therapy). Based on the predicted mechanism of KPL-301-mediated GM-CSF-Receptor blockade in GCA, KPL-301 is expected to reduce IL-17 and IL-6 (a key co-factor for IL-17) as well as to reduce GM-CSF-dependent dendritic cell activation and T-cell recruitment. Therefore, GM-CSF-Receptor blockade has the potential to modify the inflammatory response and thus disease course in both glucocorticoid-responsive and

-resistant patients. KPL-301 may permit tapering of steroids, or their replacement, in steroid-responsive patients and achieve a response in steroid-refractory patients.

The steroid taper chosen for this study is based on a standard taper used in clinical practice as well as prior clinical trials (Stone et al, 2017), with patients starting the study on the dose of prednisone they were previously taking and following the taper accordingly. For subjects starting on 20 mg or 25 mg prednisone, their dose will be held at ≥ 20 mg for the first 3 weeks of the study, as these subjects may be more liable to flare if their taper were to proceed too rapidly.

For this study, the SC route of administration, via prefilled syringe, was chosen over the IV route as it provides a more convenient method of administration in this elderly population of patients with GCA (e.g., home administration, no requirement for venous access).

8.2 Selection of Doses in the Study

Subjects randomized to KPL-301 will receive 150 mg every other week by SC injection coadministered with a 26-week steroid taper. This dose was chosen based on the outcomes of previous dose-ranging assessments in Phase 2 clinical trials in patients with RA and on PK/PD modeling.

Study CD-IA-CAM-3001-1071 (randomized, double-blind, placebo-controlled, parallel group, multicenter study evaluating the efficacy and safety of 3 SC doses of KPL-301 (CAM-3001) [30, 100, and 150 mg] administered every other week for 24 weeks in combination with MTX to 326 subjects with adult onset RA, and an inadequate response to one or more conventional disease modifying anti-rheumatic drugs (DMARDs) and at least moderately active disease (Disease Activity Score of 28 joints based on CRP [DAS28 (CRP) ≥ 3.2] and at least 4 swollen joints despite treatment with MTX) identified the greatest treatment effect in the 150 mg dose group. Both co-primary endpoints were met; the change from Day 1 in DAS28 (CRP) score at Week 12 and the American College of Rheumatology definition of improvement by 20% (ACR20) response rate at Week 24 were statistically significantly greater for all three KPL-301 (CAM-3001) groups compared with placebo.

- For mean change in DAS28 (CRP) the magnitude of response was dose dependent and statistically significant ($p < 0.001$), with the greatest treatment effect observed in the 150 mg dose group (more than 73.4% of subjects in the 150 mg KPL-301 [CAM-3001] group achieved an ACR20 response at Week 24, compared to 24.7% on placebo)
- Secondary efficacy analyses identified significant treatment effects ($p < 0.001$) vs placebo in the 150 mg KPL-301 (CAM-3001) group (ACR50 response at day 169, 40.5% vs 12.3%; DAS28 (CRP) < 2.6 sustained at day 169, 16.5% vs 0; DAS28 (CRP) low disease activity at day 169, 41.8% vs 8.6%), and the 150 mg group included the highest proportion of European League Against Rheumatism (EULAR) (Aletaha et al, 2010; Felson et al, 2011) moderate and good responders.
- Anti-drug antibodies (ADA) were absent in the 150 mg KPL-301 (CAM-3001) group (detected in subjects in the placebo and 30 mg and 100 mg KPL-301 [CAM-3001] groups)

A mechanistic population PK model was developed to describe the observed single-dose PK profiles of KPL-301 (CAM-3001) in subjects with RA. From stochastic clinical trial simulations using the population PK/PD model, maximum efficacy (ACR20 response rate) is reached at 150 mg KPL-301 (CAM-3001) every other week. The 150 mg KPL-301 (CAM-3001) dose is predicted to be more effective than the 100 mg dose, and the steady-state serum concentrations of KPL-301 (CAM-3001) were maintained above ACR20 90% efficacy concentration (3.4 µg/mL) in more than 90% of RA subjects.

8.3 Justification for Placebo

The proposed study is a placebo-controlled, double-blind study of SC doses of KPL-301 coadministered with a 26-week taper of oral prednisone. The double-blind, placebo-controlled, randomized clinical study design is considered the gold standard for the safety and efficacy assessment of a new therapy both by clinicians and regulatory authorities. In this study subjects will receive oral prednisone starting at 20 to 60 mg/day as per the Investigators judgment in addition to KPL-301 or placebo to control their disease activity. Subjects are also allowed to receive permitted concomitant medications in line with current SoC practices for GCA. Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse must discontinue the assigned study drug (KPL-301 or placebo) and should receive escape therapy in accordance with local SoC. Subjects are not allowed to receive biologic DMARDs while receiving KPL-301 during the study to mitigate potential safety risks of administering KPL-301 concomitantly with other biologics. In addition, any subject who discontinues treatment will have an EOT and will be followed for the intended duration of the study.

8.4 Methodology

8.4.1 Main Study

This Phase 2 randomized, placebo-controlled POC study will evaluate the efficacy and safety of KPL-301 co-administered with a 26-week corticosteroid taper in patients with GCA. The study will consist of a Screening Period (up to 6 weeks); a 26-week Double-Blind placebo-controlled Period during which subjects will receive blinded KPL-301 or placebo coadministered with a 26-week corticosteroid taper and a 12-week Washout Safety Follow-up Period.

Following signing of the ICF, potential subjects 50-85 years of age (inclusive) will be screened for meeting study-specified diagnostic criteria for GCA.

- Acute Phase Reactants - Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/dL

  AND

- Signs/Symptoms - At least one of the following:

  i. Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp, or temporal artery pain or tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

  ii. Unequivocal extra-cranial symptoms of GCA, such as claudication of the extremities

  iii. Symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

  AND

- Diagnostic Criteria - At least one of the following:

  i. TAB or ultrasound revealing features of GCA

  ii. Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRI, CT/ CTA, or PET-CT of the aorta or other great vessels

Upon successful completion of the screening procedures, eligible subjects will be stratified for randomized study treatment into two cohorts according to whether subjects have new-onset disease or relapsing/refractory (hereafter, "relapsing" for brevity) disease:

- New-onset - The new-onset disease cohort includes subjects who have been newly diagnosed within 6 weeks of Day 0 using the above Acute Phase Reactant, Signs/Symptoms and Diagnosis criteria.
- Relapsing/refractory – (either or)
    - The relapsing disease cohort includes subjects having prior documented diagnosis of GCA as per above Diagnostic Criteria > 6 weeks before Day 0 and who have active GCA disease defined as Acute Phase Reactants and Signs/Symptoms within 6 weeks of Day 0.
    - The refractory nonremitting disease subject has no remission since the diagnosis of disease as per clinical expectations Thus, the subject has documentation of prior diagnosis of GCA as per above Diagnostic Criteria > 6 weeks before Day 0; however, presence of Acute Phase Reactants and Signs/Symptoms as per above persists within 6 weeks of Day 0.

Subjects who complete screening procedures and are not considered eligible (screen failures) may be rescreened one time provided there is reason to believe that eligibility criteria will be met.

Stratified eligible subjects will enter the double-blind treatment period after randomization 3:2 to blinded treatment with KPL-301 150 mg or placebo administered SC every other week (every 2 weeks). All subjects will also receive an unblinded 26-week oral prednisone taper according to a standardized tapering protocol.

Prior to first administration of KPL-301 or placebo, all subjects are required to achieve remission (i.e., resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour). Should a subject in screening not achieve remission by > 6 weeks of onset they can be rescreened using their prior flare documentation following the relapsing/refractory non-remitting inclusion criteria.

The first administration of subcutaneous KPL-301/placebo and oral prednisone taper will take place at the study site on Day 0. Subsequent doses of KPL-301/placebo will be administered at the study site in conjunction with a scheduled study visit or administered by the subject on an outpatient basis in accordance to the dosing schedule. The oral steroid taper will be self-administered by study subjects on a daily basis.

Subjects will be followed at the study site at Weeks 1, 2, 3, 4, and approximately every 4 weeks thereafter (see Table 1). Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study site at any time.

If a flare/relapse is suspected, the Investigator must consult the Contract Research Organization (CRO)-designated Medical Expert to review and harmonize the elements of the diagnostic work-up.

Flare/relapse is defined as a re-increase of CRP from normal to 1 mg/dL or greater and/or of ESR from less than 20 mm in the first hour to 30 mm or greater AND at least one of the following signs or symptoms attributed by the Investigator to new, worsening, or recurrent GCA:

- Cranial symptoms
  - 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
- Extracranial symptoms
  - 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)
- 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 in the opinion of the Investigator related to worsening GCA, such as sustained daily recurrent fever with a temperature over 38°C for more than 1 week, chronic anemia, or unexplained weight loss.

All elements of the diagnostic work-up pertinent to the Investigator diagnosis of a flare/relapse (i.e., the primary clinical endpoint) should be reviewed with the CRO-designated Medical Expert and entered into the eCRF promptly.

Flare/relapse is defined as major if cranial symptoms or ischemia-related visual loss are present, or if there is clear evidence of new onset large vessel vasculitis (e.g., subclavian artery). In all other situations flare/relapse attributed to PMR, vascular or other symptoms should be regarded as minor.

Subjects who experience a flare or subjects who cannot adhere to the protocol-defined steroid taper due to a flare should be managed to ensure the best possible care of the subject. The subject must discontinue the assigned study drug (KPL-301 or placebo) and should receive escape therapy in accordance with local SoC, which may include, for example, dose modifications of corticosteroids, other immunomodulatory agents, and/or approved therapies (e.g. tocilizumab). Escape corticosteroid therapy can be escalated immediately. Due to possible safety and pharmacologic effects resulting from overlapping exposures to immunomodulatory agents on top of coadministered corticosteroids, the investigator should consider a washout period of at least 35 days (based on elimination half-lives) after the last dose of study drug if deemed clinically appropriate. The dosages of all concomitant medications used to treat the GCA flare must be entered into the eCRF.

Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an EOT visit and will be followed for the intended duration of study treatment (i.e., through Week 26 and Washout Safety Follow-up) to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug) must complete at a minimum the Final Washout Safety Follow-up visit 84 ± 3 days from the last dose administered. Additional follow-up using public records may be captured where possible.

An analysis of the study will be performed when the last subject reaches Week 26 according to the SAP.

8.4.2 Washout Safety Follow-up

After subjects complete the 26-week double-blind treatment period, they will discontinue and wash off of blinded KPL-301 or placebo during a 12-week Washout Safety Follow-up Period, which includes close safety follow-up and monitoring for potential GCA flares. During this time, it is recommended that subjects, regardless of remission status, receive SoC therapy, taking into consideration that they have just completed treatment with what may have been an efficacious therapy which supported the tapering off of standard of care concomitant oral corticosteroids. Clinicians may choose to observe subjects closely during the washout period without any change in concomitant medications or may choose (consistent with current SoC guidelines) to increase the daily corticosteroid dose prophylactically/empirically by approximately 10mg above the prednisone dose administered at Week 26. The prednisone dose can then be tapered, increased or maintained throughout the remainder of the 12-week Washout Safety Follow-up Period as per Investigator discretion. After the Final Washout Safety Follow-up visit (Week 38) has been completed, the subjects will exit the trial and should be transitioned to SoC per investigator judgement. It is not required that the steroid taper have been completed (0 mg) prior to subjects exiting the trial at Week 38.

8.5 Study Duration

Subjects will complete the screening period in up to 6 weeks. Eligible subjects will be randomized and receive KPL-301 or placebo for 26 weeks (unless a subject discontinues treatment prematurely). Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12-week Washout Safety Follow-up period in which they may receive study supplied oral prednisone per the Investigator's discretion. Thus, the total study duration will be up to approximately 38-44 weeks (including Screening Period).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

8.6 Number of Planned Subjects

Approximately 70 patients with GCA will be randomized as study subjects. For the primary endpoint analysis, the aim is to have 42 subjects assigned to KPL-301 and 28 subjects assigned to placebo, with balanced randomization in the two randomization cohorts.

The sample size was chosen on an empirical basis, based on experience with other KPL-301 trials and other research in this patient population.

8.7 Eligibility Criteria

8.7.1 Inclusion Criteria

To be eligible to participate in the trial, a subject must meet all of the following criteria:

Inclusion Criteria

1. Able and willing to provide written informed consent and to comply with the study protocol
2. Age of ≥ 50 to 85 inclusive

3. Diagnosis of new-onset or relapsing GCA classified according to the following criteria:

   New-onset: Initial diagnosis of GCA within 6 weeks of Day 0

   a) Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/dL

   b) AND at least one of the following:

      i. Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery pain or tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

      ii. Unequivocal extracranial symptoms of GCA such as claudication of the extremities

      iii. Symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

   c) AND at least one of the following:

      i. TAB or ultrasound revealing features of GCA

      ii. Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRI, CT/CTA, or PET-CT of the aorta or other great vessels

   Relapsing: Diagnosis of GCA > 6 weeks before Day 0 AND

   Active GCA within 6 weeks of Day 0 defined as clinical sign/symptom(s) and Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/ dL

   Refractory nonremitting: Diagnosis of GCA > 6 weeks before Day 0 AND

   No remission since the diagnosis of disease as per clinical expectations i.e. Presence of sign/symptoms as per above and Westergren ESR > 30mm/hour or CRP ≥ 1 mg/dL within 6 weeks of Day 0

4. Remission of GCA at or before Day 0 (resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour), such that the subject can safely participate in the study and follow the protocol defined procedures, including initiation of the prednisone taper at the protocol-specified starting dose (i.e., ≤60 mg/day)
5. At Day 0, receiving or able to receive oral prednisone up to 60 mg/day for the treatment of active GCA
6. If using MTX, oral or parenteral up to 25mg/week is permitted during screening if started more than 6 weeks prior to Day 0 and should be tapered to zero by Day 0.
7. Willing to receive antiplatelet therapy depending on the Investigator's decision
8. Willing to receive treatment for prevention of corticosteroid-induced osteopenia/osteoporosis depending on the Investigator's decision
9. Female subjects must be:

   a) postmenopausal, defined as at least 12 months post cessation of menses (without an alternative medical cause), or

b) permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation or having a male partner with vasectomy as affirmed by the subject, or
c) nonpregnant, nonlactating, and if sexually active having agreed to use a highly effective method of contraception (i.e., hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Screening Visit until the Final Washout Safety Follow-up visit 84± 3 days from EOT Visit.

10. Male subjects must have documented vasectomy or if sexually active must agree to use a highly effective method of contraception with their partners of childbearing potential (i.e., hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Day 0 until the Final Washout Safety Follow-up visit 84± 3 days from EOT Visit. Male subjects must agree to refrain from donating sperm during this time period.

8.7.2 Exclusion Criteria

A subject who meets any of the following criteria will not be eligible to participate in the trial:

General Exclusion Criteria

1. Major surgery within 8 weeks prior to Screening or planned major surgery within 12 months after randomization
2. Transplanted organs (except corneal transplant performed more than 3 months prior to randomization)
3. Major ischemic event unrelated to GCA within 12 weeks of Screening

Exclusions Related to Prior or Concomitant Therapy

4. Concurrent enrollment in another clinical study, with the exception of observational studies
5. Previous treatment with KPL-301
6. Treatment with any non-biologic investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, prior to Screening
7. Any cell-depleting biological therapies (e.g., anti-CD20) within 12 months prior to Day 0; or previous treatment with noncell-depleting biologic therapies (such as anti-TNF, anakinra, anti-IL-6 [tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to Screening
8. Treatment with alkylating agents within 12 weeks prior to Screening
9. Intramuscular, Intra-articular, or IV corticosteroids within 4 weeks prior to Screening
10. Receipt of live (attenuated) vaccine within the 4 weeks before Day 0
11. Treatment with hydroxychloroquine, cyclosporine A, azathioprine, cyclophosphamide, or MMF within 4 weeks of Screening

Relating to Medical History

12. Female subjects who are pregnant, intending to become pregnant, or are breastfeeding
13. Any condition that, in the opinion of the Investigator, could interfere with evaluation of KPL-301 or interpretation of subject safety or confound the results of the study

14. Known history of allergy or reaction to any component of the KPL-301 or placebo formulation or to any other biologic therapy or prednisone or any of its excipients
15. Positive (or 2 indeterminate) QuantiFERON test results.
16. Clinically significant active infection including signs/symptoms suggestive of infection, any significant recurrent or chronic infection (including positive HCVAb), or any episode of infection requiring hospitalization or treatment with IV antibiotics within 12 weeks before Screening. Subjects with any opportunistic infection within 6 months before Screening will be excluded from the study.
17. Subjects with chronic active hepatitis B infection as defined below will be excluded from the study:
    - HbsAg positive
    - Hepatitis B anti-core antibody positive but anti-surface antibody negative
18. Subjects at a high risk of infection (e.g., history of hereditary or acquired immune deficiency disorder including a history of known HIV infection), a history of an infected joint prosthesis at any time with that prosthesis still in situ, leg ulcers, indwelling urinary catheter, or persistent or recurrent chest infections
19. History of cancer within the last 10 years except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured
20. Evidence of clinically uncontrolled respiratory disease. The Investigator should review the data from subjects' respiratory assessments including chest x-ray and PFTs including DLCO performed during the screening period or within 12 weeks prior to Day 0 if results of prior assessments are available. Available PFT and DLCO assessments must have had values ≥ 60% of predicted for measurements performed and no uncontrolled lung disease. A subject's medical regimen should not have been significantly intensified to control lung disease within 12 weeks prior to Day 0.
21. History of chronic respiratory tract infections
22. Congestive heart failure of New York Heart Association classification III or IV
23. At screening blood tests, any of the following:
    a) AST > 2 × ULN
    b) ALT > 2 × ULN
    c) Hemoglobin < 75 g/L
    d) Neutrophils < 1.5×10^9/L
    e) CrCl < 30 mL/min

8.8 Removal of Subjects from Therapy or Assessments

Subjects may withdraw from the study drug treatment or from the study as a whole at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with and withdraw subjects from the study for any of the following reasons:

- Adverse event or Life threatening or other unacceptable toxicity, for example:
    - Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN, assessed as related to investigational product

- CTCAE Grade 4 (life-threatening) anaphylaxis or hypersensitivity reactions
- CTCAE Grade 4 (life-threatening) serious infection or opportunistic infection (including septic shock). In addition, subjects with a diagnosis or reactivation of TB, hepatitis B, or hepatitis C will not receive any further investigational product.
- CTCAE Grade 4 (life-threatening) neutropenia
- Adverse events of malignancy of any grade; except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured.

- Subject requires use of a prohibited concomitant medication or therapy
- General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion
- Severe noncompliance
- Lost to follow-up
- Pregnancy or a decision to become pregnant
- Subjects who request to be permanently discontinued from further receipt of investigational product, regardless of the reason (Subject withdrawal of consent)
- A decision to modify or discontinue development of the drug

Any subject who prematurely discontinues the study drug treatment will be followed for the intended duration of study treatment. If the subject withdraws consent for the study (i.e., all study procedures in addition to study drug), the subject should complete the EOT Visit and proceed to the Washout Safety Follow-up period, or at a minimum the Final Washout Safety Follow-up visit is to be completed within 84 days (± 3 days) after the last study drug dose. Additional follow-up using public records may be captured where possible.

9 *Investigational Medicinal Products*

Throughout this protocol, study drug refers to the investigational medicinal products (IMPs)—KPL-301 injection and placebo injection—as well as the prednisone tablets to be used for the protocol-defined steroid taper. Certain other corticosteroids dosing regimens (including higher doses of prednisone or IV corticosteroids) prescribed by the Investigator in case of a major GCA relapse/flare on-treatment are referred to as escape therapy.

9.1 KPL-301

KPL-301 is a liquid product intended for SC administration. It must be stored at 2°C to 8°C (36°C to 46°F). [redacted] The investigational product is supplied as a sterile clear to opalescent, colorless to slightly brown-yellow liquid, free from visible particles, in a 1mL prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, accessorized with a needle guard, and extended finger flange and a plunger rod. Each syringe contains 150 mg (nominal) of active investigational product.

9.2 Placebo

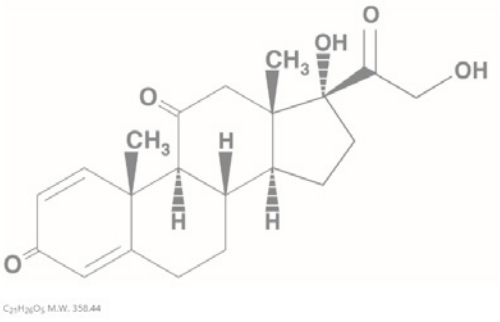
KPL-301 placebo is a liquid product intended for SC administration. It must be stored at 2°C to 8°C (36°C to 46°F). [redacted] The placebo is supplied as a sterile clear to,

colorless liquid, free from visible particles, in a 1 ml prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, accessorized with a needle guard and extended finger flange and a plunger rod.

9.3 Prednisone

Prednisone Tablets USP are available for oral administration containing either 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg or 50 mg of prednisone USP. Each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and stearic acid (1 mg, 2.5 mg, and 5 mg only).

Prednisone tablets contain prednisone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. The chemical name for prednisone is 17,21-dihydroxypregna-1,4-dienne-3,11,20-trione.



Prednisone is a white to partially white, crystalline powder. It is very slightly soluble in water; slightly soluble in alcohol, chloroform, dioxane, and methanol.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Prednisone is used as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in rheumatoid inflammation such as GCA.

On Day 0, each subject will begin the steroid taper, using oral prednisone tablets provided by the Sponsor to the study site. To ensure subjects perform the taper according to the protocol, they will be provided with a written schedule, specific to their starting dose, that instructs them on the daily dose to be taken in each week of the study. Investigator staff may contact patients between visits to ensure compliance with prednisone taper.

The duration of the steroid taper, in the absence of a GCA flare, is planned to take up to 26 weeks, depending on the starting dose of prednisone the subject was taking before enrolling in the study (see Table 3). Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed escape therapy per the Investigator. During the Washout Safety Follow-up Period, the prednisone dose can then be tapered, increased or maintained throughout the remainder of the 12-week Washout Period as per the discretion of the Investigator. After the Final Washout Safety Follow-up visit (Week 38) has been completed the subjects will exit the trial and should be transitioned to SoC per investigator judgement.

Table 3: **Prednisone Tapering Schedule**

	Prednisone Dose at Study Start (Day 0)						
Prednisone Dose (mg/day)	60 mg	50 mg	40 mg	35 mg	30 mg	25 mg	20 mg
60	Week 1						
50	Week 2	Week 1					
40	Week 3	Week 2	Week 1				
35	Week 4	Week 3	Week 2	Week 1			
30	Week 5	Week 4	Week 3	Week 2	Week 1		
25	Week 6	Week 5	Week 4	Week 3	Week 2	Week 1	
20	Week 7	Week 6	Week 5	Week 4	Week 3	Week 2-3	Week 1-3
17.5	Week 8	Week 7	Week 6	Week 5	Week 4	Week 4	Week 4
15	Week 9	Week 8	Week 7	Week 6	Week 5	Week 5	Week 5
12.5	Week 10	Week 9	Week 8	Week 7	Week 6	Week 6	Week 6
12.5	Week 11	Week 10	Week 9	Week 8	Week 7	Week 7	Week 7
10	Week 12	Week 11	Week 10	Week 9	Week 8	Week 8	Week 8
9	Week 13	Week 12	Week 11	Week 10	Week 9	Week 9	Week 9
8	Week 14	Week 13	Week 12	Week 11	Week 10	Week 10	Week 10
7	Week 15	Week 14	Week 13	Week 12	Week 11	Week 11	Week 11
6	Week 16	Week 15	Week 14	Week 13	Week 12	Week 12	Week 12
5	Week 17	Week 16	Week 15	Week 14	Week 13	Week 13	Week 13
5	Week 18	Week 17	Week 16	Week 15	Week 14	Week 14	Week 14
4	Week 19	Week 18	Week 17	Week 16	Week 15	Week 15	Week 15
4	Week 20	Week 19	Week 18	Week 17	Week 16	Week 16	Week 16
3	Week 21	Week 20	Week 19	Week 18	Week 17	Week 17	Week 17
3	Week 22	Week 21	Week 20	Week 19	Week 18	Week 18	Week 18
2	Week 23	Week 22	Week 21	Week 20	Week 19	Week 19	Week 19
2	Week 24	Week 23	Week 22	Week 21	Week 20	Week 20	Week 20
1	Week 25	Week 24	Week 23	Week 22	Week 21	Week 21	Week 21

	Prednisone Dose at Study Start (Day 0)						
Prednisone Dose (mg/day)	60 mg	50 mg	40 mg	35 mg	30 mg	25 mg	20 mg
1	Week 26	Week 25	Week 24	Week 23	Week 22	Week 22	Week 22

9.4 Method of Assigning Subjects to Treatment Groups

Subjects who are candidates for enrollment will be evaluated for eligibility by the Investigator to ensure that the criteria given in Section 8.7 have been satisfied and that the subjects are eligible for randomization.

Subjects will be randomized at a 3:2 ratio to receive either 150 mg KPL-301 or placebo. Randomization will be stratified according to whether subjects have new-onset disease or relapsing disease.

9.5 KPL-301 or Placebo Administration

The first administration of KPL-301 or placebo will take place at the study site on Day 0 by the Investigator or qualified study center staff. At this visit, subjects will be trained on self-administration of KPL-301 or placebo, such that subsequent doses, which will be administered every other week (14 ±3 days), may be self-administered by the subject or subject's caregiver as an outpatient. If a clinic visit coincides with the subject's scheduled dose, KPL-301 or placebo will be administered at the study site. If a subject is unable or does not wish to self-administer at home outside of a scheduled visit, clinic staff may administer the injections to the subject as part of an unscheduled visit. The location of and occasions when the subject or caregiver administered the SC injection should be recorded in the patient's study notes. Subjects will be instructed in proper syringe disposal and will be cautioned against reuse of these items. All used syringes must be disposed in a provided sharps container and returned to the study site for destruction. All unused KPL-301 or placebo must be returned to the study site for accountability.

Before administration, the prefilled syringe of study drug should be allowed to come to room temperature. The label on the prefilled syringe should be removed just before use and placed on the corresponding dosing diary form. Study drug will be injected in the upper arm, thigh, or abdomen and will be administered using a 27G needle. The person administering the dose will wipe the skin surface of the upper arm, thigh, or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissues overlaying the muscle. The study drug should be injected slowly (at least 5-second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection. The site as well as date and time of the injection should be documented. Immediately after injections at home, subjects must place the used syringe in a sharps container provided by the study site.

The interval between KPL-301 or placebo administrations must be at least 11 days and no more than 17 days.

Additional information regarding preparation, administration, and storage of KPL-301 or placebo will be described in the Pharmacy Manual.

9.6 Blinding

9.6.1 Methods for Ensuring Blinding

This is a double-blind study in which KPL-301 and placebo are identical in appearance/viscosity. Neither the subject nor any of the Investigator or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation [ICH] E9). If the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, the Sponsor must be notified immediately. If the Investigator intends to unblind treatment allocation for a subject, then the Sponsor should be notified immediately.

9.6.2 Unblinding

In the event of a medical emergency, the Investigator may unblind an individual subject's treatment allocation and notify the Sponsor. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received active drug. In most cases, the management of a medical emergency would be the same whether or not active drug was being received by the subject. If this were to be the case, the treatment allocation should not be unblinded.

10 Concomitant Therapy and Treatment Compliance

10.1 Concomitant Medications

Subjects should receive concomitant medications in line with current SoC practices for GCA. Such medications may include but not limited to the equivalent of the following examples: low-dose aspirin (dose allowed per SoC), pantoprazole (40 mg daily), calcium (1000 mg daily), cholecalciferol (800 U daily), and IV ibandronate 3 mg every 3 months, for the duration of the study.

Investigators may also prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 10.2. The following concomitant medications are permitted during the study:

1. Inactivated vaccines. Subjects who are eligible for yearly influenza vaccine or who require booster vaccinations for other diseases can receive vaccination with killed/toxoid vaccines consistent with normal clinical practice. The effect of KPL-301 on vaccine response is not known.
2. Vitamins and nutritional supplements.

It is strongly recommended to avoid herbal or traditional medicine treatments since no formal assessment of potential interactions, risk benefit, or a safety profile for these products is available in the context of experimental drug testing. All concomitant medications, including any changes in vitamins, supplements, and herbal or traditional remedies during the study are to be recorded.

10.2 Excluded Concomitant Medication

The introduction of the following medications is not permitted from initiation of screening through the end of the study unless indicated for escape therapy. The Sponsor is to be notified if any of the following medications are introduced to a subject during the study:

1. Investigational drug therapy other than KPL-301
2. Biologic DMARD therapies (such as anti-TNF, recombinant interleukin-1 receptor antagonist, anti-IL-6 receptor [tocilizumab], CTLA4 immunoglobulin, B-cell depleting therapies, etc)

3. Azathioprine, cyclosporine, MTX, mycophenolate mofetil, cyclophosphamide, and other alkylating agents
4. Immunization with any live or live attenuated vaccine
5. Immunoabsorption columns, plasmapheresis, and IV immunoglobulin therapy

10.3 Escape Therapy

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). These subjects are considered to have met the primary endpoint provided the flare occurs prior to Week 26.

Escape corticosteroid therapy can be escalated immediately. Due to unknown possible safety and pharmacological effects from overlapping exposures to immunomodulatory agents on top of co-administered corticosteroids, the investigator should consider a washout period of at least 35 days (based on elimination half-lives) after the last dose of study drug (KPL-301 or placebo) if deemed clinically appropriate.

10.4 Treatment Compliance

Subject compliance will be assessed by maintaining adequate administration records. Adherence to study drug administration (KPL-301/placebo and prednisone for the steroid taper) will be assessed during the study site visits. Subjects will be given a diary to record home injections of KPL-301 or placebo and intake of prednisone tablets. Subjects will be asked to return all used supply containers as well as any unused study medication at each visit along with their diary as a measure of drug accountability and subject compliance. Investigator staff may contact patients between visits to ensure compliance with protocol specified treatment regimens.

Sharps containers for any used prefilled syringes will be provided to the subjects for home usage. After home injections the used syringes must be placed into the sharps containers immediately. The sharps containers should be returned to the sites and discarded by the site staff as per local site procedure.

11 Study Periods

11.1 Screening Period

After provision of written informed consent for the study, patients will be screened for study eligibility within 6 weeks before Day 0 (first dose).

Results of SoC tests or examinations performed prior to obtaining informed consent within 6 weeks prior to Day 0 may be used; such tests do not need to be repeated for screening. Other tests required by the protocol will be conducted and reimbursed by the Sponsor as necessary. Written informed consent for study participation must be obtained before performing any study-specific screening tests or evaluations. All screening activities must be completed and eligibility confirmed before randomizing subjects and administering study drug.

The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Prior to first administration of KPL-301, all subjects are required to have achieved remission (i.e., resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour). Should a subject in screening not achieve remission by

> 6 weeks of onset they can be rescreened following the relapsing/refractory non-remitting inclusion criteria.

Refer to the Schedule of Activities in Table 1 for activities required during screening.

11.2 Double-blind Period

Following signing of the ICF and successful completion of the screening procedures, eligible subjects will be randomized 3:2 to blinded treatment with KPL-301 or placebo administered SC every other week (every 2 weeks) in the double-blind treatment period coadministered with a 26-week oral corticosteroid taper.

The first administration of subcutaneous KPL-301/placebo and oral prednisone taper will take place at the study site on Day 0. Subsequent doses of KPL-301/placebo will be administered at the study site in conjunction with a scheduled study visit or dispensed to the subject for outpatient administration. All subjects will receive oral prednisone, which will be tapered down during the double-blind base period according to a standardized tapering protocol. The steroid taper will be self-administered by study subjects on a daily basis. Subjects will be followed at the study site at Weeks 1, 2, 3, 4, and approximately every 4 weeks thereafter until week 26 (see Table 1). Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study site at any time.

Subjects who experience a flare or who cannot adhere to the protocol-defined steroid taper due to flare/relapse must discontinue the assigned study drug (KPL-301 or placebo) and should receive escape therapy in accordance with local SoC. These subjects will be considered to have met the primary endpoint if a flare has occurred prior to Week 26.

Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an EOT visit and will be followed for safety for the intended duration of the study to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug) must complete an EOT visit then proceed to the Washout Safety Follow-up Period or at a minimum have a Final Washout Safety Follow-up visit 84 ± 3 days from the last dose administered. Additional follow up using public records may be captured where possible.

12 Study Procedures

12.1 Screening and Randomization Procedures

12.1.1 Informed Consent

Written informed consent for participation in the study must be obtained before performing any study-specific screening test or evaluations. ICFs for all patients who are enrolled or who failed screening will be maintained at the study site.

12.1.2 Medical History and Demographics

General medical history and subject demographic information will be recorded on eCRF. Additional information will be captured related to GCA including disease duration, history of prior flare/relapse, as well as history of allergy or anaphylaxis. In addition, subjects will be asked to report their current use and history of tobacco and smoking as well as provide more detailed information on pulmonary history.

12.1.3 Eligibility

All subjects screened will be assessed for eligibility for randomization into the study according to the inclusion/exclusion criteria (Section 8.7). A master log will be maintained of all enrolled subjects and will

document all screening failures (i.e., subjects who are enrolled but not randomized), including reason for screen failure.

12.1.4 Subject Randomization

An Interactive Web Response System (IWRS) will be used for assignment of the Subject Identification Number at enrollment, randomization to a treatment arm (KPL-301 or placebo), and assignment of blinded investigational product. A subject is considered randomized into the study when the Investigator confirms the eligibility criteria in the IWRS and the pharmacist has been provided with the investigational product number.

12.2 Clinical GCA Related Assessments

12.2.1 Clinical GCA Assessments

Ideally clinical assessments of GCA signs/symptoms should occur prior to the investigator reviewing subject imaging, lab or acute phase reactant results at any given visit to minimize potential for assessment bias.

- Cranial symptoms
    - 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
    - TIA or stroke related to GCA in the opinion of the Investigator
- Extracranial symptoms
    - 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)
- 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 in the opinion of the Investigator related to worsening GCA, such as sustained daily recurrent fever with a temperature over 38°C for more than 1-week, chronic anaemia, or unexplained weight loss.

All elements of the diagnostic work-up pertinent to the Investigator diagnosis of GCA should be reviewed with the CRO-designated Medical Expert and entered into the eCRF promptly.

12.2.2 TAB

New-onset subjects can have an optional temporal artery biopsy taken at Screening and Week 26 as part of the study. For relapsing/refractory patients, if the subject has not had a prior a temporal biopsy an optional biopsy can be done at Screening and Week 26. If the subject has an existing biopsy sample available this can be submitted as the screening/predose sample and an optional biopsy can be performed at Week 26. Temporal biopsy specimens if available will be submitted to the central laboratory.

12.2.3 Imaging (MRI, CT, PET, or Ultrasound)

Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRI, CT/CTA, or PET-CT of the aorta or other great vessels should be performed according the schedule of activities (Table 1).

In cases where ultrasound of temporal artery was captured during the diagnosis of GCA at Screening, this procedure should be repeated at Weeks 12, 26, EOT and Week 38 as well as any instances of suspected flare over the course of the study. Imaging and relevant data should be included in any elements of the diagnostic work-up pertinent to the Investigator diagnosis of GCA.

12.2.4 CRP and ESR

Central laboratory assessments of CRP and local assessment of ESR will be performed at each study visit. Centrally determined laboratory values will be used for statistical evaluations and report writing. CRP changes and the time course to decrease and resolve CRP to normal values ≤ 0.5 mg/dL will be assessed.

If necessary local CRP tests can be used by the site to support the Investigator's clinical decisions regarding the GCA status.

12.3 Physical Examination and Vitals

12.3.1 Physical Exam

A complete physical examination as possible by local practice should include an evaluation of the head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History and Physical Examination eCRFs.

At subsequent visits, limited symptom-directed physical examinations may need to be performed in order to determine changes from baseline abnormalities and should be recorded in the subject's trial notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event CRF.

12.3.2 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Blood pressure measurements should be obtained after the subject has been seated for at least 5 minutes.

12.3.3 Body Weight and Height

Body weight and height will be measured as per SoC at the study site and will be recorded in the eCRF.

12.4 Electrocardiogram

Twelve-lead ECGs will be performed at Screening at the study site and may be performed at an unscheduled visit if determined necessary by the Investigator during the treatment period. To minimize variability, ECGs should be performed prior to meals and any scheduled vital sign measurements and blood draws. Subjects should be in a resting position for ≥ 10 minutes prior to ECG and body position should be consistently maintained and environmental distractions (e.g., TV, radio) should be avoided to prevent changes in heart rate during recording.

The digital ECG recording must be obtained and reviewed by the Investigator or designee. For safety monitoring purposes, the Investigator or designee must sign and date all ECG tracings and place the paper

copy as part of the subject's permanent study file at the site and overall ECG interpretation will be documented in eCRF.

12.5 Respiratory Evaluations

12.5.1 PFTs and DLCO

PFTs and DLCO should be obtained at Screening within 6 weeks prior to Day 0, or existing documentation within 12 weeks of day 0 can be used and reviewed by the Investigator or designee. During the course of the study PFTs and DLCO should be obtained at Weeks 12, 26 and 38 with a window of ± 14 days.

12.5.2 Chest X-Ray

Chest X-rays in accordance with local requirements should be obtained at Screening (or existing chest X-ray within 12 weeks of Day 0 can be used) and reviewed by the Investigator or designee. X-rays should be reviewed to show no clinically significant abnormality and no signs or symptoms suggestive of pulmonary disease that would exclude the potential subject.

12.5.3 TB Screening

Eligibility will be determined based on a central QuantiFERON TB test performed during screening in order to evaluate (active, untreated, or partially treated latent) infection with TB.

If a patient is suspected to have contracted tuberculosis during the study the study site may conduct a TB test in accordance with the site's normal practice to diagnose TB (PPD or local QuantiFERON).

12.5.4 Dyspnea Score and O_2 Saturation

The modified Borg scale (Borg and 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 10 (maximal). A validated version of the Borg scale in local language will be provided.

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. It is important that the pulse oximetry be performed in the same center throughout the study since oximetry readings vary with changes in altitude.

12.6 Laboratory Assessments

Laboratory assessments should be collected as per the schedule of activities (Table 1). Unscheduled laboratory assessments for safety issues are permitted as deemed necessary by the Investigator. The procedures for the collection, handling, and shipment of laboratory samples are specified in the Laboratory Manual supplied to sites by the central laboratory.

Local laboratory tests and values may be used by the Investigator as necessary to support clinical decisions but will not be captured as part of the study for analysis.

12.6.1 Serology

Rheumatoid factor, protein electrophoresis, HbsAg, HbsAb, HbcAb and HCVAb: collected at Screening only unless clinically indicated during the study.

12.6.2 Hematology

White blood cell count with differential, platelet count, red blood cell count, mean corpuscular volume, hemoglobin, mean corpuscular hemoglobin concentration.

12.6.3 Chemistry

Urea, uric acid, creatinine, glucose, potassium, sodium, chloride, calcium, phosphorus, total protein, albumin, creatinine phosphokinase, C3, and C4.

12.6.4 Liver Profile

AST, ALT, alkaline phosphatase (ALP), and total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN).

Tests for AST, ALT, ALP and total bilirubin must be conducted and assessed concurrently. Additional test may be used for follow up if values come back abnormal.

12.6.5 Fasting Lipid Panel and HbA1c

Whenever possible laboratory samples should be drawn in the morning. Subjects should fast overnight (> 8 hours) prior to blood sampling at clinic visits. Subjects will be allowed to drink only water during this time. The following panels will be taken: HbA1c, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, apolipoprotein A, and apolipoprotein B.

12.6.6 Urinalysis

Specific gravity, pH, protein, urobilinogen, ketones, glucose, blood, bilirubin, nitrite, leukocyte esterase, creatinine.

12.6.7 Pregnancy Test

For women of child bearing potential a serum pregnancy test should be performed prior to randomization at the site. Urine pregnancy tests should be performed at Day 0, Week 12, Week 26 and the Final Washout Safety Follow-up Visit. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

13 Safety Assessments

13.1 Adverse Events

13.1.1 Adverse Event Definition

An 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. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the reporting Investigator to be clinically significant; and any untoward medical occurrence.

13.1.2 Management of Specific Disease Related Events

Signs, symptoms and abnormal findings associated with active GCA should not be captured as Adverse Events in this study but rather as flare related efficacy endpoint findings. If there are questions regarding how to classify these events, Investigators should consult with the CRO-designated Medical Expert.

13.1.3 Adverse Events of Special Interest

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. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

13.1.3.1 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event. Investigational product will not be administered to any subject reporting ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN

13.1.3.2 Acute and Delayed Hypersensitivity Reactions

Biologic therapies are known to be associated with an increased risk of immediate and delayed hypersensitivity reactions as well as anaphylaxis. Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event, [redacted]

13.1.3.3 Clinically Significant Pulmonary Abnormality

Any subject who develops new clinically significant pulmonary symptoms or signs should be referred to a qualified specialist for further specific assessment. Symptoms and signs triggering such referral include but are not limited to an increase in shortness of breath or difficulty breathing, exacerbation of current respiratory symptoms, or a significant deterioration in dyspnea score. Subjects who are referred for evaluation by a specialist will undergo a diagnostic evaluation to determine the nature and origin of the pulmonary symptom(s)/sign(s) and to determine if PAP may be present. At the discretion of the investigator or specialist additional tests may be required such as a repeat chest x-ray, and/or a chest high resolution computed tomography scan, full PFTs including DLCO measurement, bronchoscopy with bronchoalveolar lavage, and cytological and/or ultrastructural evaluation of the cells recovered by lavage to identify findings consistent with a diagnosis of PAP. Any subject who has been referred for a specialist pulmonary evaluation may be instructed to stop the investigational product until the symptom(s) or sign(s) causing the referral have resolved.

13.1.3.4 Neutropenia

Adverse events of neutropenia of special interest to the sponsor are defined as an ANC < 1.0 × 109 cells/L. Investigational product will not be administered to any subject who has an ANC < 1.0 × 109 cells/L. Administration of investigational product may continue in the event that the ANC > 1.5 × 109 cells/L and following agreement with the medical monitor.

13.1.3.5 Serious Infection

Grade 3 severity infections that require treatment with IV therapy (antibiotics, antiviral, or antifungal) and opportunistic infections will be considered serious even if they do not require in-patient hospitalization. Every effort should be made to identify the causative pathogen through prompt and appropriate investigation by the investigator or reporting physician.

13.1.4 Adverse Reactions

All noxious and unintended responses to an IMP (i.e., where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

13.1.5 Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the current Investigator Brochure or is not listed at the specificity or severity that has been observed. "Unexpected" also refers to AEs or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

13.1.6 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence or effect that, at any dose:

- Results in *death* – Includes all deaths, even those that appear to be completely unrelated to study drug (e.g., car accident where subject is a passenger)
- Is *life-threatening* – in the view of the Investigator, the subject was at immediate risk of death from the event at the time of the event (i.e., it does not include an AE that might have caused death if it had occurred in a more serious form).
- Requires *in-patient hospitalization* or prolongs an existing hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF. Hospitalization is defined as an admission to the hospital ward or a short-stay-type unit longer than 24 hours. Prolongation of existing hospitalization is defined as hospital stay longer than originally anticipated for the event or development of a new AE as determined by the Investigator or treating physician.
- Results in *persistent or significant disability/incapacity* (an AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Is a congenital anomaly/birth defect.
- Is an *important medical event* – Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to

prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above, i.e., any event that the Investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the IMP.

All SAEs that occur after signing of study-related informed consent, whether or not the SAEs are related to the study drug or study procedures, must be reported.

13.1.7 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or prescribing information/summary of product characteristics for an authorized product). All relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening will be recorded and reported to the competent authorities in all the applicable countries, and to the Ethics Committee/Institutional Review Boards in conjunction with Directive 2001/20/EC.

13.2 Adverse Event Assessment

13.2.1 Relationship to Study Drug

The causal relationship between an AE and the study drug will be defined as below:

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

13.2.2 Intensity

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

- **Mild**: easily tolerated, does not interfere with normal daily activities, does not require intervention
- **Moderate**: causes some interference with daily activities; minimal, local, or noninvasive intervention indicated
- **Severe**: medically significant event; daily activities limited or completely halted; hospitalization or prolongation of hospitalization indicated

Every reasonable effort will be made to follow subjects who have AEs. Any subject who has an ongoing AE at study end or early withdrawal will be followed, where possible, until resolution.

13.3 Recording Adverse Events

Each patient should be monitored for the development of any AEs. This information should be collected by asking nonleading questions (such as "How are you feeling?") and from observations of and conversations with patients. AEs may also be collected by direct physical exam, diagnostic procedures, or any other appropriate source.

All AEs (serious and non-serious) will be documented in the patient's source documents and recorded in the eCRF. Any clinically relevant (as determined by the Investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the patient's source documents and in the eCRF.

13.3.1 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

13.3.1 Adverse Events Based on Examinations and Tests

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical rather than the laboratory term (e.g., anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AEs.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

13.4 Time Period for Collection of Adverse Events

AEs will be collected from the time of signing of informed consent through the Final Washout Safety Follow-up period (84 days ± 3 days after the EOT visit). The AE term should be reported in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For each AE, the Investigator will evaluate and report the onset, resolution, intensity, causality, action taken, seriousness, outcome (if applicable), and whether or not it caused the patient to discontinue the study. Reported AEs between consent and Day 0 will be censored in analysis.

13.5 Follow-Up of Unresolved Adverse Events

Any AEs that are unresolved at the patient's follow-up visit are to be followed up by the Investigator for as long as medically indicated. Additional information for any patient with an ongoing AE at the end of the follow-up period may be requested by the Sponsor, as needed.

13.6 Reporting Serious Adverse Events

All SAEs, whether or not considered causally related to study drug or to the study procedure(s), have to be reported. SAEs will be recorded in the eCRF within 24 hours of discovery.

In case the eCRF is inaccessible, the Investigator must report all SAEs to the Safety Department and Sponsor within 24 hours of discovery via the SAE reporting form to:

24 Hour Safety Hotline: +44 1223 374 240

24 Hour Safety Hotline Fax: +44 1223 374 102

US 24 Hour Safety Hotline: 1 888-483-7729

US 24 Hour Safety Hotline Fax: 1 888-529-3580

Additional follow-up information, if required or available, should be sent to the Safety Department within 1 business day of receipt and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Information on non-serious AEs that become serious must also be reported to the Safety Department as soon as it is available.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as applicable per institutional policy.

The Sponsor or designee will provide regulatory authorities, IRBs, IECs, and principal investigators with clinical safety updates/reports according to local requirements.

13.7 Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator without delay. If pregnancy is confirmed, the Investigator must notify the Sponsor within 24 hours and the subject must not receive (additional) study drug and must be discharged from the study. The subject must be asked regarding their willingness to complete the EOT visit.

In the event that a subject is found to be pregnant after having received at least one study drug dose, the pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Instances of perinatal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment, will be reported to the Sponsor within 24 hours.

14 Statistical Methods

14.1 General Considerations

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.4 or later. A statistical analysis plan (SAP) will be written and approved prior to performing the first review of the data.

All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables.

Unless otherwise specified, all tests will be two-tailed using a 0.05 level of significance. All confidence intervals (CIs) will be two-sided 95% confidence intervals.

14.1.1 Handling Dropouts and Missing Data

Criteria for removal of subjects from therapy or assessments are explained in Section 8.8. Subjects who discontinue will not be replaced. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. Unless otherwise specified, missing data will not be imputed and only the observed data will be used in the analyses.

14.1.2 Multiplicity Adjustment

Multiplicity adjustment with respect to the primary efficacy and secondary efficacy endpoints will be performed using the gate-keeping hierarchical testing procedure. The order of the secondary endpoints will be described in the SAP. 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 and the test statistic shows KPL-301 is superior than placebo, 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.

14.2 Determination of Sample Size

Assuming 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 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.

14.3 Analysis Sets

14.3.1 Modified Intent-to-Treat Analysis Set

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

14.3.2 Safety Analysis Set

All randomized subjects who take at least 1 dose of 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.

14.3.3 Per Protocol (PP) Analysis Set

All mITT subjects without protocol deviations deemed to impact efficacy or ethical conduct will be included in the PP analysis set.

[redacted]

14.4 Endpoints

Efficacy Endpoints:

Primary Endpoint:

- Time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period

Secondary Endpoints:

- Sustained remission rate 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
- 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 and at the end of the Washout Safety Follow-up Period

[redacted]

Safety Endpoints:

- Incidence of treatment emergent adverse events
- Change in physical exam results
- Change in vital signs
- Change in clinical laboratory parameters
  - Serum chemistry
  - Hematology
  - Urinalysis

14.5 Analysis of Efficacy

All efficacy analyses will be performed on the mITT analysis set. Analyses will be repeated using the PP set to assess the sensitivity of the results to important deviations of the protocol.

14.5.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period. Detailed censoring rules will be provided in the SAP.

The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the treatment period will be summarized for each treatment group. Time to flare by week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare by Week 26. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as a covariate and stratified by randomization strata.

The protocol definition of flare includes multiple components. Supportive analyses will be performed based on each individual component. The details will be described in the SAP. In addition, a sensitivity analysis will be performed using the same method described above for the PP analysis set.

14.5.2 Secondary Efficacy Endpoint Analysis

Sustained remission rate at Week 26 will be estimated and compared using the Kaplan-Meier method.

The following endpoints will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization strata.

- 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 have completed the corticosteroid taper and who have no signs/symptoms of GCA or new or worsening vasculitis by imaging by Week 26

The following time-to-event endpoints will be analyzed using the same method for the primary efficacy endpoint.

- 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 by imaging by Week 26

The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate. Details will be provided in the SAP.

- Cumulative corticosteroid dose at Week 26 and at the end of the Washout Safety Follow-up period

[redacted]

[redacted]

14.6 Analysis of Safety

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.

14.6.1 Adverse Events

Adverse events will be mapped to preferred term (PT) and system organ class (SOC) using the most up to date version of Medical Dictionary for Regulatory Activities (MedDRA). AEs that begin after the first administration of investigational products or existing AEs that worsen after the first dose of study medication are considered treatment emergent AEs (TEAEs). The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by MedDRA SOC and PT, by severity, and by relationship to study treatment. Drug-related AEs will be considered those to be at least possibly related to investigational product based on the investigator's assessment. The number and percentage of subjects with serious AEs, AESI, and the number and percentage of subjects with AEs leading to treatment discontinuation will also be summarized for each treatment group by MedDRA system organ class and preferred term.

14.6.2 Clinical and Laboratory Events and Analyses

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 each post baseline time point will be presented.

14.6.3 Vital Signs

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

14.6.4 Physical Examination

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 subject listings.

14.6.5 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary and will be classified by Anatomical Therapeutic Class (ATC) level 4 and preferred term (PT) for the Safety Analysis Set. Frequencies and percentages of subjects using each concomitant medication will be presented for the Safety Analysis Set overall, and by treatment group. All medication use will be listed regardless of the timing of the start of the medication.

[redacted]

14.8 Quality Assurance and Quality Control

14.8.1 Audit and Inspection

The study may be selected for audit originating from the Sponsor or external organizations acting on behalf of the Sponsor. Audits will be followed by internal reports and corrective actions, if needed.

The Investigator agrees to cooperate with the auditor to ensure that any problems detected in the course of these audit visits are resolved. The anonymity of the patients must be safeguarded and data checked during audits remain confidential.

14.8.2 Monitoring

Data for each subject will be recorded in source records and in the eCRF. Data collection must be completed for each subject who signs an ICF.

The Investigator will permit study-related monitoring, audits, ethics committee review and regulatory inspection(s), providing direct access to source data and documents.

For each patient enrolled, the Investigator or designee will document in the source records of the patient that the patient is enrolled in this study along with all safety and efficacy information. The Investigator is responsible for maintaining adequate case histories in the source records of each patient. Source data should be preserved for the maximum period of time permitted by the hospital/institution and made available by the Investigator in the cases described above.

In accordance with current Good Clinical Practice (GCP) and International Conference on Harmonisation (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

14.8.3 Data Management and Coding

The Sponsor or Clinical Research Organization (CRO) will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant Standard Operating Procedures (SOPs) of the Sponsor or CRO.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and World Health Organization (WHO) Drug for therapies.

14.8.4 Record Keeping

It is the responsibility of the Investigator to ensure all essential trial documentation and source records (e.g., signed ICFs, Study Site/Clinic files, patients' hospital notes, copies of eCRFs, etc.) at their site are securely retained. The Sponsor will inform the Investigator of the time periods for retaining study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations; otherwise, the retention period by default will be 15 years.

15 Records and Supplies

15.1 Drug Accountability

The sites will receive study drug for on-site administration at study site visits. On receipt of study drug, the Investigator (or deputy) will conduct an inventory of the supplies and verify that the supplies are received intact and in the correct amounts prior to completing a supplies receipt. The Investigator will retain a copy of this receipt at the study site and return the original receipt to the drug depot. The inventory of supplies at each study site will be reviewed by the study monitor.

Study drug will be disseminated to the trial subjects for outpatient self-administration according to a supply chain described in the Pharmacy Manual.

All used and unused study drug containers must be retained by the study site/clinic and subject for cataloguing and documentation of compliance. The full process for drug dispensing, documentation and destruction will be described in the Pharmacy Manual.

A full drug accountability log will be maintained at the study site at all times.

16 Ethics

16.1 Institutional Review Board

Before initiation of the study at each investigational site, the protocol, all protocol amendments, the ICF, and any other relevant study documentation will be submitted to the appropriate IRB or IEC. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the study drug is released to the Investigator. Any necessary extensions or renewals of IRB/IEC approval must be obtained, in particular, for changes to the study such as modification of the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. On completion of the study, the Sponsor will notify the IRB/IEC that the study has ended.

16.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the most recent version of the Declaration of Helsinki in which the Sponsor intends to publish the results regardless of the study outcome, and local regulations.

16.3 Subject Information and Consent

The Investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject and/or legal guardian has given written informed consent to participate in the study. The written consent must be given by the subject and/or the legal guardian of the subject, after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

Subjects and/or legal guardians will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IRB/IEC, Sponsor, and/or CRO personnel.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

16.4 Subject Confidentiality

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and according to national and/or local laws and regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the ethics committees approving this research, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

17 Study Termination

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

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2. Subject enrollment is unsatisfactory
3. Non-compliance that might significantly jeopardize the validity or integrity of the study
4. Recommendation to suspend or terminate the study by independent body such as DMC or Health Authority
5. Sponsor decision to terminate development

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

17.1 Study Stopping Criteria

If the sponsor receives a report of an event consistent with any one of the following, the medical monitor or designee will immediately assess the event by gathering all available information including, where possible, direct telephone contact with the reporter. A prompt review of the data will be initiated by the sponsor, and the information will be referred to the DMC within 1 business day of the receipt of the initial report by the Sponsor.

1. Any CTCAE grade 5 (death) assessed as related to the investigational product
2. Any CTCAE grade 4 (life-threatening) assessed as related to the investigational product
3. Any CTCAE grade 4 (life-threatening) of anaphylaxis
4. Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN, assessed as related to investigational product

5. Any unforeseen events that, in the opinion of the DMC and the Sponsor, may contraindicate further dosing
6. Clinically-significant pulmonary abnormalities that in the opinion of the DMC and the Sponsor may contraindicate further dosing

If any above-listed events occur, the Sponsor will promptly conduct a cumulative review of safety data, including the DMC assessment of the event, and the circumstances of the event in question to determine whether the study should be modified, suspended or terminated.

18 Reporting and Publication

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator(s) will be subject to mutual agreement between the Investigator and Kiniksa as outlined in the study agreement.

19 References

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20 Appendices

20.1 Appendix 1: Investigator Signature Page

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

Protocol Number: KPL-301-C001

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and I will conduct the study as described in compliance with this protocol, GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Kiniksa Pharmaceuticals Ltd. (Kiniksa) and of the IEC/IRB. I will submit the protocol modifications and/or any ICF modifications to Kiniksa and IEC/IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all Case Report Forms, laboratory samples or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Kiniksa, to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

20.3 Appendix 3: Summary of Changes

20.3.1 Protocol Amendment v2.0

Rationale for Amendment – **Protocol Amendment v2.0** was completed to clarify aspects of protocol version 1.0 as well as to incorporate feedback from global Regulatory and Ethical bodies. Substantial changes to this version include:

- Limiting the double-blind period to 26-weeks total, removing the extended exposure for patients who enroll earlier in the study.
- Removal of the Open-Label Extension – Per Regulatory feedback, open-label KPL-301 should only be provided to patients after proof of efficacy has been established
- Addition of 12-week Washout Safety Follow-up period to ensure patients have continued access to open-label study supplied prednisone and are adequately followed and weaned back to Standard of Care
- Updated inclusion criteria regarding pregnancy and contraception methods to ensure highly effective methods of contraception are reflected
- Provided clarification on sample size and event calculations
- Addition of Serum Pregnancy test during screening, additional urine pregnancy tests, safety labs, [redacted]
- Addition of Definition of SUSAR and defined Study Termination criteria

Please see the below summary of changes for more details on the changes incorporated into this version. Bold indicates addition, underline indicates removal.

Change ID	Section(s)	Current Text	Revised Text	Rationale
1	Cover page (pg 1)		IND Number 139,960	Added US IND number
2	Cover page (pg 1)	Medical Monitor: [redacted]	[redacted]	Change in Sponsor Medical Monitor
3	Cover page (pg 1), Header throughout	4-Apr 2018 Version 1.0	**12 Oct** 2018 Version **2**.0	Updated to reflect Amendment date and versioning
4	Throughout document	-	-	Administrative and formatting changes for ease of reading
5	Synopsis (pg 5) Section 8.4.1 (pg 33)	…until the last subject has reached the 26-week time point and the results from the 26-week time point have been analyzed, and an Open-Label Extension (OLE) for an additional 26-week period.	…**and a 12-week Washout Safety Follow-up Period during which subjects will discontinue and wash off blinded KPL-301 or placebo.**	Wording updated to reflect that the double-blind period will end at 26 weeks and subjects will enter a 12- week Washout Safety Follow-up Period.
6	Synopsis (pg 5) Section 8.4.1 (pg 33)	-	Acute Phase Reactants Signs/Symptoms Diagnostic Criteria	Added labels to provide clarity and assist in understanding of Screening/Diagnostic Criteria.
7	Synopsis (pg 5) Section 8.4.1 (pg 34)	The new-onset disease cohort includes subjects who have been diagnosed within 6 weeks of Day 0. The relapsing disease cohort includes subjects diagnosed with GCA > 6 weeks before Day 0 and who have at least one of the following 1) active GCA disease within 6 weeks of Day 0 (relapsing/refractory) or 2) no remission since the diagnosis of disease as per clinical expectations (refractory nonremitting)	**New-onset** - The new-onset disease cohort includes subjects who have been diagnosed within 6 weeks of Day 0 **using the above Acute Phase Reactants, Signs/Symptoms and Diagnostic Criteria.** **Relapsing/refractory** - The relapsing disease cohort includes subjects **having prior documented** diagnosis of GCA **as per Diagnostic Criteria above** > 6 weeks before Day 0 and who have active GCA disease **defined by Acute Phase Reactants and Signs/Symptoms** within 6 weeks of Day 0 or **The refractory nonremitting disease subject has had** no remission since the diagnosis of disease as per clinical expectations. **Thus, the subject has documentation of prior diagnosis of GCA as per**	Added specificity as to which criteria are relevant for each strata for clarity.

			Diagnostic criteria above > 6 weeks before Day 0; however, presence of Acute Phase Reactants and Signs/Symptoms as per above persists within 6 weeks of Day 0.	
8	Synopsis (pg 6) Section 8.4.1 (pg 34)	Subjects who complete screening procedures and are not considered eligible (screen failures) may be rescreened provided there is reason to believe that eligibility criteria will be met.	Subjects who complete screening procedures and are not considered eligible (screen failures) may be rescreened **one time** provided there is reason to believe that eligibility criteria will be met.	Clarified subjects should only be rescreened one time
9	Synopsis (pg 6)	-	**Although either acute phase reactant (CRP or ESR) may be used during the study for eligibility and to determine remission or flares, it is advisable that the same acute phase reactant used to determine remission at screening also be used to determine flares during the treatment period.**	Additional text to provide guidance for interpretation of Acute Phase Reactants from remission in case of suspected flare during treatment period.
10	Synopsis (pg 7) Section 8.4.1 (pg 36) Section 8.8 (pg 40) Section 11.2 (pg 46)	Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an End-of-Treatment (EOT) visit and will be followed for the intended duration of study treatment (i.e., until the blind is broken) to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug) must complete a Safety Follow-up visit 28 ± 3 days from the last dose administered. Additional follow up using public records may be captured where possible. An analysis of the study will be performed when the last subject reaches Week 26 according to the Statistical Analysis Plan (SAP). Based on the results of this analysis, all subjects will be offered open-label KPL-301 in the OLE portion of the trial, or the study will be discontinued. All subjects who do not proceed to the OLE must complete a Safety Follow-up visit 28 ± 3 days from the last dose administered	Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an End-of-Treatment (EOT) visit and will be followed for the intended duration of study treatment (i.e., **through Week 26 and Washout Safety Follow-up**) to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug **administration**) must complete **at a minimum the Final Washout** Safety Follow-up visit **84** ± 3 days from the last dose administered. Additional follow-up using public records may be captured where possible.	Removed and replaced language regarding the extension of the double-blind period past week 26 with language for the Washout Safety Follow-up Period
11	Synopsis (pg 7) Section 8.4.2 (pg 36) Section 11.3 (pg 46)	Open-Label Extension: Depending on the results from the analysis of the 26-week placebo-controlled base study, all subjects may be offered KPL-301 in an OLE. The OLE will continue for up to 6 months. During the OLE, subjects will be followed for safety information and will continue to follow study protocols from the double-blind period in the event of a flare and for steroid tapering procedures. During the OLE subjects may wean off KPL-301 onto SoC as determined by the Investigator.	**Washout Safety Follow-up:** **After subjects complete the 26-week double blind treatment period, they will discontinue and wash off of blinded KPL-301 or placebo during a 12-week Washout Safety Follow-up Period, which includes close safety follow-up and monitoring for potential GCA flares. During this time, it is recommended that subjects, regardless of remission status, receive SoC oral prednisone therapy, taking into consideration that they have just completed treatment with what may have been an efficacious therapy which supported the tapering off of standard of care concomitant oral corticosteroids. Clinicians may choose to observe subjects closely during the washout period without any change in concomitant medications or may choose (consistent with current SoC guidelines) to increase the daily**	Removed open label extension per Regulatory Agency feedback and replaced with Washout Safety Follow-up period to ensure subjects are adequately followed and weaned back to Standard of Care.

			corticosteroid dose prophylactically/empirically by approximately 10 mg above the prednisone dose administered at Week 26. The prednisone dose can then be tapered or maintained throughout the remainder of the 12-week Washout Safety Follow-up Period as per Investigator discretion. After the Final Washout Safety Follow-up visit (Week 38) has been completed, the subjects will exit the trial and should be transitioned to SoC per investigator judgement. It is not required that the steroid taper have been completed, (0 mg) prior to subjects exiting the trial at Week 38.	
12	Synopsis (pg 8)	For the primary endpoint analysis, the aim is to have approximately 36 subjects assigned to KPL-301 and approximately 24 subjects assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	**Approximately 60 subjects will be randomized at a 3:2 allocation ratio.** Approximately 36 subjects **will be** assigned to KPL-301, and approximately 24 subjects **will be** assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	Clarification
13	Inclusion Criteria 3 Synopsis (pg 9) Section 8.7.1 (pg 37)	…New-onset: Initial diagnosis of GCA within 6 weeks of Day 0, defined as: … …Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)… ...Relapsing: Diagnosis of GCA > 6 weeks before Day 0 AND at least one of the following: Active GCA within 6 weeks of Day 0 defined as clinical sign/symptom(s) and Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/ dL OR No remission since the diagnosis of disease as per clinical expectations. (refractory nonremitting)	…New-onset: Initial diagnosis of GCA within 6 weeks of Day 0, **defined as:** … ….Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery **pain or** tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)… Relapsing: Diagnosis of GCA > 6 weeks before Day 0 AND: Active GCA within 6 weeks of Day 0 defined as clinical sign/symptom(s) **as per above** and Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/ dL **Refractory nonremitting: Diagnosis of GCA > 6 weeks before Day 0 AND** No remission since the diagnosis of disease as per clinical expectations. **i.e. Presence of sign/symptoms as per above and Westergren ESR>30mm/hour or CRP ≥ 1 mg/ dL within 6 weeks of Day 0.**	Clarification and formatting for ease of understanding
14	Inclusion Criteria 4 Synopsis (pg 9) Section 8.7.1 (pg 37)	Remission of GCA at Day 0 (resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour)...	Remission of GCA at **or before** Day 0 (resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour)…	Clarification

15	Inclusion Criteria 6 Synopsis (pg 9) Section 8.7.1 (pg 37)	If using methotrexate (MTX), oral or parenteral up to 25mg/week is permitted in screening if started more than 6 weeks prior to Day 0 and should be stable or decreasing with the intention to discontinue use by Day 0.	If using methotrexate (MTX), oral or parenteral up to 25mg/week is permitted in screening if started more than 6 weeks prior to Day 0 and should be **tapered to zero** by Day 0.	Clarification that MTX use is excluded during the study.
16	Inclusion Criteria 9 Synopsis (pg 9,10) Section 8.7.1 (pg 38)	Female subjects must be:.. ...c) nonpregnant, nonlactating, and having agreed to use an effective method of contraception (i.e., hormonal contraceptives, intrauterine device (IUD), or double barrier methods such as condom plus diaphragm or diaphragm plus spermicide or condom plus spermicide) from Screening visit until 12 weeks after final study drug administration	Female subjects must be:.. ...c) nonpregnant, nonlactating, **and if sexually active** having agreed to use a **highly** effective method of contraception (i.e., hormonal contraceptives **associated with inhibition of ovulation** or intrauterine device **[**IUD**]**, **or intrauterine hormone-releasing system [IUS], or sexual abstinence**) from Screening **V**isit until **the Final Washout Safety Follow-up visit 84 ± 3 days from EOT Visit.**	Text added per regulatory feedback
17	Inclusion Criteria 10 Synopsis (pg 10) Section 8.7.1 (pg 38)	Male subjects must have documented vasectomy or must agree to use double barrier methods of contraception (such as condom plus diaphragm or diaphragm plus spermicide or condom plus spermicide) or use condom plus hormonal contraceptives or condom plus IUD with their partners of childbearing potential from Day 0 until the Safety Follow-up visit. Male subjects must agree to refrain from donating sperm from Day 0 until the Safety Follow-up visit.	Male subjects must have documented vasectomy or **if sexually active** must agree to use **a highly effective method of contraception** with their partners of childbearing potential **(i.e., hormonal contraceptives associated with the inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence)** from Day 0 until the **Final Washout** Safety Follow-up visit **84± 3 days from EOT Visit.** Male subjects must agree to refrain from donating sperm **during this time period.**	
18	Exclusion Criteria 6 Synopsis (pg 10) Section 8.7.2 (pg 38)	Treatment with any investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, prior to Screening	Treatment with any **non-biologic** investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, prior to Screening	Text added for clarification
19	Exclusion Criteria 9 Synopsis (pg 10) Section 8.7.2 (pg 38)	Intramuscular, IV corticosteroids within 4 weeks prior to Screening	Intramuscular, **Intra-articular,** or IV corticosteroids within 4 weeks prior to Screening	Text added for clarification
20	Exclusion Criteria 11 Synopsis (pg 10) Section 8.7.2 (pg 38)	Treatment with hydroxychloroquine, cyclosporine A, azathioprine, or mycophenolate mofetil (MMF) within 4 weeks of Screening	Treatment with hydroxychloroquine, cyclosporine A, azathioprine, **cyclophosphamide,** or mycophenolate mofetil (MMF) within 4 weeks of Screening	Text added for clarification
21	Exclusion Criteria 15 Synopsis (Pg 11)	Active, untreated or partially treated latent tuberculosis (TB)	**Positive (or 2 indeterminate) QuantiFERON test results.**	Text changed for clarification

	Section 8.7.2 (pg 39)			
22	Exclusion Criteria 19 Synopsis (pg 11) Section 8.7.2 (pg 39)	History of cancer within the last 10 years (20 years for breast cancer) except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured	History of cancer within the last 10 years - except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured	To allow for consistency of exclusion of all cancer including breast cancer within the last 10 years.
23	Exclusion Criteria 20 Synopsis (pg 11) Section 8.7.2 (pg 39)	Evidence of clinically uncontrolled respiratory disease. The Investigator should review the data from subjects' respiratory assessments including chest x-ray and pulmonary function tests (PFTs) performed within 12 weeks prior to Day 0. The subjects must have had values ≥ 60% of predicted for measurements performed and no uncontrolled lung disease. A subject's medical regimen should not have been significantly intensified to control lung disease within 12 weeks prior to Day 0.	Evidence of clinically uncontrolled respiratory disease. The Investigator should review the data from subjects' respiratory assessments including chest x-ray and pulmonary function tests (PFTs) **including DLCO** performed **during the screening period** or within 12 weeks prior to Day 0 **if results of prior assessments are available. Available PFT and DLCO assessments** must have had values ≥ 60% of predicted for measurements performed and no uncontrolled lung disease. A subject's medical regimen should not have been significantly intensified to control lung disease within 12 weeks prior to Day 0.	Text added for clarification
24	Test Products, Dosage and Mode of Administration Synopsis (pg 12)	Cases of GCA flare should be treated according to the Investigator's judgment and SoC to ensure the best possible care of the subject. In general, the subject should continue to receive the assigned KPL-301 or placebo and should also receive an increased dose of coadministered prednisone, as determined by the Investigator, generally of up to 60 mg/day. The dosages of all concomitant medications used to treat the GCA flare must be documented. If a flare, particularly a major flare, should require a dose of corticosteroid higher than prednisone 60 mg/day, in the judgment of the Investigator, steroid escape therapy is allowed (i.e., doses of prednisone > 60 mg/day, or equivalent, or IV corticosteroids) until clinical remission is achieved. If the clinical response is positive, after an appropriate period of clinical stabilization, as determined by the Investigator, (usually 1-2 weeks) the subject may resume the protocol-defined steroid taper, starting at the dose at which remission was achieved or prednisone 60 mg/day, whichever is lower. Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed to receive a more gradual Investigator-defined steroid taper and will continue to receive the assigned KPL-301 or placebo.	-	Text deleted as it is duplicate of what is described in the Base Treatment Period section of the synopsis on pg 7.
25	Test Products, Dosage and Mode of	During the OLE, subjects will receive open-label KPL-301 150 mg every 2 weeks for up to 6 additional months and may wean off KPL-301 onto	**After subjects have completed the 26-week double blind treatment period, they will discontinue and wash off blinded KPL-301 or**	Removed text regarding Open-label Extension and

	Administration Synopsis (pg 12)	SoC, according to the Investigator's judgment.	**placebo during a 12-week Washout Period. During the Washout Safety Follow-up Period, patients may be closely observed with no additional therapeutic or may receive prophylactic prednisone and tapered as per Investigator discretion. After the Final Washout Safety Follow-up visit 84 ± 3 days from the EOT Visit has been completed subjects will exit the trial and should be transitioned to SoC per investigator judgement, regardless of what dose of prednisone subjects are on.**	replaced it with information for the Washout Safety Follow-up period
26	Concomitant Medication Synopsis (pg 12) Section 10.1 (pg 44)	Subjects should receive concomitant medications in line with current SoC practices for GCA. Such medications may include the equivalent of the following: low-dose aspirin (dose allowed per SoC), pantoprazole (40 mg daily), calcium (1000 mg daily), cholecalciferol (800 U daily), and IV ibandronate 3 mg every 3 months, for the duration of the study.	Subjects should receive concomitant medications in line with current SoC practices for GCA. Such medications may include **but not limited to** the equivalent of the following **examples**: low-dose aspirin (dose allowed per SoC), pantoprazole (40 mg daily), calcium (1000 mg daily), cholecalciferol (800 U daily), and IV ibandronate 3 mg every 3 months, for the duration of the study.	Text added for clarification
27	Duration of Treatment Synopsis (pg 12) Section 8.5 (pg 36)	Subjects will receive SC KPL-301 or placebo as well as coadministered oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Subjects will receive KPL-301 or placebo for a minimum of 26 weeks (unless a subject discontinues study drug treatment prematurely). Duration of treatment will differ according to when each subject is enrolled, with the first enrolling subjects receiving treatment for longer than those who enroll later. By the time all subjects have completed 26 weeks of treatment and the 26-week results have been analyzed, some subjects (those who enroll early in the recruitment process) will have received blinded KPL-301 or placebo for approximately 18 months. Depending on the results from the 26-week analysis, all subjects may be offered open-label KPL-301 for an additional 6 months. Thus, the approximate total duration of treatment will be up to approximately 24 months.	Subjects will receive SC KPL-301 or placebo as well as coadministered **study-supplied** oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Subjects will receive KPL-301 or placebo for 26 weeks (unless a subject discontinues study drug treatment prematurely). **Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12- week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion.** Thus, the total **study** duration will be up to approximately **38-44 weeks (including 6-week Screening Period).**	Changed text to limit treatment exposure to 26 weeks total and added text regarding the 12-week Washout Safety Follow-up Period.
28	Efficacy Measures Synopsis (pg 12)	- Clinical laboratory analyses (e.g., CRP, ESR) - Clinical GCA assessments, including, for example, [redacted] - Imaging studies (as applicable), including ultrasound, MRI, CT/CTA, PET-CT, TAB (if applicable) [redacted]	- Clinical laboratory analyses (e.g., CRP, ESR, **signs/symptoms**) - Clinical GCA assessments, including, **signs/symptom(s),** [redacted] - Imaging studies (as applicable), including ultrasound, MRI, CT/CTA, PET-CT, TAB (if applicable) [redacted]	Text added for clarification
29	Other Measures(s) Synopsis (pg 12)	[redacted]	[redacted]	[redacted]

30	Overview of Trial Design Synopsis (pg 13) Figure 5 (pg 31)	-	-	Design diagram replaced to reflect 26-week exposure and 12-week Washout Safety Follow-up period.
31	Statistical Methods Synopsis (pg 14) Section 14.1 (pg 57)	General Methods All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding.	General Methods All statistical analyses will be performed using SAS® Version 9**.3** or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding.	Change of text to allow use of SAS Version 9.3 or higher
32	Statistical Methods Synopsis (pg 14) Section 14.3.1 (pg 58)	Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and are assessed for at least 1 day in the double-blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment.	Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and at least **have** 1 **assessment** in the double-blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment.	Text changed for clarification
33	Statistical Methods Synopsis (pg 14) Section 14.3.3 (pg 58)	Per Protocol Analysis Set All randomized subjects who complete Week 26 in the double blind period without protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) set.	Per Protocol Analysis Set All **mITT** subjects without protocol deviations deemed to impact efficacy or **ethical conduct** will be included in the per-protocol (PP) set.	Text changed to better reflect Per Protocol Analysis set after limiting the 26 week exposure.
34	Statistical Methods Synopsis (pg 14,15) Section 14.4 (pg 58- 59) Section 14.5.1 (pg 59,60) Section 14.5.2 (pg 60)	Primary Efficacy Endpoint Analysis The primary objective of this POC study is to evaluate the efficacy of KPL-301 versus placebo, coadministered with a 26 week steroid taper, for maintaining sustained remission for 26 weeks in subjects with new-onset or relapsing/refractory GCA. Sustained remission is defined as the absence of flare (as defined above) from the start of double-blind treatment through Week 26. The primary efficacy analysis variable is time from start of double-blind treatment until the first flare occurring	Primary Efficacy Endpoint Analysis The primary efficacy **endpoint** is time **to flare by Week 26 defined as time from randomization** to the **date of** first flare occurring within the 26-week period. Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit.	Text changed to provide clarification as well as to limit endpoint collection to the 26 Week exposure.

	Section 14.5.3 (pg 60)	within the 26-week period. Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit. The number and percentage of subjects who remain in remission, who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. Duration of remission will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test will be used to compare KPL-301 and placebo with respect to the duration of remission. Kaplan-Meier estimates of remission at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment and randomization stratum as covariates. As a secondary efficacy endpoint, duration of remission during the entire double-blind treatment period will be analyzed using the same methods described above. Subjects who do not experience flare during double-blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow-up prior to experiencing a flare at any time during double-blind treatment will be censored at the time of their last available visit. Additional secondary efficacy endpoints include the following dichotomous endpoints that will be analyzed descriptively by treatment group. Treatment comparisons will be performed using Cochran-Mantel-Haenszel test controlling for the randomized stratum: • Percentage of subjects at Week 26 with normal ESR • Percentage of subjects at the end of randomized treatment with normal ESR • Percentage of subjects at Week 26 with normal CRP • Percentage of subjects at the end of randomized treatment with normal CRP The following continuous secondary efficacy endpoints will be analyzed descriptively by treatment group. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate: • Time to steroid dose of zero • Cumulative steroid dose at Week 26 and at the end of the double-blind treatment period	The number and percentage of subjects who remain in remission (**no flare**), who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. **Time to flare by Week 26** will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test **stratified by randomization strata** will be used to compare KPL-301 and placebo with respect to **time to flare by Week 26**. Kaplan-Meier estimates of remission **rate** at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate. As a key secondary efficacy endpoint, **time to flare by week 26 in the per protocol population** will be analyzed using the same methods described above. Subjects who do not experience flare during double-blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow-up prior to experiencing a flare at any time during double-blind treatment will be censored at the time of their last available visit. Additional secondary efficacy endpoints include the following endpoints that will be analyzed. Treatment comparisons will be performed using Cochran-Mantel-Haenszel test controlling for the randomized stratum. • Percentage of subjects **who have completed the** 26-**week corticosteroid taper and who have a** normal ESR • Percentage of subjects **who have completed the 26-week corticosteroid taper and who have a** normal CRP • **Percentage of subjects who have completed the 26-week corticosteroid taper and who have no signs/symptoms of GCA** The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate: • Time to **corticosteroid** dose of zero **mg/day** • Cumulative steroid dose at Week 26 and at the end of the **Washout Safety Follow-up period** [redacted]	

		[redacted]	[redacted]	
35	Statistical Methods Synopsis (pg 15) Section 14.2 (pg 57,58)	Sample Size Estimation With 36 subjects randomized to KPL-301 and 24 subjects randomized to placebo, a two-sided log-rank test for equality of survival curves with a 0.05 significance level will have approximately 89% power to detect a 37.5% difference (20% placebo vs 57.5% KPL-301) in the proportion of subjects who experience sustained remission during the 26-week double-blind base period. It is expected that the trial will have equal numbers of subjects in the two randomization strata. Assuming that the percentage of subjects experiencing sustained remission in the new onset stratum is 70% for KPL-301 and 30% for placebo. The percentage of subjects experiencing sustained remission in the relapsing/refractory stratum is 45% for KPL-301 and 10% for placebo. A two-sided log-rank test with 0.1 significance level will have 75% power to detect a treatment difference within the stratum.	Sample Size Estimation **Assuming that time to flare follows an exponential distribution and the proportion of subjects without a flare by Week 26 will be 20% in placebo and 57 5% in KPL-301, the median time to flare would be estimated to be approximately 11.20 weeks in placebo and 32.57 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) would be estimated to be approximately 0.3438. With a 2-sided significance level of 0.05 and a 3:2 randomization ratio for KPL-301 vs. placebo, it would require approximately 34 events to achieve 86% power using a two- sided log rank test.** **Approximately 60 subjects will be randomized by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo at a 3:2 allocation ratio.** **Subject disposition and the flare event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion. If there is a high dropout rate and/or the event accrual rate is significantly slower than anticipated, up to 10 additional subjects may be randomized to obtain the target number of events required for the analysis of primary efficacy endpoint.**	Text changed to provide clarification
36	Schedule of Activities Synopsis (pg 16)	Removed: Schedule of Assessments • **Every 4 weeks thereafter visit and associated assessments** • **OLE visit and assessments** • **Fasting lipid panel and HbA1c during screening**	Added: Schedule of **Activities** • Week 30, Week 34, Week 38 Visits • Ultrasound at or before Day 0 and at Week 38 • Pulmonary function tests including DLCO at Week 38 • Serum pregnancy test during screening • Urine pregnancy test at Day 0, Week 12, Week 26 and Week 38 • Safety Labs (Hematology, Chemistry & Liver profile) at Week 4 and Week 38 • Fasting lipid panel and HbA1c at Day 0 [redacted]	Activities removed to limit double-blind Period to 26 Weeks. Activities changed to remove Open-label extension and replace with Washout Safety Follow-up Period. Additional safety labs and procedures added per Ethic and Regulatory feedback.

37	Schedule of Activities Footnotes Synopsis (pg 17)	Footnotes a. Monthly visits are conducted until the last subject completes the 26-week double-blind analysis period and the analysis is complete. e. Open-label extension visits occur monthly for up to 6 months. During the open-label extension subjects may wean off KPL-301 onto standard of care at the discretion of the investigator. f. During the open-label extension all subjects participating will receive open-label KPL-301. Any subjects on steroids at the end of the double-blind period should taper steroids at the discretion of the investigator. m. Electrocardiogram or chest X-ray (or high res CT) are not required at an EOT visit but may be performed at a UNS visit	-	Footnotes removed per updated schedule of Activities
38	Schedule of Activities Footnotes Synopsis (pg 17)	c. In the event of an unscheduled visit, only the relevant assessments pertaining to the visit need to be captured. Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study clinic at any time. This visit can be combined with the EOT visit in which all necessary assessments should be completed.	b. In the event of an unscheduled visit, only the relevant assessments/**activities** pertaining to the visit need to be captured. Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study clinic at any time. This visit can be combined with the EOT visit in which all necessary **EOT related** assessments/**activities** should be completed.	Footnotes updated or added to provide clarity
39	Schedule of Activities Footnotes Synopsis (pg 17) Section 8.8 (pg 40)	d. All subjects, including subjects who prematurely discontinue the study (i.e., withdraw consent), must complete a safety follow up visit 28 ± 3 days after the last dose of KPL-301 or placebo. Additional follow up using public records may be captured if possible.	**c.** All subjects, including subjects who prematurely discontinue the study (i.e., withdraw consent), must complete **at a minimum the Final** Safety Follow up visit **84** ± 3 days after the **EOT Visit**. Additional follow up using public records may be captured if possible.	Footnotes updated or added to provide clarity
40	Schedule of Activities Footnotes Synopsis (pg 17)	g. At baseline, subject and/or caregiver should be trained on proper self-administration and handling and accountability of IMP. This training should be documented and can be repeated as necessary throughout the study.	**d.** At baseline, subject and/or caregiver should be trained on proper self-administration and handling and accountability of **study drug**. This training should be documented and can be repeated as necessary throughout the study.	Footnotes updated or added to provide clarity
41	Schedule of Activities Footnotes	h. If a study site or clinic visit coincides with the subject's scheduled dose, study treatment will be administered at the study site or clinic. Study treatment should be dispensed as necessary to the subject for home	**e.** If a study site or clinic visit coincides with the subject's scheduled dose, study treatment will be administered at the study site or clinic. Study **drug** treatment should be dispensed as necessary to the subject	Footnotes updated or added to provide clarity

	Synopsis (pg 17)	administration to ensure dosing compliance. Investigator staff may contact patients between visits to ensure compliance with protocol specified treatment regimens.	for home administration to ensure dosing compliance. Investigator staff may contact patients between visits to ensure compliance with protocol-specified treatment regimens.	
42	Schedule of Activities Footnotes Synopsis (pg 17)	i. New-onset subjects can have an optional temporal artery biopsy taken at Screening and Week 26 as part of the study. For relapsing/refractory patients, if the subject has not had a prior a temporal biopsy an optional biopsy can be done at Screening and Week 26. If the subject has an existing biopsy sample available this can be submitted as the screening/predose sample and an optional biopsy can be performed at Week 26.	**f.** New-onset subjects can have an optional temporal artery biopsy taken at Screening **(or otherwise available from diagnostic workup)** and Week 26 as part of the study. For relapsing/refractory patients, if the subject has not had a prior a temporal biopsy an optional biopsy can be done at Screening and Week 26. If the subject has an existing biopsy sample available this can be submitted as the screening/predose sample and an optional biopsy can be performed at Week 26.	Footnotes updated or added to provide clarity
43	Schedule of Activities Footnotes Synopsis (pg 17)	j. Chest X-ray (or high res CT), DLCO, and PFTs should be obtained at Screening, or existing documentation within 12 weeks of Day 0 can be used and reviewed by the Investigator or designee.	**g.** Chest X-ray (or high res CT), DLCO, and PFTs should be obtained at Screening, or existing documentation **(if available)** within 12 weeks of Day 0 can be used and reviewed by the Investigator or designee.	Footnotes updated or added to provide clarity
44	Schedule of Activities Footnotes Synopsis (pg 17)	k. PFTs and DLCO should be performed at Screening 6-12 weeks prior to Day 0. They should also be performed at Weeks 12 and 26 with a window of ±14 days; after Week 26 PFTs and DLCO should be performed every 6 months ± 14 days; if the EOT visit is > 3 months of the prior test, the assessment should be performed.	**h.** PFTs and DLCO should be performed at Screening **within** 6 weeks prior to Day 0 **(or documented report available from PFT &/or DLCO from within 12 weeks prior to Day 0**). They should also be performed at Weeks 12 and 26 **and 38** with a window of ±14 days;	Footnotes updated or added to provide clarity
45	Schedule of Activities Footnotes Synopsis (pg 17)	p. Clinical decisions for determination of inclusion and flare will be based upon local laboratory values.	**l.** Clinical decisions for determination of inclusion and flare will be based upon local laboratory values **either ESR and/or CRP**.	Footnotes updated or added to provide clarity
46	Schedule of Activities Footnotes Synopsis (pg 17)	q. The imaging technique used during screening to diagnose GCA should be repeated throughout the study. If ultrasound is available at screening for diagnosis of GCA this should be conducted again at weeks 12, 26 and then every 6 months thereafter, or in case of a suspected flare of GCA with no other imaging (MRI, CT/CTA or PET-CT) required. If MRI, CT/CTA or PET-CT was used at screening for diagnosis of GCA and no ultrasound is available this should be repeated at week 26 then every six months thereafter or in case a suspected flare as necessary in order to reduce the exposure of radiation to the subject.	m. The imaging technique used during screening to diagnose GCA should be repeated **at week 26 for** the study. If ultrasound is available at screening for diagnosis of GCA this should be conducted again at weeks 12, 26 and **38**, or in case of a suspected flare of GCA with no other imaging (MRI, CT/CTA or PET-CT) required. If MRI, CT/CTA or PET-CT was used at screening for diagnosis of GCA and no ultrasound is available, **the same imaging technique used at screening** should be repeated at week 26 or **as necessary for diagnosis** in case a suspected flare.	Footnotes updated or added to provide clarity

47	Schedule of Activities Footnotes Synopsis (pg 17)	-	**n. Ultrasound imaging if clinically relevant should be performed at or before Day 0 to support clinical remission decision making unless there is no evidence of temporal artery inflammation and diagnosis of GCA is confined to large vessels (By MRI or CT).**	Footnote added to provide clarity
48	Section 9.1 (pg 40)	…The investigational product is supplied as a sterile clear to opalescent, colorless to slightly brown-yellow liquid, free from visible particles, in a prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, and sealed with an aluminium overseal. Each syringe contains 150 mg (nominal) of active investigational product.	…The investigational product is supplied as a sterile clear to opalescent, colorless to slightly brown-yellow liquid, free from visible particles, in a **1mL** prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, **accessorized with a needle guard, and extended finger flange and a plunger rod.** Each syringe contains 150 mg (nominal) of active investigational product.	Text changed to provide clarity
49	Section 9.2 (pg 41)	…The placebo is supplied as a sterile clear to slightly opalescent, colorless to slightly yellow liquid, free from visible particles, in a prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, and sealed with an aluminium overseal.	…The placebo is supplied as a sterile clear to, colorless liquid, free from visible particles, in a **1 ml** prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, **accessorized with a needle guard and extended finger flange and a plunger rod.**	Text changed to provide clarity
50	Section 9.3 (pg 42)	… During the OLE, subjects will continue to follow study protocols from the double-blind period in the event of a flare and for steroid tapering procedures unless indicated otherwise as per the discretion of the Investigator.	... During the Washout Safety Follow-up Period, the prednisone dose can then be tapered or maintained throughout the remainder of the 12-week Washout Period as per the discretion of the Investigator. After the Final Washout Safety Follow-up visit (Week 38) has been completed the subjects will exit the trial and should be transitioned to SoC per investigator judgement.	Text added to replace OLE with Washout Safety Follow-up Period
51	Section 9.4 (pg 42,43)	Subjects who are candidates for enrollment will be evaluated for eligibility by the Investigator to ensure that the criteria given in Section 8.7 have been satisfied and that the patients are eligible for randomization. Subjects will be randomized at a 3:2 ratio to receive either 150 mg KPL-301 or placebo. Randomization will be stratified according to whether subjects have new-onset disease or relapsing disease. Additional strata may be identified and described within the SAP.	Subjects who are candidates for enrollment will be evaluated for eligibility by the Investigator to ensure that the criteria given in Section 8.7 have been satisfied and that the **subjects** are eligible for randomization. Subjects will be randomized at a 3:2 ratio to receive either 150 mg KPL-301 or placebo. Randomization will be stratified according to whether subjects have new-onset disease or relapsing disease.	Text removed
52	Section 9.6.2 (pg 43,44)	In the event of a medical emergency, the Investigator may unblind an individual subject's treatment allocation in consultation with the Sponsor. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received active drug. In most cases, the management of a medical emergency would be the same whether or not active drug was received by the	In the event of a medical emergency, the Investigator may unblind an individual subject's treatment allocation **and notify** the Sponsor. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received active drug. In most cases, the management of a medical emergency would be the same whether or not active drug was **being** received by the	Text removed and changed to provide clarity

		subject. If this were to be the case, the treatment allocation should not be unblinded. Depending on the results of the Week 26 analysis, all subjects may be offered open-label KPL-301 in the OLE portion of the trial or the study will be discontinued after the double-blind period. If the study is discontinued after the double-blind period, subjects will not be unblinded (except for the reasons listed above) until the clinical database has been locked.	subject. If this were to be the case, the treatment allocation should not be unblinded.	
53	Section 12.2.1 (pg 47)	-	**Ideally clinical assessments of GCA signs/symptoms should occur prior to the investigator reviewing subject imaging, lab or acute phase reactant results at any given visit to minimize potential for assessment bias.**	Text added for clarity
54	Section 12.2.3 (pg 47)	In cases where ultrasound of temporal artery was captured during the diagnosis of GCA at Screening, this procedure should be repeated at Weeks 12, 26, EOT and every 6 months thereafter as well as any instances of suspected flare over the course of the study. Imaging and relevant data should be included in any elements of the diagnostic work-up pertinent to the Investigator diagnosis of GCA.	In cases where ultrasound of temporal artery was captured during the diagnosis of GCA at Screening, this procedure should be repeated at Weeks 12, 26, EOT and **Week 38** as well as any instances of suspected flare over the course of the study. Imaging and relevant data should be included in any elements of the diagnostic work-up pertinent to the Investigator diagnosis of GCA.	Text changed to incorporate Week 38 visit
55	Section 12.3.1 (pg 48)	A complete physical examination as possible by local practice should include an evaluation of the head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History and Physical Examination eCRFs.	A complete physical examination **as possible by local practice** should include an evaluation of the head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History and Physical Examination eCRFs.	Text added for clarity
56	Section 12.4 (pg 48)	The digital ECG recording must be obtained and reviewed by the Investigator or designee. For safety monitoring purposes, the Investigator or designee must sign and date all ECG tracings and place the paper copy as part of the subject's permanent study file at the site. ECG characteristics, including heart rate, QS duration, and RR, PR, and QT intervals will be recorded on the eCRF. QTcB (Bazett's correction) and QTcF (Fridericia's corrections) will be calculated. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented in eCRF.	The digital ECG recording must be obtained and reviewed by the Investigator or designee. For safety monitoring purposes, the Investigator or designee must sign and date all ECG tracings and place the paper copy as part of the subject's permanent study file at the site and overall ECG interpretation will be documented in eCRF.	Text removed for consistency with data collection
57	Section 12.5.1 (pg 49)	PFTs and DLCO should be obtained at Screening 6 weeks prior to Day 0, or existing documentation within 12 weeks of day 0 can be used and reviewed by the Investigator or designee. During the course of the study	PFTs and DLCO should be obtained at Screening 6 weeks prior to Day 0, or existing documentation within 12 weeks of day 0 can be used and reviewed by the Investigator or designee. During the course of the study	Text changed to reflect updated schedule of activities

		PFTs and DLCO should be obtained at Weeks 12 and 26 with a window of ± 14 days. After Week 26, PFTs and DLCO should be performed every 6 months ± 14 days. In the event that a subject's EOT visit is > 3 months of the prior PFT and DLCO assessment, an additional assessment should be obtained.	PFTs and DLCO should be obtained at Weeks 12, 26 **and 38** with a window of ± 14 days.	
58	Section 12.5.3 (pg 49)	Based on the study site's normal practice and acceptable clinical practice in each country (PPD vs QuantiFERON) a TB test may be performed in order to evaluate an eventual (active, untreated, or partially treated latent) infection with TB.	**Eligibility will be determined based on a central** QuantiFERON TB test performed **during screening** in order to evaluate (active, untreated, or partially treated latent) infection with TB. If a patient is suspected to have contracted tuberculosis during the study the study site may conduct a TB test in accordance with the site's normal practice to diagnose TB (PPD or local QuantiFERON).	Text changed for clarity
59	Section 12.5.4 (pg 49)	The modified Borg scale (Borg, 1982) is a validated patient reported outcome and will be used to assess subjects' perceived sensation of difficulty in breathing (dyspnea). This scale is a linear scale of numbers ranking the magnitude of difficulty in breathing, ranging from 0 (nothing at all) to 10 (maximal). An example of the Borg scale for reference is provide in Appendix 2.	The modified Borg scale (Borg , 1982) 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 10 (maximal). A **validated version** of the Borg scale **in local language will be** provided.	Text changed for clarity
60	Section 12.6.7 (pg 50)	Urine Pregnancy Test For women of child bearing potential a urine pregnancy tests should be performed prior to enrolment at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	Pregnancy Test For women of child bearing potential a **serum** pregnancy test should be performed prior to enrolment at the site. **Urine pregnancy tests should be performed at Day 0, Week 12, Week 26 and the Final Safety Follow-up Visit.** Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	Text changed to add serum pregnancy test prior to randomization
61	Section 12.7.2 (pg 50)	[redacted]	[redacted]	Text changed to reflect updated schedule of activities
62	Section 12.8 (pg 51) Appendix 3, 5 & 6	[redacted]	-	Samples of the Patient Scales and Assessments have been removed from the protocol as validated versions in local language will be provided
63	Section 13.1.3.2 (pg 52)	Biologic therapies are known to be associated with an increased risk of immediate and delayed hypersensitivity reactions as well as anaphylaxis. Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event.	Biologic therapies are known to be associated with an increased risk of immediate and delayed hypersensitivity reactions as well as anaphylaxis. Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event, [redacted]	Text added for clarity

			[redacted]	
64	Section 13.1.3.3 (pg 52)	…Any subject who has been referred for a specialist pulmonary evaluation should not receive the investigational product until the symptom(s) or sign(s) causing the referral have resolved.	…Any subject who has been referred for a specialist pulmonary evaluation **may be instructed to stop** the investigational product until the symptom(s) or sign(s) causing the referral have resolved.	Text changed for clarity
65	Section 13.1.7 (pg 54)	-	**Suspected Unexpected Serious Adverse Reaction** A Suspected Unexpected Serious Adverse Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or prescribing information/summary of product characteristics for an authorized product). All relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening will be recorded and reported to the competent authorities in all the applicable countries, and to the Ethics Committee/Institutional Review Boards in conjunction with Directive 2001/20/EC.	Text added per Ethics/Regulatory request
66	Section 13.4 (Pg 55)	AEs will be collected from the time of signing of informed consent through the final Safety Follow-up period (24 days ± 3days after the last dose of study drug).	AEs will be collected from the time of signing of informed consent through the Final **Washout** Safety Follow-up period (**84** days ± 3 days after the **EOT visit**).	Text changed for consistency with schedule of activities
67	Section 14.1.2 (pg 57)	The primary objective of this study is to evaluate the efficacy of KPL-301 versus placebo, in combination with steroid taper, for maintaining sustained remission for 26 weeks. The primary efficacy analysis entails the inferential comparison of KPL-301 to placebo with respect to time from start of double-blind treatment until the first flare occurring within the first 26-weeks of the double-blind period. The key secondary efficacy analysis entails inferential comparison of KPL-301 to placebo with respect to time from start of double-blind treatment until the first flare anytime during the double-blind period. Multiplicity with respect to these two inferential efficacy analyses will be managed via the gated hierarchical testing procedure. If and only if the primary comparison results in a statistically significant difference between KPL-301 and placebo at 0.05 level of significance, the key secondary comparison may be conducted at alpha 0.05 as well. All other secondary endpoints are considered exploratory, and no adjustment for multiple testing of secondary efficacy endpoints will be performed.	Multiplicity with respect to **the primary efficacy endpoint and the key secondary efficacy endpoints** will be managed via the gated hierarchical testing procedure. If and only if the primary comparison results in a statistically significant difference between KPL-301 and placebo at 0.05 level of significance, the key secondary comparison **will** be conducted at alpha 0.05 as well. All other secondary endpoints are considered exploratory, and no adjustment for multiple testing of secondary efficacy endpoints will be performed.	Text updated for clarity
68	Section 16.2 (pg 63)	This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the Declaration of Helsinki, and local regulations.	This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the **most recent version of the** Declaration of Helsinki	Text updated for clarity

			in which the Sponsor intends to publish the results regardless of the study outcome, and local regulations.	
69	Section 17 (pg 64)	-	**Study Termination** **The Sponsor reserves the right to temporarily suspend or terminate this study in part or whole at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to:** **The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects** **Subject enrollment is unsatisfactory** **Non-compliance that might significantly jeopardize the validity or integrity of the study** **Recommendation to suspend or terminate the study by independent body such as DMC or Health Authority** **Sponsor decision to terminate development** **Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IECs when applicable) will be obtained prior to resuming the study.**	Text added per Ethics/Regulatory request

20.3.2 Protocol Amendment v3.0

Rationale for Amendment – **Protocol Amendment v3.0** was completed to clarify aspects of protocol version 2.0 as well as to incorporate feedback from global Regulatory bodies. Substantial changes to this version include:

- Discontinuation of study drug (KPL-301 or placebo) in the event of a GCA Flare
- [redacted]
- Clarification of individual patient and study stopping criteria
- Correction of the US Safety contact number

Please see the below summary of changes for more details on the changes incorporated into this version. Bold indicates addition, underline indicates removal.

Change ID	Section(s)	Current Text	Revised Text	Rationale
1	Title Page (pg 1) Header throughout	Date of Protocol: 15 Oct 2018 Version of Protocol: 2.0	Date of Protocol: 15 **Nov** 2018 Version of Protocol: **3**.0	Administrative
2	Section 2 (pg 2) Section 13.6 (pg 55)	US 24 Hour Safety Hotline: 1 888-483-77729	**US 24 Hour Safety Hotline: 1 888-483-7729**	Administrative correction
3	Synopsis (pg 7) Section 8.4.1 (pg 32)	Cases of flare should be treated according to the Investigator's judgment and standard of care (SoC) to ensure the best possible care of the subject. In general: • The subject should continue to receive the assigned KPL-301 or placebo and should also receive an increased dose of coadministered prednisone, as determined by the Investigator, generally of up to 60 mg/day. The dosages of all concomitant medications used to treat the GCA flare must be entered into the eCRF. • If a flare, particularly a major flare, should require a dose of corticosteroid higher than prednisone 60 mg/day, in the judgment of the Investigator, steroid escape therapy is allowed (i.e., doses of prednisone > 60 mg/day or equivalent, or intravenous (IV) corticosteroids) until clinical remission is achieved. If the clinical response is positive, after an appropriate period of clinical stabilization, as determined by the Investigator, the subject may resume the protocol-defined steroid taper, starting at the dose at which remission was achieved or prednisone 60 mg/day, whichever is lower. Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed to receive a more gradual Investigator-defined steroid taper and will continue to receive the assigned KPL-301 or placebo. These subjects will be considered to have met the primary endpoint if a flare has occurred prior to Week 26.	**Subjects who experience a** flare **or subjects who cannot adhere to the protocol-defined steroid taper due to a flare** should be **managed** to ensure the best possible care of the subject: • The subject **must dis**continue the assigned **study drug (**KPL-301 or placebo**)** and should receive **escape therapy in accordance with local SoC**, as determined by the Investigator, **which may include, for example, dose modifications of corticosteroids, other immunomodulatory agents, and/or approved therapies (e.g., tocilizumab)**. The dosages of all concomitant medications used to treat the GCA flare must be entered into the eCRF. • **Escape corticosteroid therapy can be escalated immediately. Due to possible safety and pharmacologic effects resulting from overlapping exposures to immunomodulatory agents on top of co-administered corticosteroids, the investigator should consider a washout period of at least 35 days (based on elimination half-lives) after the last dose of study drug if deemed clinically appropriate.**	Text updated per regulatory feedback

4	Synopsis (pg 11)	Subjects will receive SC KPL-301 or placebo as well as coadministered study-supplied oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Subjects will receive KPL-301 or placebo for 26 weeks (unless a subject discontinues study drug treatment prematurely). Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12-week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion. Thus, the total study duration will be up to approximately 38-44 weeks (including 6-week Screening Period).	Subjects will receive SC KPL-301 or placebo as well as coadministered study-supplied oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12-week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion. Thus, the total study duration will be up to approximately 38-44 weeks (including 6-week Screening Period).	Removed redundant text
5	Synopsis (pg 7) Section 8.4.2 (pg 35) Section 9.3 (pg 40)	…The prednisone dose can then be tapered or maintained throughout the remainder of the 12-week Washout Safety Follow-up Period as per Investigator discretion…	…The prednisone dose can then be tapered, **increased** or maintained throughout the remainder of the 12-week Washout Safety Follow-up Period as per Investigator discretion...	Text added for clarity
6	Table 1 Schedule of Activities (pgs 15- 16)	[redacted]	[redacted]	[redacted]
7	Section 8.3 (pg 32)	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will follow a different Investigator-defined steroid therapy/taper but will continue to receive the assigned KPL-301 or placebo. Subjects are not allowed to receive biologic DMARDs other than KPL-301 during the study to mitigate potential safety risks of administering KPL-301 concomitantly with other biologics…	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse **must** discontinue the assigned **study drug** (KPL-301 or placebo) **and should receive escape therapy in accordance with local SoC**. Subjects are not allowed to receive biologic DMARDs **while receiving** KPL-301 during the study to mitigate potential safety risks of administering KPL-301 concomitantly with other biologics...	Text updated per regulatory feedback

8	Section 8.8 (pgs 38-39)	Subjects may withdraw from the study drug treatment or from the study as a whole at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with and withdraw subjects from the study for any of the following reasons: Adverse event Life threatening or other unacceptable toxicity Subject requires use of a prohibited concomitant medication or therapy General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion Severe noncompliance Lost to follow-up Subject withdrawal of consent A decision to modify or discontinue development of the drug	Subjects may withdraw from the study drug treatment or from the study as a whole at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with and withdraw subjects from the study for any of the following reasons: Adverse event or Life threatening or other unacceptable toxicity, for example: Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN, assessed as related to investigational product CTCAE Grade 4 (life-threatening) anaphylaxis or hypersensitivity reactions CTCAE Grade 4 (life-threatening) serious infection or opportunistic infection (including septic shock). In addition, subjects with a diagnosis or reactivation of TB, hepatitis B, or hepatitis C will not receive any further investigational product. CTCAE Grade 4 (life-threatening) neutropenia Adverse events of malignancy of any grade; except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured. Subject requires use of a prohibited concomitant medication or therapy General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion Severe noncompliance Lost to follow-up Pregnancy or a decision to become pregnant Subjects who request to be permanently discontinued from further receipt of investigational product, regardless of the reason (Subject withdrawal of consent) A decision to modify or discontinue development of the drug	Text updated per regulatory feedback
9	Section 9.3 (pg 40)	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed steroid escape therapy per the Investigator <u>such as prednisone or similar > 60 mg/day or IV corticosteroids but will continue to receive the KPL-301 or placebo</u>…	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed escape therapy per the Investigator….	Text removed per regulatory feedback

10	Section 10.2 (pg 43)	The introduction of the following medications is not permitted from initiation of screening through the end of the study.	The introduction of the following medications is not permitted from initiation of screening through the end of the study **unless indicated for escape therapy**.	Text add for clarity
11	Section 10.3 (pg 43)	Subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed steroid escape therapy per the Investigator, such as prednisone or similar > 60mg/day or IV corticosteroids and will continue to receive the assigned study drug treatment (KPL-301 or placebo). These subjects are considered to have met the primary endpoint provided the flare occurs prior to Week 26.	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). These subjects are considered to have met the primary endpoint provided the flare occurs prior to Week 26. Escape corticosteroid therapy can be escalated immediately. Due to unknown possible safety and pharmacological effects from overlapping exposures to immunomodulatory agents on top of co-administered corticosteroids, the investigator should consider a washout period of at least 35 days (based on elimination half-lives) after the last dose of study drug (KPL-301 or placebo) if deemed clinically appropriate.	Text updated per regulatory feedback
12	Section 11.2 (pg 45)	In cases of flare, the prednisone dose may be increased. Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed to receive a more gradual Investigator-defined steroid taper and will continue to receive the assigned KPL-301 or placebo. These subjects will be considered to have met the primary endpoint if a flare has occurred prior to Week 26.	**Subjects who experience a flare or** who cannot adhere to the protocol-defined steroid taper due to flare/relapse **must dis**continue the assigned **study drug (**KPL-301 or placebo**) and should receive escape therapy in accordance with local SoC.** These subjects will be considered to have met the primary endpoint if a flare has occurred prior to Week 26.	Text updated per regulatory feedback
13	Section 12.6.7 (pg 49)	For women of child bearing potential a serum pregnancy test should be performed prior to enrolment at the site. Urine pregnancy tests should be performed at Day 0, Week 12, Week 26 and the Final Washout Safety Follow-up Visit. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	For women of child bearing potential a serum pregnancy test should be performed prior to **randomization** at the site. Urine pregnancy tests should be performed at Day 0, Week 12, Week 26 and the Final Washout Safety Follow-up Visit. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	Text changed for clarification

14	Section 17.1 (pg 63)	-	17.1 Study Stopping Criteria If the sponsor receives a report of an event consistent with any one of the following, the medical monitor or designee will immediately assess the event by gathering all available information including, where possible, direct telephone contact with the reporter. A prompt review of the data will be initiated by the sponsor, and the information will be referred to the DMC within 1 business day of the receipt of the initial report by the Sponsor. Any CTCAE grade 5 (death) assessed as related to the investigational product Any CTCAE grade 4 (life-threatening) assessed as related to the investigational product Any CTCAE grade 4 (life-threatening) of anaphylaxis Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN, assessed as related to investigational product Any unforeseen events that, in the opinion of the DMC and the Sponsor, may contraindicate further dosing Clinically-significant pulmonary abnormalities that in the opinion of the DMC and the Sponsor may contraindicate further dosing If any above-listed events occur, the Sponsor will promptly conduct a cumulative review of safety data, including the DMC assessment of the event, and the circumstances of the event in question to determine whether the study should be modified, suspended or terminated.	Text added per regulatory feedback

20.3.3 Protocol Amendment v4.0

Rationale for Amendment – **Protocol Amendment v4.0** was completed to clarify aspects of protocol version 3.0 as well as to incorporate feedback from global Regulatory bodies. Substantial changes to this version include:

- Updated secondary endpoints and analysis; and inserted study endpoints into the Synopsis Objective section.
- The planned number of subjects to be enrolled in the study was updated from approximately 60 to approximately 70 subjects (42 subjects planned to be assigned to the KPL-301 arm and 28 subjects planned to be assigned to the placebo arm) to align with the updated sample size estimation.
- Added clarification that SAEs will be recorded in the eCRF within 24 hours of discovery.

Please see the below summary of changes for more details on the changes incorporated into this version. Bold indicates addition, underline indicates removal.

Change ID	Section(s)	Current Text	Revised Text	Rationale
1	Cover page, Header throughout	Date of Protocol: 15 Nov 2018 Version of Protocol: 3.0	Date of Protocol: **30 Mar 2020** Version of Protocol: **4.0**	Updated to reflect Amendment date and versioning
2	1. Protocol Approval	Sponsor Signatory: [redacted] Chief Medical Officer Kiniksa Pharmaceuticals Ltd. 100 Hayden Ave Lexington, MA 02421 USA	[redacted] **Senior Vice President** **Clinical Development** Kiniksa Pharmaceuticals Ltd. 100 Hayden Ave Lexington, MA 02421 USA	Change in Sponsor Signatory
3	Throughout document	-	-	Minor administrative editing and formatting changes for ease of reading
4	Synopsis: Objective(s) Section	**Objective(s):** Primary: The primary objective of the study is to evaluate the efficacy of KPL-301 versus placebo, coadministered with a 26-week steroid taper, for maintaining sustained remission for 26 weeks in subjects with new-onset or relapsing/refractory giant cell arteritis (GCA). Secondary: The secondary objectives of the study, in subjects with new-onset and relapsing/refractory GCA, are: a.) To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose. [redacted] c.) To evaluate the safety and tolerability of KPL-301. [redacted]	**Objective(s):** Primary: The primary objective of the study is to evaluate the efficacy of KPL-301 versus placebo, coadministered with a 26-week steroid taper, for maintaining sustained remission for 26 weeks in subjects with new-onset or relapsing/refractory giant cell arteritis (GCA). Secondary: The secondary objectives of the study, in subjects with new-onset and relapsing/refractory GCA, are: a.) To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose. [redacted] c.) To evaluate the safety and tolerability of KPL-301. [redacted]	Added endpoints to synopsis.

Change ID	Section(s)	Current Text	Revised Text	Rationale
		[redacted]	[redacted] **Efficacy Endpoints:** **Primary Endpoint:** • **Time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period** **Secondary Endpoints:** • **Sustained remission rate 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 have completed the corticosteroid taper and who have neither signs/symptoms of GCA nor new or worsening vasculitis by imaging by 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 by imaging by Week 26** • **Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up Period** [redacted]	

Change ID	Section(s)	Current Text	Revised Text	Rationale

			[redacted]
			Safety Endpoints:
			• **Incidence of treatment emergent adverse events**
			• **Change in physical exam results**
			• **Change in vital signs**
			• **Change in clinical laboratory parameters**
			  ○ **Serum chemistry**
			  ○ **Hematology**
			  ○ **Urinalysis**	

5	Synopsis: Number of Subjects and Overview of Trial Design Figure	Approximately 60 subjects will be randomized at a 3:2 allocation ratio. Approximately 36 subjects will be assigned to KPL-301, and approximately 24 subjects will be assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	Approximately **70** subjects will be randomized at a 3:2 allocation ratio. Approximately **42** subjects will be assigned to KPL-301, and approximately **28** subjects will be assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	Updated the planned number of subjects to address potential early dropout.
6	Synopsis: Statistical Methods	General Methods All statistical analyses will be performed using SAS® Version 9.3 or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding. Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and at least have 1 assessment in the double blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment. Safety Analysis Set All randomized subjects who take at least 1 dose of 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.	General Methods All statistical analyses will be performed using SAS® Version 9.**4** or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding. Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and at least have 1 assessment in the double blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment **assignment.** Safety Analysis Set All randomized subjects who take at least 1 dose of 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.	Updated text to allow use of SAS Version 9.4 or higher Updated text in Endpoint Analysis subsection for clarification and new statistical assumptions. Sustained remission rate at Week 26 was added as a standalone secondary efficacy endpoint. Time to elevated ESR and CRP by Week 26 and time to sign/symptoms of GCA or new or worsening vasculitis by imaging by Week 26 were added as secondary efficacy endpoints in response to request from the FDA.

Change ID	Section(s)	Current Text	Revised Text	Rationale
		Per Protocol Analysis Set All mITT subjects without protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) set. Primary Efficacy Endpoint Analysis The primary efficacy endpoint is time to flare by Week 26 defined as time from randomization to the date of first flare occurring within the 26-week period. Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit. The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare by Week 26. Kaplan-Meier estimates of remission rate at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate. As a key secondary efficacy endpoint, time to flare by week 26 in the per protocol population will be analyzed using the same methods described above. Subjects who do not experience flare during double-blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow-up prior to experiencing a flare at any time during double-blind treatment will be censored at the time of their last available visit. Additional secondary efficacy endpoints include the following endpoints that will be analyzed. Treatment comparisons will be performed using Cochran-Mantel-Haenszel test controlling for the randomized stratum. • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal ESR • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal CRP by Week 26	Per Protocol Analysis Set All mITT subjects without **important** protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) **analysis** set. Primary Efficacy Endpoint Analysis The primary efficacy endpoint is time to flare by Week 26 defined as time from randomization to the first flare occurring within the **treatment** period. **Detailed censoring rules** will be **provided in** the **SAP**. The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the **treatment** period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare by Week 26. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as **a** covariate **and stratified by the randomization strata.** **The protocol definition of flare includes multiple components. Supportive analyses will be performed based on each individual component. The details will be described in the SAP. In addition, a sensitivity analysis will be performed using the same method described above for the per-protocol analysis set.** **Secondary Efficacy Endpoint Analysis** **Sustained remission rate at Week 26 will be estimated and compared using the Kaplan-Meier method** **The following endpoints will be analysed using the Cochran-Mantel-Haenszel test, stratified by the randomized stratum:** • 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 have completed the corticosteroid taper and who have **neither** signs/symptoms of GCA **nor new or**	The key secondary endpoint time to flare by Week 26 in the Per Protocol population was deleted as it will be handled as a sensitivity analysis. Deleted time to corticosteroid dose of zero mg/day as a secondary efficacy endpoint because patients enter the study with varying doses of steroids. Updated the planned number of subjects to address potential early dropout. Updated statistical assumptions based on review of Phase 3 Tocilizumab data.

Change ID	Section(s)	Current Text	Revised Text	Rationale
		• Percentage of subjects who have completed the 26-week corticosteroid taper and who have no signs/symptoms of GCA The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate: • Time to corticosteroid dose of zero mg/day • Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted] Safety Analyses Descriptive statistics will be used to summarize all safety endpoints, by treatment group and study visit. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed parameters such as incidence of adverse events (AEs), clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, PFT and diffusing capacity for carbon monoxide (DLCO) parameters, and physical exam, where available. [redacted] Sample Size Estimation Assuming that time to flare follows an exponential distribution and the proportion of subjects without a flare by Week 26 will be 20% in placebo and 57.5% in KPL-301, the median time to flare would be estimated to be approximately 11.20 weeks in placebo and 32.57 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) would be estimated to be approximately 0.3438. With a 2-sided significance level of 0.05 and a 3:2 randomization ratio for KPL-301 vs. placebo, it would require approximately 34 events to achieve 86% power using a two-sided log rank test.	**worsening vasculitis by imaging by Week 26** **The following time to event endpoints will be analyzed using the same methods used for the primary efficacy endpoint:** • **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 by imaging by Week 26** The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate. **Details will be described in the SAP:** • Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted] Safety Analyses Descriptive statistics will be used to summarize all safety endpoints, by treatment group and study visit. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed parameters such as incidence of adverse events (AEs), clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, PFT and diffusing capacity for carbon monoxide (DLCO) parameters, and physical exam, where available. [redacted] Sample Size Estimation Assuming 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 is estimated to be	

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		Approximately 60 subjects will be randomized by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo at a 3:2 allocation ratio. Subject disposition and the flare event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion. If there is a high dropout rate and/or the event accrual rate is significantly slower than anticipated, up to 10 additional subjects may be randomized to obtain the target number of events required for the analysis of primary efficacy endpoint.	approximately **26** weeks in placebo and **111** weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) **is** estimated to 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.	
7	Section 8.6	Approximately 60 patients with GCA will be randomized as study subjects. For the primary endpoint analysis, the aim is to have 36 subjects assigned to KPL-301 and 24 subjects assigned to placebo, with balanced randomization in the two randomization cohorts.	Approximately **70 patients** with GCA will be randomized as study subjects. For the primary endpoint analysis, the aim is to have 42 subjects assigned to KPL-301 and 28 subjects assigned to placebo, with balanced randomization in the two randomization cohorts.	Updated the planned number of subjects to address potential early dropout.
8	Section 12.5.4	The modified Borg scale (Borg, 1982) 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 10 (maximal). A validated version of the Borg scale in local language will be provided.	The modified Borg scale (Borg **and 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 10 (maximal). A validated version of the Borg scale in local language will be provided.	Updated citation for modified Borg scale.
9	Section 13.6	All SAEs, whether or not considered causally related to study drug or to the study procedure(s), have to be reported. All SAEs will be recorded in the eCRF. The Investigator must report all SAEs to the Safety Department and Sponsor within 24 hours of discovery via the SAE reporting form to: **24 Hour Safety Hotline: +44 1223 374 240** **24 Hour Safety Hotline Fax: +44 1223 374 102** **US 24 Hour Safety Hotline: 1 888-483-7729** **US 24 Hour Safety Hotline Fax: 1 888-529-3580**	All SAEs, whether or not considered causally related to study drug or to the study procedure(s), have to be reported. SAEs will be recorded in the eCRF **within 24 hours of discovery.** **In case the eCRF is inaccessible,** the Investigator must report all SAEs to the Safety Department and Sponsor within 24 hours of discovery via the SAE reporting form to: **24 Hour Safety Hotline: +44 1223 374 240** **24 Hour Safety Hotline Fax: +44 1223 374 102** **US 24 Hour Safety Hotline: 1 888-483-7729** **US 24 Hour Safety Hotline Fax: 1 888-529-3580**	Updated text upon request from Slovenian Inspection.
10	Section 14.1	All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.3 or later. A statistical analysis plan (SAP) will be written and approved prior to performing the first review of the data.	All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.**4** or later. A statistical analysis plan (SAP) will be written and approved prior to performing the first review of the data.	Updated text to allow use of SAS Version 9.4 or higher

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11	Section 14.1.2	14.1.2 Multiple Comparisons/Multiplicity Multiplicity with respect to the primary efficacy endpoint and the key secondary efficacy endpoints will be managed via the gated hierarchical testing procedure. If and only if the primary comparison results in a statistically significant difference between KPL-301 and placebo at 0.05 level of significance, the key secondary comparison will be conducted at alpha 0.05 as well. All other secondary endpoints are considered exploratory, and no adjustment for multiple testing of secondary efficacy endpoints will be performed.	14 1 2 Multiplicity **Adjustment** Multiplicity **adjustment** with respect to the primary efficacy **and secondary efficacy endpoints will be performed using** the **gate-keeping** hierarchical testing procedure. **The order of the secondary endpoints will be described in the SAP. 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 ≤0.05 and the test statistic shows KPL-301 is superior than placebo, 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.**	Clarified language in response to request from the FDA.
12	Section 14.2	Approximately 60 subjects will be randomized 3:2 by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo. Assuming that time to flare follows an exponential distribution and the proportion of subjects without a flare by week 26 will be 20% in placebo and 57.5% in KPL-301, the median time to flare would be estimated to be approximately 11.20 weeks in placebo and 32.57 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) would be estimated to be approximately 0.3438. With a 2-sided significance level of 0.05 and a 3:2 randomization ratio for KPL-301 vs. placebo, it would require approximately 34 events to achieve 86% power using a two- sided log rank test. Approximately 60 subjects will be randomized by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo at a 3:2 allocation ratio. Subject disposition and the flare event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion. If there is a high dropout rate and/or the event accrual rate is significantly slower than anticipated, up to 10 additional subjects may be randomized to obtain the target number of events required for the analysis of primary efficacy endpoint.	Assuming 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 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.	Updated the planned number of subjects to address potential early dropout. Updated statistical assumptions based on review of Phase 3 Tocilizumab data.
13	Section 14.4	Efficacy Endpoints: Primary Endpoint: • Time to flare by Week 26 defined as time from randomization to the first flare occurring within the first 26-weeks of the double-blind period Key secondary endpoint:	Efficacy Endpoints: Primary Endpoint: • Time to flare by Week 26 defined as time from randomization to the first flare occurring within the **treatment** period Secondary Endpoints:	Updated text in Efficacy Endpoints for clarification. Sustained remission rate at Week 26 was added as a standalone secondary efficacy endpoint.

Change ID	Section(s)	Current Text	Revised Text	Rationale
		• Time to flare by week 26 from randomization to first flare occurring within the first 26 weeks of the double-blind period in the per protocol population Additional Secondary Endpoints: • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal ESR • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal CRP • Percentage of subjects who completed the 26-week corticosteroid taper and who have no signs/symptoms of GCA • Time to corticosteroid dose of zero mg/day • Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up Period [redacted] Safety Endpoints • Incidence of treatment emergent adverse events • Change in physical exam results • Change in vital signs • Change in clinical laboratory parameters o Serum chemistry o Hematology o Urinalysis	• **Sustained remission rate 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** • **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 and at the end of the Washout Safety Follow-up Period [redacted] Safety Endpoints • Incidence of treatment emergent adverse events • Change in physical exam results • Change in vital signs • • Change in clinical laboratory parameters o Serum chemistry o Hematology	Time to elevated ESR and CRP by Week 26 and time to sign/symptoms of GCA or new or worsening vasculitis by imaging by Week 26 were added as secondary efficacy endpoints in response to request from the FDA. The key secondary endpoint time to flare by Week 26 in the Per Protocol population was deleted as it will be handled as a sensitivity analysis. Deleted time to corticosteroid dose of zero mg/day as a secondary efficacy endpoint because patients enter the study with varying doses of steroids.

Change ID	Section(s)	Current Text	Revised Text	Rationale
			o Urinalysis	
14	Section 14.5	14.5 Analysis of Efficacy All efficacy analyses will be performed on the mITT analysis set. The primary and key secondary efficacy Analyses will be repeated using the PP set to assess the sensitivity of the results to major deviations/violations of the protocol. All efficacy data including those collected during the open label extension will be listed by subject. 14.5.1 Primary Efficacy Analysis The primary efficacy endpoint is time to flare by Week 26 defined in 14.1 Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit. The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. Time to flare by week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare. The Kaplan-Meier estimates of remission rate at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate. 14.5.2 Key Secondary Efficacy Analysis The key secondary efficacy endpoint is time to flare by week 26 in the per protocol population and will be analyzed using the same methods as described above. Subjects who do not experience flare during double blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow up prior to experiencing a flare at any time during double blind treatment will be censored at the time of their last available visit. 14.5.3 Additional Secondary Efficacy Analysis The number and percentage of subjects with normal ESR at Week 26 as well as the number and percentage of subjects with normal CRP at Week 26 will be analyzed. Treatment groups will be compared using a Cochran-Mantel-Haenszel test controlling for the randomized strata. Confidence	14 5 Analysis of Efficacy All efficacy analyses will be performed on the mITT analysis set. Analyses will be repeated using the PP set to assess the sensitivity of the results to **important** deviations of the protocol. 14 5 1 Primary Efficacy **Endpoint** Analysis The primary efficacy endpoint is time to flare by Week 26 defined **as time from randomization to the first** flare **occurring within the treatment** period. **Detailed censoring rules will be provided in the SAP.** The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the **treatment** period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare **by Week 26**. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as **a** covariate **and stratified by randomization strata.** **The protocol definition of flare includes multiple components. Supportive analyses will be performed based on each individual component. The details will be described in the SAP. In addition, a sensitivity analysis will be performed using the same method described above for the PP analysis set.** **14 5 2** Secondary Efficacy **Endpoint** Analysis **Sustained remission rate** at Week 26 will be **estimated and** compared using **the Kaplan-Meier method.** **The following endpoints will be analyzed using the** Cochran-Mantel-Haenszel test **stratified by the randomization strata.** • **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**	Updated text for clarification and new statistical assumptions. Sustained remission rate at Week 26 was added as a standalone secondary efficacy endpoint. Time to elevated ESR and CRP by Week 26 and time to sign/symptoms of GCA or new or worsening vasculitis by imaging by Week 26 were added as secondary efficacy endpoints in response to request from the FDA. The key secondary endpoint time to flare by Week 26 in the Per Protocol population was deleted as it will be handled as a sensitivity analysis. Deleted time to corticosteroid dose of zero mg/day as a secondary efficacy endpoint because patients enter the study with varying doses of steroids. Updated the planned number of subjects to address potential early drop-out. Updated statistical assumptions based on review of Phase 3

Change ID	Section(s)	Current Text	Revised Text	Rationale
		intervals for the difference of proportions between treatment groups will be displayed.with normal ESR at Week 26 as well as the number and with normal CRP at Week 26. Time to steroid dose of zero will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. The following continuous secondary efficacy endpoints will be analyzed. The details will be provided in the SAP. • Cumulative corticosteroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted]	• **Percentage of subjects who have completed the corticosteroid taper and who have neither signs/symptoms of GCA or new or worsening vasculitis by imaging by Week 26** **The following time-to event endpoints will be analyzed using the same method for the primary efficacy endpoint.** • **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 by imaging by Week 26** The following continuous secondary efficacy endpoints will be analyzed. **The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate. Details will be** provided in the SAP. • Cumulative corticosteroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted]	Tocilizumab data.
15	Section 19	Borg GAJ. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982:14:37781.	**Borg G, Borg E. The Borg CR Scales® Folder. Hasselby, Sweden: Borg Perception; 2010.**	Updated reference for the modified Borg scale.

Clinical Study Protocol

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

Protocol Number:	KPL-301-C001
EudraCT Number:	2018-001003-36
IND Number:	139,960
Investigational Medicinal Product:	KPL-301 (CAM-3001)
Phase:	Phase 2
Sponsor:	Kiniksa Pharmaceuticals, Ltd. Hamilton, Bermuda c/o Kiniksa Pharmaceuticals Corp. 100 Hayden Ave Lexington, Massachusetts 02421
Medical Monitor:	
Date of Protocol:	30 March 2020
Version of Protocol:	4.0

1 Protocol Approval

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

Protocol Number: KPL-301-C001

This study will be conducted in compliance with the clinical study protocol, ICH Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Senior Vice President
Clinical Development
Kiniksa Pharmaceuticals Ltd.
100 Hayden Ave
Lexington, MA 02421 USA

[redacted]
Signature

30 MAR 2020
Date

2 *Investigator and Administrative Structure*

Sponsor:	Kiniksa Pharmaceuticals, Ltd. Hamilton, Bermuda c/o Kiniksa Pharmaceuticals Corp. 100 Hayden Ave Lexington, Massachusetts 02421
Sponsor's Medical Contact:	Kiniksa Pharmaceuticals Corp. 100 Hayden Ave Lexington, Massachusetts 02421 [redacted]
Drug safety/SAE-reporting:	**24 Hour Safety Hotline: +44 1223 374 240** **24 Hour Safety Hotline Fax: +44 1223 374 102** **US 24 Hour Safety Hotline: 1 888-483-7729** **US 24 Hour Safety Hotline Fax: 1 888-529-3580**
Responsible CRO:	[redacted]

3 Synopsis

Trial Number:

KPL-301-C001

Trial Title:

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

Trial Centers:

Multi-center Global Study

Development Phase: 2

Objective(s):

Primary:

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

Secondary:

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

a) To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose.

[redacted]).

c) To evaluate the safety and tolerability of KPL-301.

[redacted]

Efficacy Endpoints:

Primary Endpoint:

- Time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period

Secondary Endpoints:

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

[redacted]

Safety Endpoints:

- Incidence of treatment emergent adverse events
- Change in physical exam results
- Change in vital signs
- Change in clinical laboratory parameters
  - Serum chemistry
  - Hematology
  - Urinalysis

Methodology:

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 patients with GCA. The study will consist of a Screening Period (up to 6 weeks), a 26-week Double-Blind placebo-controlled Period during which subjects will receive blinded KPL-301 or placebo coadministered with a 26-week corticosteroid taper, and a 12-week Washout Safety Follow-up Period during which subjects will discontinue and wash off blinded KPL-301 or placebo.

Screening/Diagnostic Period:

Following signing of the informed consent form (ICF), potential subjects 50-85 years of age (inclusive) will be screened for meeting study-specified diagnostic criteria for GCA.

- Acute Phase Reactants - Westergren erythrocyte sedimentation rate (ESR) > 30 mm/hour or C-reactive protein (CRP) ≥ 1 mg/dL

  AND
- Signs/Symptoms - At least one of the following:
  i. Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp, or temporal artery pain or tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

ii. Unequivocal extra-cranial symptoms of GCA, such as claudication of the extremities

iii. Symptoms of polymyalgia rheumatica (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

AND

- Diagnostic Criteria - At least one of the following:
  i. Temporal artery biopsy (TAB) or ultrasound revealing features of GCA
  ii. Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as magnetic resonance imaging (MRI), computed tomography (CT)/computed tomography angiography (CTA) or positron emission tomography (PET)-CT of the aorta or other great vessels

Upon successful completion of the screening procedures, diagnosis criteria will be entered into an IWRS, and eligible subjects will be stratified for randomized study treatment into two cohorts according to whether subjects have new-onset disease or relapsing/refractory (hereafter, "relapsing" for brevity) disease.

- **New-onset** - The new-onset disease cohort includes subjects who have been diagnosed within 6 weeks of Day 0 using the above Acute Phase Reactants, Signs/Symptoms and Diagnostic Criteria.
- **Relapsing/refractory** – (either or)
  - The relapsing disease cohort includes subjects having prior documented diagnosis of GCA as per Diagnostic Criteria above > 6 weeks before Day 0 and who have active GCA disease defined by Acute Phase Reactants and Signs/Symptoms within 6 weeks of Day 0.
  - The refractory nonremitting disease subject has had no remission since the diagnosis of disease as per clinical expectations. Thus, the subject has documentation of prior diagnosis of GCA as per Diagnostic criteria above > 6 weeks before Day 0; however, presence of Acute Phase Reactants and Signs/Symptoms as per above persists within 6 weeks of Day 0.

Subjects who complete screening procedures and are not considered eligible (screen failures) may be rescreened one time provided there is reason to believe that eligibility criteria will be met.

Base Treatment Period:

Stratified eligible subjects will enter the double-blind treatment period after randomization 3:2 to blinded treatment with KPL-301 150 mg or placebo administered subcutaneously (SC) every other week (every 2 weeks). All subjects will also receive an unblinded 26-week oral prednisone taper according to a standardized tapering protocol.

Prior to first administration of KPL-301 or placebo, all subjects are required to have achieved remission (i.e., resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour). Should a subject in screening not achieve remission within the initial screening period they can be rescreened using their prior flare documentation following the relapsing/refractory non-remitting inclusion criteria.

The first administration of SC KPL-301/placebo and oral prednisone taper will take place at the study site on Day 0. Subsequent doses of KPL-301/placebo will be administered at the study site in conjunction with a scheduled study visit or administered by the subject on an outpatient basis in accordance with the dosing schedule. The oral steroid taper will be self-administered by study subjects on a daily basis.

Subjects will be followed at the study site at Weeks 1, 2, 3, 4, and approximately every 4 weeks thereafter (see Table 1). Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study site at any time.

If a flare/relapse is suspected during the treatment period, the Investigator must consult the Contract Research Organization (CRO)-designated Medical Expert to review and harmonize the elements of the diagnostic work-up. Flare/relapse is defined as a re-increase of CRP from normal to 1 mg/dL or greater and/or of ESR from less than 20 mm in the first hour to 30 mm or greater AND at least one of the following signs or symptoms attributed by the Investigator to new, worsening, or recurrent GCA:

- Cranial symptoms
  - 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
- Extracranial symptoms
  - 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)
- 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 in the opinion of the Investigator 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.

Although either acute phase reactant (CRP or ESR) may be used during the study for eligibility and to determine remission or flares, it is advisable that the same acute phase reactant used to determine remission at screening also be used to determine flares during the treatment period.

All elements of the diagnostic work-up pertinent to the Investigator diagnosis of a flare/relapse (i.e., the primary efficacy endpoint) should be reviewed with the CRO-designated Medical Expert and entered into the electronic Case Report Form (eCRF) promptly.

Flare/relapse is defined as major if cranial symptoms or ischemia-related visual loss are present or if there is clear evidence of new onset large vessel vasculitis (e.g., subclavian artery). In all other situations, flare/relapse attributed to PMR, vascular or other symptoms should be regarded as minor.

Subjects who experience a flare or subjects who cannot adhere to the protocol-defined steroid taper due to a flare should be managed to ensure the best possible care of the subject:

- The subject must discontinue the assigned study drug (KPL-301 or placebo) and should receive escape therapy in accordance with local SoC, as determined by the Investigator, which may include, for example, dose modifications of corticosteroids, other immunomodulatory agents, and/or approved therapies (e.g., tocilizumab). The dosages of all concomitant medications used to treat the GCA flare must be entered into the eCRF.
- Escape corticosteroid therapy can be escalated immediately. Due to possible safety and pharmacologic effects resulting from overlapping exposures to immunomodulatory agents on top of co-administered corticosteroids, the investigator should consider a washout period of at least 35

days (based on elimination half-lives) after the last dose of study drug if deemed clinically appropriate.

Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an End-of-Treatment (EOT) visit and will be followed for the intended duration of study treatment (i.e., through Week 26 and Washout Safety Follow-up) to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug administration) must complete at a minimum the Final Washout Safety Follow-up visit 84 ± 3 days from the last dose administered. Additional follow up using public records may be captured where possible.

Washout Safety Follow-up:

After subjects complete the 26-week double blind treatment period, they will discontinue and wash off of blinded KPL-301 or placebo during a 12-week Washout Period, which includes close safety follow-up and monitoring for potential GCA flares. During this time, it is recommended that subjects, regardless of remission status, receive SoC oral prednisone therapy, taking into consideration that they have just completed treatment with what may have been an efficacious therapy which supported the tapering off of standard of care concomitant oral corticosteroids. Clinicians may choose to observe subjects closely during the washout period without any change in concomitant medications or may choose (consistent with current SoC guidelines) to increase the daily corticosteroid dose prophylactically/empirically by approximately 10 mg above the prednisone dose administered at Week 26. The prednisone dose can then be tapered, increased or maintained throughout the remainder of the 12-week Washout Period as per Investigator discretion. After the Final Washout Safety Follow-up visit (Week 38) has been completed, the subjects will exit the trial and should be transitioned to SoC per investigator judgement. It is not required that the steroid taper have been completed (0 mg) prior to subjects exiting the trial at Week 38.

Number of Subjects:

Approximately 70 subjects will be randomized at a 3:2 allocation ratio. Approximately 42 subjects will be assigned to KPL-301, and approximately 28 subjects will be assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.

Eligibility Criteria:

Inclusion Criteria

1. Able and willing to provide written informed consent and to comply with the study protocol
2. Age of ≥ 50 to 85 inclusive
3. Diagnosis of new-onset or relapsing GCA classified according to the following criteria:

   New-onset: Initial diagnosis of GCA within 6 weeks of Day 0, defined as:

   a) Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/dL

   b) AND at least one of the following:

      i. Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery pain or tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

      ii. Unequivocal extracranial symptoms of GCA such as claudication of the extremities

      iii. Symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

   c) AND at least one of the following:

i. TAB or ultrasound revealing features of GCA

ii. Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRI, CT/CTA, or PET-CT of the aorta or other great vessels

Relapsing: Diagnosis of GCA > 6 weeks before Day 0 AND:

Active GCA within 6 weeks of Day 0 defined as clinical sign/symptom(s) as per above and Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/ dL

Refractory nonremitting: Diagnosis of GCA > 6 weeks before Day 0 AND:

No remission since the diagnosis of disease as per clinical expectations. i.e. Presence of sign/symptoms as per above and Westergren ESR>30mm/hour or CRP ≥ 1 mg/ dL within 6 weeks of Day 0.

4. Remission of GCA at or before Day 0 (resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour), such that the subject can safely participate in the study and follow the protocol-defined procedures, including initiation of the prednisone taper at the protocol-specified starting dose (i.e., ≤60 mg/day)
5. At Day 0, receiving or able to receive oral prednisone up to 60 mg/day for the treatment of GCA
6. If using methotrexate (MTX), oral or parenteral up to 25mg/week is permitted in screening if started more than 6 weeks prior to Day 0 and should be tapered to zero by Day 0
7. Willing to receive antiplatelet therapy depending on the Investigator's decision
8. Willing to receive treatment for prevention of corticosteroid-induced osteopenia/osteoporosis depending on the Investigator's decision
9. Female subjects must be:
   a) postmenopausal, defined as at least 12 months post cessation of menses (without an alternative medical cause), or
   b) permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation or having a male partner with vasectomy as affirmed by the subject, or
   c) nonpregnant, nonlactating, and if sexually active having agreed to use a highly effective method of contraception (i.e., hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Screening Visit until the Final Washout Safety Follow-up visit 84 ± 3 days from EOT Visit.
10. Male subjects must have documented vasectomy or if sexually active must agree to use a highly effective method of contraception with their partners of childbearing potential (i.e., hormonal contraceptives associated with the inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Day 0 until the Final Washout Safety Follow-up visit 84± 3 days from EOT Visit. Male subjects must agree to refrain from donating sperm during this time period.

Exclusion Criteria:

General Exclusion Criteria

1. Major surgery within 8 weeks prior to Screening or planned major surgery within 12 months after randomization
2. Transplanted organs (except corneal transplant performed more than 3 months prior to randomization)
3. Major ischemic event unrelated to GCA within 12 weeks of Screening

Exclusions Related to Prior or Concomitant Therapy

4. Concurrent enrollment in another clinical study, with the exception of observational studies
5. Previous treatment with KPL-301
6. Treatment with any non-biologic investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, prior to Screening
7. Any cell-depleting biological therapies (e.g., anti-CD20) within 12 months prior to Day 0; or previous treatment with noncell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-Interleukin [IL]-6 receptor [e.g. tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to Screening
8. Treatment with alkylating agents within 12 weeks prior to Screening
9. Intramuscular, Intra-articular or IV corticosteroids within 4 weeks prior to Screening
10. Receipt of live (attenuated) vaccine within the 4 weeks before Day 0
11. Treatment with hydroxychloroquine, cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil (MMF) within 4 weeks of Screening

Relating to Medical History

12. Female subjects who are pregnant, intending to become pregnant, or are breastfeeding
13. Any condition that, in the opinion of the Investigator, could interfere with evaluation of KPL-301 or interpretation of subject safety or confound the results of the study
14. Known history of allergy or reaction to any component of the KPL-301 or placebo formulation or to any other biologic therapy or prednisone or any of its excipients
15. Positive (or 2 indeterminate) QuantiFERON test results.
16. Clinically significant active infection including signs/symptoms suggestive of infection, any significant recurrent or chronic infection (including positive hepatitis C virus antibody [HCVAb]), or any episode of infection requiring hospitalization or treatment with IV antibiotics within 12 weeks before Screening. Subjects with any opportunistic infection within 6 months before Screening will be excluded from the study.
17. Subjects with chronic active hepatitis B infection as defined below will be excluded from the study:
    - Hepatitis B surface antigen (HbsAg) positive
    - Hepatitis B anti-core antibody positive but anti-surface antibody negative
18. Subjects at a high risk of infection (e.g., history of hereditary or acquired immune deficiency disorder including a history of known human immunodeficiency virus [HIV] infection), a history of an infected joint prosthesis at any time with that prosthesis still in situ, leg ulcers, indwelling urinary catheter, or persistent or recurrent chest infections
19. History of cancer within the last 10 years - except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured
20. Evidence of clinically uncontrolled respiratory disease. The Investigator should review the data from subjects' respiratory assessments including chest x-ray and pulmonary function tests (PFTs) including DLCO performed during the screening period or within 12 weeks prior to Day 0 if results of prior assessments are available. Available PFT and DLCO assessments must have had values ≥ 60% of predicted for measurements performed and no uncontrolled lung disease. A subject's medical regimen should not have been significantly intensified to control lung disease within 12 weeks prior to Day 0.
21. History of chronic respiratory tract infections
22. Congestive heart failure of New York Heart Association classification III or IV

23. At screening blood tests, any of the following:
    a) Aspartate transaminase (AST) > 2 × upper limit of normal (ULN)
    b) Alanine transaminase (ALT) > 2 × ULN
    c) Hemoglobin < 75 g/L
    d) Neutrophils < 1.5×10^9/L
    e) Creatinine clearance (CrCl) <30 mL/min

Test Products, Dosage, and Mode of Administration:

Subjects will be permitted to have received steroids (prednisone or equivalent) prior to inclusion in the study.

During the double-blind period, subjects will receive blinded KPL-301 150 mg or placebo, every 2 weeks, by SC injection, in addition to a protocol-specified oral corticosteroid taper.

Oral prednisone will be started at a dose between 20 mg/day to 60 mg/day (inclusive) at Day 0 depending on the subject's previous corticosteroid treatment, disease status, and Investigator discretion. The prednisone dose will then be tapered over the subsequent 26 weeks in accordance with the following tapering schedule shown in Table 3, with subjects entering the taper at different points, depending on their prednisone dose at Day 0.

After subjects have completed the 26-week double-blind treatment period, they will discontinue and wash off blinded KPL-301 or placebo during a 12-week Washout Period. During the Washout Safety Follow-up Period, patients may be closely observed with no additional therapeutic or may receive prophylactic prednisone and tapered as per Investigator discretion. After the Final Washout Safety Follow-up visit 84 ± 3 days from the EOT Visit has been completed, subjects will exit the trial and should be transitioned to SoC per investigator judgement, regardless of what dose of prednisone subjects are on.

Concomitant Medication:

Subjects should receive concomitant medications in line with current SoC practices for GCA. Such medications may include but not limited to the equivalent of the following examples: low-dose aspirin (dose allowed per SoC), pantoprazole (40 mg daily), calcium (1000 mg daily), cholecalciferol (800 U daily), and IV ibandronate 3 mg every 3 months, for the duration of the study.

Duration of Treatment:

Subjects will receive SC KPL-301 or placebo as well as coadministered study-supplied oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12-week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion. Thus, the total study duration will be up to approximately 38-44 weeks (including 6-week Screening Period).

Efficacy Measures:

- Clinical laboratory analyses (e.g., CRP, ESR, signs/symptoms)
- Clinical GCA assessments, including, signs/symptom(s), [redacted]
- Imaging studies (as applicable), including ultrasound, MRI, CT/CTA, PET-CT, TAB (if applicable)
- [redacted]

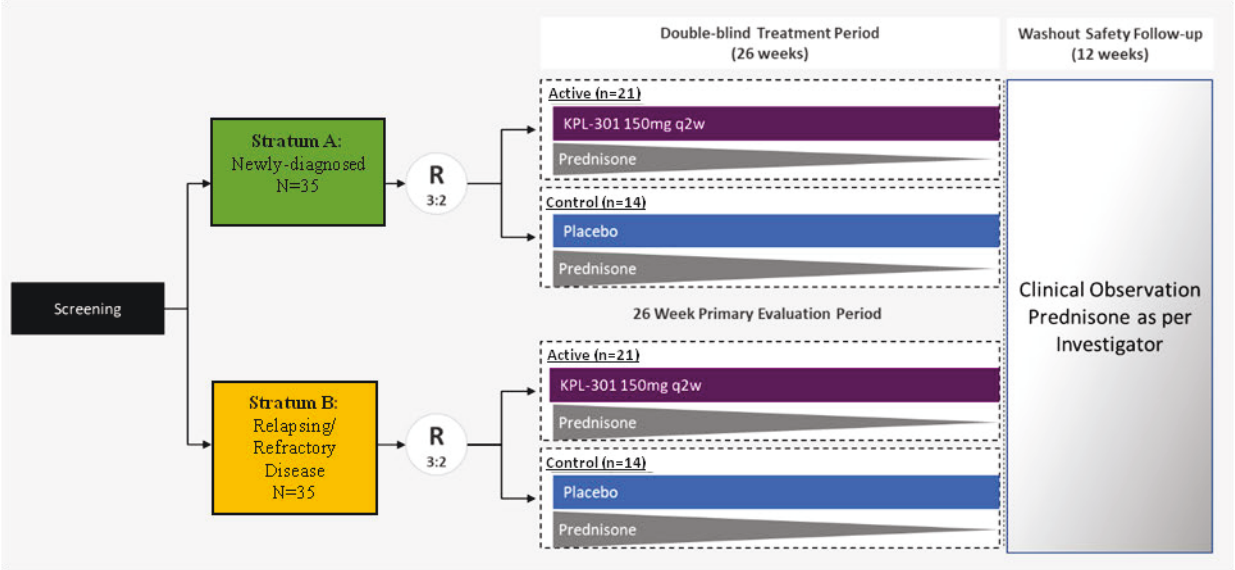
Safety Measure(s):

Safety measures include adverse events and clinical laboratory analyses (including chemistry, hematology, urinalysis, liver profiles, lipid panel, hemoglobin A1c [HbA1c], and anti-drug antibodies), vital sign measurements, electrocardiograms (ECGs), and physical examination findings.

[redacted]

[redacted].

Overview of Trial Design



Statistical Methods:

General Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding.

Modified Intent-to-Treat Analysis Set

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

Safety Analysis Set

All randomized subjects who take at least 1 dose of 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.

Per Protocol Analysis Set

All mITT subjects without important protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) analysis set.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period. Detailed censoring rules will be provided in the SAP.

The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the treatment period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare by Week 26. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as a covariate and stratified by the randomization strata.

The protocol definition of flare includes multiple components. Supportive analyses will be performed based on each individual component. The details will be described in the SAP. In addition, a sensitivity analysis will be performed using the same method described above for the per-protocol analysis set.

Secondary Efficacy Endpoint Analysis

Sustained remission rate at Week 26 will be estimated and compared using the Kaplan-Meier method

The following endpoints will be analysed using the Cochran-Mantel-Haenszel test, stratified by the randomized stratum:

- 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 have completed the corticosteroid taper and who have no signs/symptoms of GCA nor new or worsening vasculitis by imaging by Week 26

The following time to event endpoints will be analyzed using the same methods used for the primary efficacy endpoint:

- 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 by imaging by Week 26

The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate. Details will be described in the SAP:

- Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up period
- [redacted]
- [redacted]

[redacted]

- [redacted]

Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints, by treatment group and study visit. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed parameters such as incidence of adverse events (AEs), clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, PFT, and diffusing capacity for carbon monoxide (DLCO) parameters, and physical exam, where available.

[redacted]

[redacted]

Sample Size Estimation

Assuming 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 is estimated to be approximately 26 weeks in placebo and 111 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) is estimated to 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.

Table 1: **Schedule of Activities**

	Screening	Double – Blind Treatment Period (± 3 days)											Washout Safety Follow-up (± 3 days)		
Assessment	**Up to 6 weeks**	**Baseline/ Day 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26 / EOT[ac]**	**UNS[b]**	**Week 30**	**Week 34**	**Final Safety Follow-up[c] / Week 38**
Informed consent	X															
Demographics	X															
Medical history	X															
Eligibility	X	X														
Subject randomization		X														
Physical exam	X											X	X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X						X		X		X	X			X
Height	X															
Electrocardiogram	X												X			
Chest X-ray	X[g]												X			
Clinical GCA assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Temporal biopsy	X[f]											X[f]				
Imaging (ultrasound)	X[m]	X[n]						X[m]				X[m]	X[m]			X[m]
Imaging (MRI, CT/CTA, or PET-CT)	X[m]											X[m]	X[m]			
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local CRP	X[l]	X[l]											X[l]			
Pulmonary function tests	X[gh]							X[h]				X[h]	X			X[h]
DLCO	X[gh]							X[h]				X[h]	X			X[h]
Dyspnea score and O_2 saturation	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology	X															
TB screening	X															
Serum pregnancy test	X															
Urine pregnancy test		X						X				X	X			X
Hematology	X	X				X		X		X		X	X			X
Chemistry	X	X				X		X		X		X	X			X
Liver profile	X	X				X		X		X		X	X			X
Fasting lipid panel and HbA1c		X										X	X			X
Urinalysis		X										X	X			X

[redacted]

	Screening	Double – Blind Treatment Period (± 3 days)											UNS[b]	Washout Safety Follow-up (± 3 days)		
Assessment	**Up to 6 weeks**	**Baseline/ Day 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26 / EOT[ac]**		**Week 30**	**Week 34**	**Final Safety Follow-up[c] / Week 38**
[redacted]																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KPL-301 or PBO administration/dispensing		X[de]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]			
Prednisone dispensing[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

CRP=C-reactive protein; CT=computed tomography; CTA=computed tomography angiography; DLCO= diffusing capacity for carbon monoxide; EOT=end of treatment; ESR= erythrocyte sedimentation rate; GCA= giant cell arteritis; Hb1Ac= haemoglobin A1c (glycolysed haemoglobin); IMP = KPL-301 or placebo; MRI=magnetic resonance imaging; [redacted] O_2=oxygen; PBO=placebo; PET=positron emission tomography; [redacted]; TB=tuberculosis; UNS=unscheduled visit;

a. EOT visit must be conducted in the event the subject permanently discontinues KPL-301 or placebo. After the EOT visit, subjects who discontinue treatment should continue attending their remaining scheduled visits for the duration of the study.

b. In the event of an unscheduled visit, only the relevant assessments/activities pertaining to the visit need to be captured. Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study clinic at any time. This visit can be combined with the EOT visit in which all necessary EOT related assessments/activities should be completed.

c. All subjects, including subjects who prematurely discontinue the study (i.e., withdraw consent), must complete at a minimum the Final Safety Follow up visit 84 ± 3 days after the EOT Visit. Additional follow up using public records may be captured if possible.

d. At baseline, subject and/or caregiver should be trained on proper self-administration and handling and accountability of study drug. This training should be documented and can be repeated as necessary throughout the study.

e. If a study site or clinic visit coincides with the subject's scheduled dose, study treatment will be administered at the study site or clinic. Study drug treatment should be dispensed as necessary to the subject for home administration to ensure dosing compliance. Investigator staff may contact patients between visits to ensure compliance with protocol-specified treatment regimens.

f. New-onset subjects can have an optional temporal artery biopsy taken at Screening (or otherwise available from diagnostic workup) and Week 26 as part of the study. For relapsing/refractory patients, if the subject has not had a prior a temporal biopsy an optional biopsy can be done at Screening and Week 26. If the subject has an existing biopsy sample available this can be submitted as the screening/predose sample and an optional biopsy can be performed at Week 26.

g. Chest X-ray (or high res CT), DLCO, and PFTs should be obtained at Screening, or existing documentation (if available) within 12 weeks of Day 0 can be used and reviewed by the Investigator or designee.

h. PFTs and DLCO should be performed at Screening within 6 weeks prior to Day 0 (or documented report available from PFT &/or DLCO from within 12 weeks prior to Day 0). They should also be performed at Weeks 12 and 26 and 38 with a window of ±14 days.

[redacted]

k. Subjects will be given prednisone as necessary and instructed to dose in alignment with their prednisone taper. Investigator staff may contact patients between visits to ensure compliance with protocol specified treatment regimens.

l. Clinical decisions for determination of inclusion and flare will be based upon local laboratory values either ESR and/or CRP.

m. The imaging technique used during screening to diagnose GCA should be repeated at week 26 for the study. If ultrasound is available at screening for diagnosis of GCA this should be conducted again at weeks 12, 26 and 38, or in case of a suspected flare of GCA with no other imaging (MRI, CT/CTA or PET-CT) required. If MRI, CT/CTA or PET-CT was used at screening for diagnosis of GCA and no ultrasound is available, the same imaging technique used at screening should be repeated at week 26 or as necessary for diagnosis in case a suspected flare.

n. Ultrasound imaging if clinically relevant should be performed at or before Day 0 to support clinical remission decision making unless there is no evidence of temporal artery inflammation and diagnosis of GCA is confined to large vessels (By MRI or CT).

4 Table of Contents

[redacted]

[redacted]

[redacted]

[redacted]

List of Tables

List of Figures

5 List of Abbreviations and Definition of Terms

ACR20	American College of Rheumatology definition of improvement by 20%
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDUS	color Doppler ultrasound
CI	confidence interval
CrCl	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
CTA	computed tomography angiography
DLCO	diffusing capacity for carbon monoxide
DMARD	disease modifying anti-rheumatic drug
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of Treatment
ESR	erythrocyte sedimentation rate
[redacted]	
GCA	giant cell arteritis
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony growth factor
HbA1c	hemoglobin A1c (glycosylated hemoglobin)
HbsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
[redacted]	
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IWRS	Interactive Web Response System
KPL-301	Study Drug; nomenclature of mavrilimumab in this protocol
mITT	modified intent to treat
MMF	mycophenolate mofetil
MoDC	monocyte-derived dendritic cell
MRI	magnetic resonance imaging
MTX	methotrexate
[redacted]	
OLE	open-label extension

PD	pharmacodynamic
PET	positron emission tomography
PFT	pulmonary function test
PK	pharmacokinetics
PMR	polymyalgia rheumatica
POC	proof of concept
PP	per protocol
Q1	first quartile
Q3	third quartile
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
[redacted]	
SoC	standard of care
TAB	temporal artery biopsy
TB	tuberculosis
TIA	transient ischemic attack
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States of America

20.3 Appendix 3: Summary of Changes

20.3.1 Protocol Amendment v2.0

Rationale for Amendment – **Protocol Amendment v2.0** was completed to clarify aspects of protocol version 1.0 as well as to incorporate feedback from global Regulatory and Ethical bodies. Substantial changes to this version include:

- Limiting the double-blind period to 26-weeks total, removing the extended exposure for patients who enroll earlier in the study.
- Removal of the Open-Label Extension – Per Regulatory feedback, open-label KPL-301 should only be provided to patients after proof of efficacy has been established
- Addition of 12-week Washout Safety Follow-up period to ensure patients have continued access to open-label study supplied prednisone and are adequately followed and weaned back to Standard of Care
- Updated inclusion criteria regarding pregnancy and contraception methods to ensure highly effective methods of contraception are reflected
- Provided clarification on sample size and event calculations
- Addition of Serum Pregnancy test during screening, additional urine pregnancy tests, safety labs, [redacted]
- Addition of Definition of SUSAR and defined Study Termination criteria

Please see the below summary of changes for more details on the changes incorporated into this version. Bold indicates addition, underline indicates removal.

Change ID	Section(s)	Current Text	Revised Text	Rationale
1	Cover page (pg 1)		IND Number 139,960	Added US IND number
2	Cover page (pg 1)	Medical Monitor: [redacted]	[redacted]	Change in Sponsor Medical Monitor
3	Cover page (pg 1), Header throughout	4-Apr 2018 Version 1.0	**12 Oct** 2018 Version **2**.0	Updated to reflect Amendment date and versioning
4	Throughout document	-	-	Administrative and formatting changes for ease of reading
5	Synopsis (pg 5) Section 8.4.1 (pg 33)	…until the last subject has reached the 26-week time point and the results from the 26-week time point have been analyzed, and an Open-Label Extension (OLE) for an additional 26-week period.	…**and a 12-week Washout Safety Follow-up Period during which subjects will discontinue and wash off blinded KPL-301 or placebo.**	Wording updated to reflect that the double-blind period will end at 26 weeks and subjects will enter a 12- week Washout Safety Follow-up Period.
6	Synopsis (pg 5) Section 8.4.1 (pg 33)	-	Acute Phase Reactants Signs/Symptoms Diagnostic Criteria	Added labels to provide clarity and assist in understanding of Screening/Diagnostic Criteria.
7	Synopsis (pg 5) Section 8.4.1 (pg 34)	The new-onset disease cohort includes subjects who have been diagnosed within 6 weeks of Day 0. The relapsing disease cohort includes subjects diagnosed with GCA > 6 weeks before Day 0 and who have at least one of the following 1) active GCA disease within 6 weeks of Day 0 (relapsing/refractory) or 2) no remission since the diagnosis of disease as per clinical expectations (refractory nonremitting)	**New-onset** - The new-onset disease cohort includes subjects who have been diagnosed within 6 weeks of Day 0 **using the above Acute Phase Reactants, Signs/Symptoms and Diagnostic Criteria.** **Relapsing/refractory** - The relapsing disease cohort includes subjects **having prior documented** diagnosis of GCA **as per Diagnostic Criteria above** > 6 weeks before Day 0 and who have active GCA disease **defined by Acute Phase Reactants and Signs/Symptoms** within 6 weeks of Day 0 or **The refractory nonremitting disease subject has had** no remission since the diagnosis of disease as per clinical expectations. **Thus, the subject has documentation of prior diagnosis of GCA as per**	Added specificity as to which criteria are relevant for each strata for clarity.

			Diagnostic criteria above > 6 weeks before Day 0; however, presence of Acute Phase Reactants and Signs/Symptoms as per above persists within 6 weeks of Day 0.	
8	Synopsis (pg 6) Section 8.4.1 (pg 34)	Subjects who complete screening procedures and are not considered eligible (screen failures) may be rescreened provided there is reason to believe that eligibility criteria will be met.	Subjects who complete screening procedures and are not considered eligible (screen failures) may be rescreened **one time** provided there is reason to believe that eligibility criteria will be met.	Clarified subjects should only be rescreened one time
9	Synopsis (pg 6)	-	**Although either acute phase reactant (CRP or ESR) may be used during the study for eligibility and to determine remission or flares, it is advisable that the same acute phase reactant used to determine remission at screening also be used to determine flares during the treatment period.**	Additional text to provide guidance for interpretation of Acute Phase Reactants from remission in case of suspected flare during treatment period.
10	Synopsis (pg 7) Section 8.4.1 (pg 36) Section 8.8 (pg 40) Section 11.2 (pg 46)	Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an End-of-Treatment (EOT) visit and will be followed for the intended duration of study treatment (i.e., until the blind is broken) to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug) must complete a Safety Follow-up visit 28 ± 3 days from the last dose administered. Additional follow up using public records may be captured where possible. An analysis of the study will be performed when the last subject reaches Week 26 according to the Statistical Analysis Plan (SAP). Based on the results of this analysis, all subjects will be offered open-label KPL-301 in the OLE portion of the trial, or the study will be discontinued. All subjects who do not proceed to the OLE must complete a Safety Follow-up visit 28 ± 3 days from the last dose administered	Any subject who prematurely discontinues the study drug treatment for safety or other reason will have an End-of-Treatment (EOT) visit and will be followed for the intended duration of study treatment (i.e., **through Week 26 and Washout Safety Follow-up**) to address potential issues of informative censoring. Any subject who withdraws consent from the trial (i.e., all study procedures in addition to study drug **administration**) must complete **at a minimum the Final Washout** Safety Follow-up visit **84** ± 3 days from the last dose administered. Additional follow-up using public records may be captured where possible.	Removed and replaced language regarding the extension of the double-blind period past week 26 with language for the Washout Safety Follow-up Period
11	Synopsis (pg 7) Section 8.4.2 (pg 36) Section 11.3 (pg 46)	Open-Label Extension: Depending on the results from the analysis of the 26-week placebo-controlled base study, all subjects may be offered KPL-301 in an OLE. The OLE will continue for up to 6 months. During the OLE, subjects will be followed for safety information and will continue to follow study protocols from the double-blind period in the event of a flare and for steroid tapering procedures. During the OLE subjects may wean off KPL-301 onto SoC as determined by the Investigator.	**Washout Safety Follow-up:** **After subjects complete the 26-week double blind treatment period, they will discontinue and wash off of blinded KPL-301 or placebo during a 12-week Washout Safety Follow-up Period, which includes close safety follow-up and monitoring for potential GCA flares. During this time, it is recommended that subjects, regardless of remission status, receive SoC oral prednisone therapy, taking into consideration that they have just completed treatment with what may have been an efficacious therapy which supported the tapering off of standard of care concomitant oral corticosteroids. Clinicians may choose to observe subjects closely during the washout period without any change in concomitant medications or may choose (consistent with current SoC guidelines) to increase the daily**	Removed open label extension per Regulatory Agency feedback and replaced with Washout Safety Follow-up period to ensure subjects are adequately followed and weaned back to Standard of Care.

			corticosteroid dose prophylactically/empirically by approximately 10 mg above the prednisone dose administered at Week 26. The prednisone dose can then be tapered or maintained throughout the remainder of the 12-week Washout Safety Follow-up Period as per Investigator discretion. After the Final Washout Safety Follow-up visit (Week 38) has been completed, the subjects will exit the trial and should be transitioned to SoC per investigator judgement. It is not required that the steroid taper have been completed, (0 mg) prior to subjects exiting the trial at Week 38.	
12	Synopsis (pg 8)	For the primary endpoint analysis, the aim is to have approximately 36 subjects assigned to KPL-301 and approximately 24 subjects assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	**Approximately 60 subjects will be randomized at a 3:2 allocation ratio.** Approximately 36 subjects **will be** assigned to KPL-301, and approximately 24 subjects **will be** assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	Clarification
13	Inclusion Criteria 3 Synopsis (pg 9) Section 8.7.1 (pg 37)	…New-onset: Initial diagnosis of GCA within 6 weeks of Day 0, defined as: … …Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)… ...Relapsing: Diagnosis of GCA > 6 weeks before Day 0 AND at least one of the following: Active GCA within 6 weeks of Day 0 defined as clinical sign/symptom(s) and Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/ dL OR No remission since the diagnosis of disease as per clinical expectations. (refractory nonremitting)	…New-onset: Initial diagnosis of GCA within 6 weeks of Day 0, **defined as:** … ….Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery **pain or** tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)… Relapsing: Diagnosis of GCA > 6 weeks before Day 0 AND: Active GCA within 6 weeks of Day 0 defined as clinical sign/symptom(s) **as per above** and Westergren ESR > 30 mm/hour or CRP ≥ 1 mg/ dL **Refractory nonremitting: Diagnosis of GCA > 6 weeks before Day 0 AND** No remission since the diagnosis of disease as per clinical expectations. **i.e. Presence of sign/symptoms as per above and Westergren ESR>30mm/hour or CRP ≥ 1 mg/ dL within 6 weeks of Day 0.**	Clarification and formatting for ease of understanding
14	Inclusion Criteria 4 Synopsis (pg 9) Section 8.7.1 (pg 37)	Remission of GCA at Day 0 (resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour)...	Remission of GCA at **or before** Day 0 (resolution of GCA symptom(s) and CRP < 1.0 mg/dL or ESR < 20 mm in the first hour)…	Clarification

15	Inclusion Criteria 6 Synopsis (pg 9) Section 8.7.1 (pg 37)	If using methotrexate (MTX), oral or parenteral up to 25mg/week is permitted in screening if started more than 6 weeks prior to Day 0 and should be stable or decreasing with the intention to discontinue use by Day 0.	If using methotrexate (MTX), oral or parenteral up to 25mg/week is permitted in screening if started more than 6 weeks prior to Day 0 and should be **tapered to zero** by Day 0.	Clarification that MTX use is excluded during the study.
16	Inclusion Criteria 9 Synopsis (pg 9,10) Section 8.7.1 (pg 38)	Female subjects must be:.. ...c) nonpregnant, nonlactating, and having agreed to use an effective method of contraception (i.e., hormonal contraceptives, intrauterine device (IUD), or double barrier methods such as condom plus diaphragm or diaphragm plus spermicide or condom plus spermicide) from Screening visit until 12 weeks after final study drug administration	Female subjects must be:.. ...c) nonpregnant, nonlactating, **and if sexually active** having agreed to use a **highly** effective method of contraception (i.e., hormonal contraceptives **associated with inhibition of ovulation** or intrauterine device **[**IUD**]**, **or intrauterine hormone-releasing system [IUS], or sexual abstinence**) from Screening **V**isit until **the Final Washout Safety Follow-up visit 84 ± 3 days from EOT Visit.**	Text added per regulatory feedback
17	Inclusion Criteria 10 Synopsis (pg 10) Section 8.7.1 (pg 38)	Male subjects must have documented vasectomy or must agree to use double barrier methods of contraception (such as condom plus diaphragm or diaphragm plus spermicide or condom plus spermicide) or use condom plus hormonal contraceptives or condom plus IUD with their partners of childbearing potential from Day 0 until the Safety Follow-up visit. Male subjects must agree to refrain from donating sperm from Day 0 until the Safety Follow-up visit.	Male subjects must have documented vasectomy or **if sexually active** must agree to use **a highly effective method of contraception** with their partners of childbearing potential **(i.e., hormonal contraceptives associated with the inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence)** from Day 0 until the **Final Washout** Safety Follow-up visit **84± 3 days from EOT Visit.** Male subjects must agree to refrain from donating sperm **during this time period.**	
18	Exclusion Criteria 6 Synopsis (pg 10) Section 8.7.2 (pg 38)	Treatment with any investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, prior to Screening	Treatment with any **non-biologic** investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, prior to Screening	Text added for clarification
19	Exclusion Criteria 9 Synopsis (pg 10) Section 8.7.2 (pg 38)	Intramuscular, IV corticosteroids within 4 weeks prior to Screening	Intramuscular, **Intra-articular,** or IV corticosteroids within 4 weeks prior to Screening	Text added for clarification
20	Exclusion Criteria 11 Synopsis (pg 10) Section 8.7.2 (pg 38)	Treatment with hydroxychloroquine, cyclosporine A, azathioprine, or mycophenolate mofetil (MMF) within 4 weeks of Screening	Treatment with hydroxychloroquine, cyclosporine A, azathioprine, **cyclophosphamide,** or mycophenolate mofetil (MMF) within 4 weeks of Screening	Text added for clarification
21	Exclusion Criteria 15 Synopsis (Pg 11)	Active, untreated or partially treated latent tuberculosis (TB)	**Positive (or 2 indeterminate) QuantiFERON test results.**	Text changed for clarification

	Section 8.7.2 (pg 39)			
22	Exclusion Criteria 19 Synopsis (pg 11) Section 8.7.2 (pg 39)	History of cancer within the last 10 years (20 years for breast cancer) except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured	History of cancer within the last 10 years - except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured	To allow for consistency of exclusion of all cancer including breast cancer within the last 10 years.
23	Exclusion Criteria 20 Synopsis (pg 11) Section 8.7.2 (pg 39)	Evidence of clinically uncontrolled respiratory disease. The Investigator should review the data from subjects' respiratory assessments including chest x-ray and pulmonary function tests (PFTs) performed within 12 weeks prior to Day 0. The subjects must have had values ≥ 60% of predicted for measurements performed and no uncontrolled lung disease. A subject's medical regimen should not have been significantly intensified to control lung disease within 12 weeks prior to Day 0.	Evidence of clinically uncontrolled respiratory disease. The Investigator should review the data from subjects' respiratory assessments including chest x-ray and pulmonary function tests (PFTs) **including DLCO** performed **during the screening period** or within 12 weeks prior to Day 0 **if results of prior assessments are available. Available PFT and DLCO assessments** must have had values ≥ 60% of predicted for measurements performed and no uncontrolled lung disease. A subject's medical regimen should not have been significantly intensified to control lung disease within 12 weeks prior to Day 0.	Text added for clarification
24	Test Products, Dosage and Mode of Administration Synopsis (pg 12)	Cases of GCA flare should be treated according to the Investigator's judgment and SoC to ensure the best possible care of the subject. In general, the subject should continue to receive the assigned KPL-301 or placebo and should also receive an increased dose of coadministered prednisone, as determined by the Investigator, generally of up to 60 mg/day. The dosages of all concomitant medications used to treat the GCA flare must be documented. If a flare, particularly a major flare, should require a dose of corticosteroid higher than prednisone 60 mg/day, in the judgment of the Investigator, steroid escape therapy is allowed (i.e., doses of prednisone > 60 mg/day, or equivalent, or IV corticosteroids) until clinical remission is achieved. If the clinical response is positive, after an appropriate period of clinical stabilization, as determined by the Investigator, (usually 1-2 weeks) the subject may resume the protocol-defined steroid taper, starting at the dose at which remission was achieved or prednisone 60 mg/day, whichever is lower. Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed to receive a more gradual Investigator-defined steroid taper and will continue to receive the assigned KPL-301 or placebo.	-	Text deleted as it is duplicate of what is described in the Base Treatment Period section of the synopsis on pg 7.
25	Test Products, Dosage and Mode of	During the OLE, subjects will receive open-label KPL-301 150 mg every 2 weeks for up to 6 additional months and may wean off KPL-301 onto	**After subjects have completed the 26-week double blind treatment period, they will discontinue and wash off blinded KPL-301 or**	Removed text regarding Open-label Extension and

	Administration Synopsis (pg 12)	SoC, according to the Investigator's judgment.	**placebo during a 12-week Washout Period. During the Washout Safety Follow-up Period, patients may be closely observed with no additional therapeutic or may receive prophylactic prednisone and tapered as per Investigator discretion. After the Final Washout Safety Follow-up visit 84 ± 3 days from the EOT Visit has been completed subjects will exit the trial and should be transitioned to SoC per investigator judgement, regardless of what dose of prednisone subjects are on.**	replaced it with information for the Washout Safety Follow-up period
26	Concomitant Medication Synopsis (pg 12) Section 10.1 (pg 44)	Subjects should receive concomitant medications in line with current SoC practices for GCA. Such medications may include the equivalent of the following: low-dose aspirin (dose allowed per SoC), pantoprazole (40 mg daily), calcium (1000 mg daily), cholecalciferol (800 U daily), and IV ibandronate 3 mg every 3 months, for the duration of the study.	Subjects should receive concomitant medications in line with current SoC practices for GCA. Such medications may include **but not limited to** the equivalent of the following **examples**: low-dose aspirin (dose allowed per SoC), pantoprazole (40 mg daily), calcium (1000 mg daily), cholecalciferol (800 U daily), and IV ibandronate 3 mg every 3 months, for the duration of the study.	Text added for clarification
27	Duration of Treatment Synopsis (pg 12) Section 8.5 (pg 36)	Subjects will receive SC KPL-301 or placebo as well as coadministered oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Subjects will receive KPL-301 or placebo for a minimum of 26 weeks (unless a subject discontinues study drug treatment prematurely). Duration of treatment will differ according to when each subject is enrolled, with the first enrolling subjects receiving treatment for longer than those who enroll later. By the time all subjects have completed 26 weeks of treatment and the 26-week results have been analyzed, some subjects (those who enroll early in the recruitment process) will have received blinded KPL-301 or placebo for approximately 18 months. Depending on the results from the 26-week analysis, all subjects may be offered open-label KPL-301 for an additional 6 months. Thus, the approximate total duration of treatment will be up to approximately 24 months.	Subjects will receive SC KPL-301 or placebo as well as coadministered **study-supplied** oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Subjects will receive KPL-301 or placebo for 26 weeks (unless a subject discontinues study drug treatment prematurely). **Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12- week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion.** Thus, the total **study** duration will be up to approximately **38-44 weeks (including 6-week Screening Period).**	Changed text to limit treatment exposure to 26 weeks total and added text regarding the 12-week Washout Safety Follow-up Period.
28	Efficacy Measures Synopsis (pg 12)	- Clinical laboratory analyses (e.g., CRP, ESR) - Clinical GCA assessments, including, for example, [redacted] - Imaging studies (as applicable), including ultrasound, MRI, CT/CTA, PET-CT, TAB (if applicable) [redacted]	- Clinical laboratory analyses (e.g., CRP, ESR, **signs/symptoms**) - Clinical GCA assessments, including, **signs/symptom(s),** [redacted] - Imaging studies (as applicable), including ultrasound, MRI, CT/CTA, PET-CT, TAB (if applicable) [redacted]	Text added for clarification
29	Other Measures(s) Synopsis (pg 12)	[redacted]	[redacted]	[redacted]

30	Overview of Trial Design Synopsis (pg 13) Figure 5 (pg 31)	-	-	Design diagram replaced to reflect 26-week exposure and 12-week Washout Safety Follow-up period.
31	Statistical Methods Synopsis (pg 14) Section 14.1 (pg 57)	General Methods All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding.	General Methods All statistical analyses will be performed using SAS® Version 9**.3** or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding.	Change of text to allow use of SAS Version 9.3 or higher
32	Statistical Methods Synopsis (pg 14) Section 14.3.1 (pg 58)	Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and are assessed for at least 1 day in the double-blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment.	Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and at least **have** 1 **assessment** in the double-blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment.	Text changed for clarification
33	Statistical Methods Synopsis (pg 14) Section 14.3.3 (pg 58)	Per Protocol Analysis Set All randomized subjects who complete Week 26 in the double blind period without protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) set.	Per Protocol Analysis Set All **mITT** subjects without protocol deviations deemed to impact efficacy or **ethical conduct** will be included in the per-protocol (PP) set.	Text changed to better reflect Per Protocol Analysis set after limiting the 26 week exposure.
34	Statistical Methods Synopsis (pg 14,15) Section 14.4 (pg 58- 59) Section 14.5.1 (pg 59,60) Section 14.5.2 (pg 60)	Primary Efficacy Endpoint Analysis The primary objective of this POC study is to evaluate the efficacy of KPL-301 versus placebo, coadministered with a 26 week steroid taper, for maintaining sustained remission for 26 weeks in subjects with new-onset or relapsing/refractory GCA. Sustained remission is defined as the absence of flare (as defined above) from the start of double-blind treatment through Week 26. The primary efficacy analysis variable is time from start of double-blind treatment until the first flare occurring	Primary Efficacy Endpoint Analysis The primary efficacy **endpoint** is time **to flare by Week 26 defined as time from randomization** to the **date of** first flare occurring within the 26-week period. Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit.	Text changed to provide clarification as well as to limit endpoint collection to the 26 Week exposure.

	Section 14.5.3 (pg 60)	within the 26-week period. Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit. The number and percentage of subjects who remain in remission, who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. Duration of remission will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test will be used to compare KPL-301 and placebo with respect to the duration of remission. Kaplan-Meier estimates of remission at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment and randomization stratum as covariates. As a secondary efficacy endpoint, duration of remission during the entire double-blind treatment period will be analyzed using the same methods described above. Subjects who do not experience flare during double-blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow-up prior to experiencing a flare at any time during double-blind treatment will be censored at the time of their last available visit. Additional secondary efficacy endpoints include the following dichotomous endpoints that will be analyzed descriptively by treatment group. Treatment comparisons will be performed using Cochran-Mantel-Haenszel test controlling for the randomized stratum: • Percentage of subjects at Week 26 with normal ESR • Percentage of subjects at the end of randomized treatment with normal ESR • Percentage of subjects at Week 26 with normal CRP • Percentage of subjects at the end of randomized treatment with normal CRP The following continuous secondary efficacy endpoints will be analyzed descriptively by treatment group. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate: • Time to steroid dose of zero • Cumulative steroid dose at Week 26 and at the end of the double-blind treatment period	The number and percentage of subjects who remain in remission (**no flare**), who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. **Time to flare by Week 26** will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test **stratified by randomization strata** will be used to compare KPL-301 and placebo with respect to **time to flare by Week 26**. Kaplan-Meier estimates of remission **rate** at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate. As a key secondary efficacy endpoint, **time to flare by week 26 in the per protocol population** will be analyzed using the same methods described above. Subjects who do not experience flare during double-blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow-up prior to experiencing a flare at any time during double-blind treatment will be censored at the time of their last available visit. Additional secondary efficacy endpoints include the following endpoints that will be analyzed. Treatment comparisons will be performed using Cochran-Mantel-Haenszel test controlling for the randomized stratum. • Percentage of subjects **who have completed the** 26-**week corticosteroid taper and who have a** normal ESR • Percentage of subjects **who have completed the 26-week corticosteroid taper and who have a** normal CRP • **Percentage of subjects who have completed the 26-week corticosteroid taper and who have no signs/symptoms of GCA** The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate: • Time to **corticosteroid** dose of zero **mg/day** • Cumulative steroid dose at Week 26 and at the end of the **Washout Safety Follow-up period** [redacted]	

		[redacted]	[redacted]	
35	Statistical Methods Synopsis (pg 15) Section 14.2 (pg 57,58)	Sample Size Estimation With 36 subjects randomized to KPL-301 and 24 subjects randomized to placebo, a two-sided log-rank test for equality of survival curves with a 0.05 significance level will have approximately 89% power to detect a 37.5% difference (20% placebo vs 57.5% KPL-301) in the proportion of subjects who experience sustained remission during the 26-week double-blind base period. It is expected that the trial will have equal numbers of subjects in the two randomization strata. Assuming that the percentage of subjects experiencing sustained remission in the new onset stratum is 70% for KPL-301 and 30% for placebo. The percentage of subjects experiencing sustained remission in the relapsing/refractory stratum is 45% for KPL-301 and 10% for placebo. A two-sided log-rank test with 0.1 significance level will have 75% power to detect a treatment difference within the stratum.	Sample Size Estimation **Assuming that time to flare follows an exponential distribution and the proportion of subjects without a flare by Week 26 will be 20% in placebo and 57 5% in KPL-301, the median time to flare would be estimated to be approximately 11.20 weeks in placebo and 32.57 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) would be estimated to be approximately 0.3438. With a 2-sided significance level of 0.05 and a 3:2 randomization ratio for KPL-301 vs. placebo, it would require approximately 34 events to achieve 86% power using a two- sided log rank test.** **Approximately 60 subjects will be randomized by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo at a 3:2 allocation ratio.** **Subject disposition and the flare event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion. If there is a high dropout rate and/or the event accrual rate is significantly slower than anticipated, up to 10 additional subjects may be randomized to obtain the target number of events required for the analysis of primary efficacy endpoint.**	Text changed to provide clarification
36	Schedule of Activities Synopsis (pg 16)	Removed: Schedule of Assessments • **Every 4 weeks thereafter visit and associated assessments** • **OLE visit and assessments** • **Fasting lipid panel and HbA1c during screening**	Added: Schedule of **Activities** • Week 30, Week 34, Week 38 Visits • Ultrasound at or before Day 0 and at Week 38 • Pulmonary function tests including DLCO at Week 38 • Serum pregnancy test during screening • Urine pregnancy test at Day 0, Week 12, Week 26 and Week 38 • Safety Labs (Hematology, Chemistry & Liver profile) at Week 4 and Week 38 • Fasting lipid panel and HbA1c at Day 0 [redacted]	Activities removed to limit double-blind Period to 26 Weeks. Activities changed to remove Open-label extension and replace with Washout Safety Follow-up Period. Additional safety labs and procedures added per Ethic and Regulatory feedback.

37	Schedule of Activities Footnotes Synopsis (pg 17)	Footnotes a. Monthly visits are conducted until the last subject completes the 26-week double-blind analysis period and the analysis is complete. e. Open-label extension visits occur monthly for up to 6 months. During the open-label extension subjects may wean off KPL-301 onto standard of care at the discretion of the investigator. f. During the open-label extension all subjects participating will receive open-label KPL-301. Any subjects on steroids at the end of the double-blind period should taper steroids at the discretion of the investigator. m. Electrocardiogram or chest X-ray (or high res CT) are not required at an EOT visit but may be performed at a UNS visit	-	Footnotes removed per updated schedule of Activities
38	Schedule of Activities Footnotes Synopsis (pg 17)	c. In the event of an unscheduled visit, only the relevant assessments pertaining to the visit need to be captured. Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study clinic at any time. This visit can be combined with the EOT visit in which all necessary assessments should be completed.	b. In the event of an unscheduled visit, only the relevant assessments/**activities** pertaining to the visit need to be captured. Subjects reporting worsening of GCA symptoms or any safety issues may be brought in for an unscheduled visit at the study clinic at any time. This visit can be combined with the EOT visit in which all necessary **EOT related** assessments/**activities** should be completed.	Footnotes updated or added to provide clarity
39	Schedule of Activities Footnotes Synopsis (pg 17) Section 8.8 (pg 40)	d. All subjects, including subjects who prematurely discontinue the study (i.e., withdraw consent), must complete a safety follow up visit 28 ± 3 days after the last dose of KPL-301 or placebo. Additional follow up using public records may be captured if possible.	**c.** All subjects, including subjects who prematurely discontinue the study (i.e., withdraw consent), must complete **at a minimum the Final** Safety Follow up visit **84** ± 3 days after the **EOT Visit**. Additional follow up using public records may be captured if possible.	Footnotes updated or added to provide clarity
40	Schedule of Activities Footnotes Synopsis (pg 17)	g. At baseline, subject and/or caregiver should be trained on proper self-administration and handling and accountability of IMP. This training should be documented and can be repeated as necessary throughout the study.	**d.** At baseline, subject and/or caregiver should be trained on proper self-administration and handling and accountability of **study drug**. This training should be documented and can be repeated as necessary throughout the study.	Footnotes updated or added to provide clarity
41	Schedule of Activities Footnotes	h. If a study site or clinic visit coincides with the subject's scheduled dose, study treatment will be administered at the study site or clinic. Study treatment should be dispensed as necessary to the subject for home	**e.** If a study site or clinic visit coincides with the subject's scheduled dose, study treatment will be administered at the study site or clinic. Study **drug** treatment should be dispensed as necessary to the subject	Footnotes updated or added to provide clarity

	Synopsis (pg 17)	administration to ensure dosing compliance. Investigator staff may contact patients between visits to ensure compliance with protocol specified treatment regimens.	for home administration to ensure dosing compliance. Investigator staff may contact patients between visits to ensure compliance with protocol-specified treatment regimens.	
42	Schedule of Activities Footnotes Synopsis (pg 17)	i. New-onset subjects can have an optional temporal artery biopsy taken at Screening and Week 26 as part of the study. For relapsing/refractory patients, if the subject has not had a prior a temporal biopsy an optional biopsy can be done at Screening and Week 26. If the subject has an existing biopsy sample available this can be submitted as the screening/predose sample and an optional biopsy can be performed at Week 26.	**f.** New-onset subjects can have an optional temporal artery biopsy taken at Screening **(or otherwise available from diagnostic workup)** and Week 26 as part of the study. For relapsing/refractory patients, if the subject has not had a prior a temporal biopsy an optional biopsy can be done at Screening and Week 26. If the subject has an existing biopsy sample available this can be submitted as the screening/predose sample and an optional biopsy can be performed at Week 26.	Footnotes updated or added to provide clarity
43	Schedule of Activities Footnotes Synopsis (pg 17)	j. Chest X-ray (or high res CT), DLCO, and PFTs should be obtained at Screening, or existing documentation within 12 weeks of Day 0 can be used and reviewed by the Investigator or designee.	**g.** Chest X-ray (or high res CT), DLCO, and PFTs should be obtained at Screening, or existing documentation **(if available)** within 12 weeks of Day 0 can be used and reviewed by the Investigator or designee.	Footnotes updated or added to provide clarity
44	Schedule of Activities Footnotes Synopsis (pg 17)	k. PFTs and DLCO should be performed at Screening 6-12 weeks prior to Day 0. They should also be performed at Weeks 12 and 26 with a window of ±14 days; after Week 26 PFTs and DLCO should be performed every 6 months ± 14 days; if the EOT visit is > 3 months of the prior test, the assessment should be performed.	**h.** PFTs and DLCO should be performed at Screening **within** 6 weeks prior to Day 0 **(or documented report available from PFT &/or DLCO from within 12 weeks prior to Day 0**). They should also be performed at Weeks 12 and 26 **and 38** with a window of ±14 days;	Footnotes updated or added to provide clarity
45	Schedule of Activities Footnotes Synopsis (pg 17)	p. Clinical decisions for determination of inclusion and flare will be based upon local laboratory values.	**l.** Clinical decisions for determination of inclusion and flare will be based upon local laboratory values **either ESR and/or CRP**.	Footnotes updated or added to provide clarity
46	Schedule of Activities Footnotes Synopsis (pg 17)	q. The imaging technique used during screening to diagnose GCA should be repeated throughout the study. If ultrasound is available at screening for diagnosis of GCA this should be conducted again at weeks 12, 26 and then every 6 months thereafter, or in case of a suspected flare of GCA with no other imaging (MRI, CT/CTA or PET-CT) required. If MRI, CT/CTA or PET-CT was used at screening for diagnosis of GCA and no ultrasound is available this should be repeated at week 26 then every six months thereafter or in case a suspected flare as necessary in order to reduce the exposure of radiation to the subject.	m. The imaging technique used during screening to diagnose GCA should be repeated **at week 26 for** the study. If ultrasound is available at screening for diagnosis of GCA this should be conducted again at weeks 12, 26 and **38**, or in case of a suspected flare of GCA with no other imaging (MRI, CT/CTA or PET-CT) required. If MRI, CT/CTA or PET-CT was used at screening for diagnosis of GCA and no ultrasound is available, **the same imaging technique used at screening** should be repeated at week 26 or **as necessary for diagnosis** in case a suspected flare.	Footnotes updated or added to provide clarity

47	Schedule of Activities Footnotes Synopsis (pg 17)	-	**n. Ultrasound imaging if clinically relevant should be performed at or before Day 0 to support clinical remission decision making unless there is no evidence of temporal artery inflammation and diagnosis of GCA is confined to large vessels (By MRI or CT).**	Footnote added to provide clarity
48	Section 9.1 (pg 40)	…The investigational product is supplied as a sterile clear to opalescent, colorless to slightly brown-yellow liquid, free from visible particles, in a prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, and sealed with an aluminium overseal. Each syringe contains 150 mg (nominal) of active investigational product.	…The investigational product is supplied as a sterile clear to opalescent, colorless to slightly brown-yellow liquid, free from visible particles, in a **1mL** prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, **accessorized with a needle guard, and extended finger flange and a plunger rod.** Each syringe contains 150 mg (nominal) of active investigational product.	Text changed to provide clarity
49	Section 9.2 (pg 41)	…The placebo is supplied as a sterile clear to slightly opalescent, colorless to slightly yellow liquid, free from visible particles, in a prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, and sealed with an aluminium overseal.	…The placebo is supplied as a sterile clear to, colorless liquid, free from visible particles, in a **1 ml** prefilled syringe at a nominal fill volume of 1.0 mL, stoppered with a Teflon-faced elastomeric stopper, **accessorized with a needle guard and extended finger flange and a plunger rod.**	Text changed to provide clarity
50	Section 9.3 (pg 42)	… During the OLE, subjects will continue to follow study protocols from the double-blind period in the event of a flare and for steroid tapering procedures unless indicated otherwise as per the discretion of the Investigator.	... During the Washout Safety Follow-up Period, the prednisone dose can then be tapered or maintained throughout the remainder of the 12-week Washout Period as per the discretion of the Investigator. After the Final Washout Safety Follow-up visit (Week 38) has been completed the subjects will exit the trial and should be transitioned to SoC per investigator judgement.	Text added to replace OLE with Washout Safety Follow-up Period
51	Section 9.4 (pg 42,43)	Subjects who are candidates for enrollment will be evaluated for eligibility by the Investigator to ensure that the criteria given in Section 8.7 have been satisfied and that the patients are eligible for randomization. Subjects will be randomized at a 3:2 ratio to receive either 150 mg KPL-301 or placebo. Randomization will be stratified according to whether subjects have new-onset disease or relapsing disease. Additional strata may be identified and described within the SAP.	Subjects who are candidates for enrollment will be evaluated for eligibility by the Investigator to ensure that the criteria given in Section 8.7 have been satisfied and that the **subjects** are eligible for randomization. Subjects will be randomized at a 3:2 ratio to receive either 150 mg KPL-301 or placebo. Randomization will be stratified according to whether subjects have new-onset disease or relapsing disease.	Text removed
52	Section 9.6.2 (pg 43,44)	In the event of a medical emergency, the Investigator may unblind an individual subject's treatment allocation in consultation with the Sponsor. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received active drug. In most cases, the management of a medical emergency would be the same whether or not active drug was received by the	In the event of a medical emergency, the Investigator may unblind an individual subject's treatment allocation **and notify** the Sponsor. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received active drug. In most cases, the management of a medical emergency would be the same whether or not active drug was **being** received by the	Text removed and changed to provide clarity

		subject. If this were to be the case, the treatment allocation should not be unblinded. Depending on the results of the Week 26 analysis, all subjects may be offered open-label KPL-301 in the OLE portion of the trial or the study will be discontinued after the double-blind period. If the study is discontinued after the double-blind period, subjects will not be unblinded (except for the reasons listed above) until the clinical database has been locked.	subject. If this were to be the case, the treatment allocation should not be unblinded.	
53	Section 12.2.1 (pg 47)	-	**Ideally clinical assessments of GCA signs/symptoms should occur prior to the investigator reviewing subject imaging, lab or acute phase reactant results at any given visit to minimize potential for assessment bias.**	Text added for clarity
54	Section 12.2.3 (pg 47)	In cases where ultrasound of temporal artery was captured during the diagnosis of GCA at Screening, this procedure should be repeated at Weeks 12, 26, EOT and every 6 months thereafter as well as any instances of suspected flare over the course of the study. Imaging and relevant data should be included in any elements of the diagnostic work-up pertinent to the Investigator diagnosis of GCA.	In cases where ultrasound of temporal artery was captured during the diagnosis of GCA at Screening, this procedure should be repeated at Weeks 12, 26, EOT and **Week 38** as well as any instances of suspected flare over the course of the study. Imaging and relevant data should be included in any elements of the diagnostic work-up pertinent to the Investigator diagnosis of GCA.	Text changed to incorporate Week 38 visit
55	Section 12.3.1 (pg 48)	A complete physical examination as possible by local practice should include an evaluation of the head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History and Physical Examination eCRFs.	A complete physical examination **as possible by local practice** should include an evaluation of the head, eye, ear, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History and Physical Examination eCRFs.	Text added for clarity
56	Section 12.4 (pg 48)	The digital ECG recording must be obtained and reviewed by the Investigator or designee. For safety monitoring purposes, the Investigator or designee must sign and date all ECG tracings and place the paper copy as part of the subject's permanent study file at the site. ECG characteristics, including heart rate, QS duration, and RR, PR, and QT intervals will be recorded on the eCRF. QTcB (Bazett's correction) and QTcF (Fridericia's corrections) will be calculated. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented in eCRF.	The digital ECG recording must be obtained and reviewed by the Investigator or designee. For safety monitoring purposes, the Investigator or designee must sign and date all ECG tracings and place the paper copy as part of the subject's permanent study file at the site and overall ECG interpretation will be documented in eCRF.	Text removed for consistency with data collection
57	Section 12.5.1 (pg 49)	PFTs and DLCO should be obtained at Screening 6 weeks prior to Day 0, or existing documentation within 12 weeks of day 0 can be used and reviewed by the Investigator or designee. During the course of the study	PFTs and DLCO should be obtained at Screening 6 weeks prior to Day 0, or existing documentation within 12 weeks of day 0 can be used and reviewed by the Investigator or designee. During the course of the study	Text changed to reflect updated schedule of activities

		PFTs and DLCO should be obtained at Weeks 12 and 26 with a window of ± 14 days. After Week 26, PFTs and DLCO should be performed every 6 months ± 14 days. In the event that a subject's EOT visit is > 3 months of the prior PFT and DLCO assessment, an additional assessment should be obtained.	PFTs and DLCO should be obtained at Weeks 12, 26 **and 38** with a window of ± 14 days.	
58	Section 12.5.3 (pg 49)	Based on the study site's normal practice and acceptable clinical practice in each country (PPD vs QuantiFERON) a TB test may be performed in order to evaluate an eventual (active, untreated, or partially treated latent) infection with TB.	**Eligibility will be determined based on a central** QuantiFERON TB test performed **during screening** in order to evaluate (active, untreated, or partially treated latent) infection with TB. If a patient is suspected to have contracted tuberculosis during the study the study site may conduct a TB test in accordance with the site's normal practice to diagnose TB (PPD or local QuantiFERON).	Text changed for clarity
59	Section 12.5.4 (pg 49)	The modified Borg scale (Borg, 1982) is a validated patient reported outcome and will be used to assess subjects' perceived sensation of difficulty in breathing (dyspnea). This scale is a linear scale of numbers ranking the magnitude of difficulty in breathing, ranging from 0 (nothing at all) to 10 (maximal). An example of the Borg scale for reference is provide in Appendix 2.	The modified Borg scale (Borg , 1982) 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 10 (maximal). A **validated version** of the Borg scale **in local language will be** provided.	Text changed for clarity
60	Section 12.6.7 (pg 50)	Urine Pregnancy Test For women of child bearing potential a urine pregnancy tests should be performed prior to enrolment at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	Pregnancy Test For women of child bearing potential a **serum** pregnancy test should be performed prior to enrolment at the site. **Urine pregnancy tests should be performed at Day 0, Week 12, Week 26 and the Final Safety Follow-up Visit.** Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	Text changed to add serum pregnancy test prior to randomization
61	Section 12.7.2 (pg 50)	[redacted]	[redacted]	Text changed to reflect updated schedule of activities
62	Section 12.8 (pg 51) Appendix 3, 5 & 6	[redacted]	-	Samples of the Patient Scales and Assessments have been removed from the protocol as validated versions in local language will be provided
63	Section 13.1.3.2 (pg 52)	Biologic therapies are known to be associated with an increased risk of immediate and delayed hypersensitivity reactions as well as anaphylaxis. Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event.	Biologic therapies are known to be associated with an increased risk of immediate and delayed hypersensitivity reactions as well as anaphylaxis. Anaphylaxis and severe hypersensitivity reactions are required to be reported within 24 hours of knowledge of the event, [redacted]	Text added for clarity

			[redacted]	
64	Section 13.1.3.3 (pg 52)	…Any subject who has been referred for a specialist pulmonary evaluation should not receive the investigational product until the symptom(s) or sign(s) causing the referral have resolved.	…Any subject who has been referred for a specialist pulmonary evaluation **may be instructed to stop** the investigational product until the symptom(s) or sign(s) causing the referral have resolved.	Text changed for clarity
65	Section 13.1.7 (pg 54)	-	**Suspected Unexpected Serious Adverse Reaction** A Suspected Unexpected Serious Adverse Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or prescribing information/summary of product characteristics for an authorized product). All relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening will be recorded and reported to the competent authorities in all the applicable countries, and to the Ethics Committee/Institutional Review Boards in conjunction with Directive 2001/20/EC.	Text added per Ethics/Regulatory request
66	Section 13.4 (Pg 55)	AEs will be collected from the time of signing of informed consent through the final Safety Follow-up period (24 days ± 3days after the last dose of study drug).	AEs will be collected from the time of signing of informed consent through the Final **Washout** Safety Follow-up period (**84** days ± 3 days after the **EOT visit**).	Text changed for consistency with schedule of activities
67	Section 14.1.2 (pg 57)	The primary objective of this study is to evaluate the efficacy of KPL-301 versus placebo, in combination with steroid taper, for maintaining sustained remission for 26 weeks. The primary efficacy analysis entails the inferential comparison of KPL-301 to placebo with respect to time from start of double-blind treatment until the first flare occurring within the first 26-weeks of the double-blind period. The key secondary efficacy analysis entails inferential comparison of KPL-301 to placebo with respect to time from start of double-blind treatment until the first flare anytime during the double-blind period. Multiplicity with respect to these two inferential efficacy analyses will be managed via the gated hierarchical testing procedure. If and only if the primary comparison results in a statistically significant difference between KPL-301 and placebo at 0.05 level of significance, the key secondary comparison may be conducted at alpha 0.05 as well. All other secondary endpoints are considered exploratory, and no adjustment for multiple testing of secondary efficacy endpoints will be performed.	Multiplicity with respect to **the primary efficacy endpoint and the key secondary efficacy endpoints** will be managed via the gated hierarchical testing procedure. If and only if the primary comparison results in a statistically significant difference between KPL-301 and placebo at 0.05 level of significance, the key secondary comparison **will** be conducted at alpha 0.05 as well. All other secondary endpoints are considered exploratory, and no adjustment for multiple testing of secondary efficacy endpoints will be performed.	Text updated for clarity
68	Section 16.2 (pg 63)	This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the Declaration of Helsinki, and local regulations.	This study will be conducted in compliance with the protocol, the ICH-GCP guideline, the **most recent version of the** Declaration of Helsinki	Text updated for clarity

			in which the Sponsor intends to publish the results regardless of the study outcome, and local regulations.	
69	Section 17 (pg 64)	-	**Study Termination** **The Sponsor reserves the right to temporarily suspend or terminate this study in part or whole at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to:** **The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects** **Subject enrollment is unsatisfactory** **Non-compliance that might significantly jeopardize the validity or integrity of the study** **Recommendation to suspend or terminate the study by independent body such as DMC or Health Authority** **Sponsor decision to terminate development** **Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IECs when applicable) will be obtained prior to resuming the study.**	Text added per Ethics/Regulatory request

20.3.2 Protocol Amendment v3.0

Rationale for Amendment – **Protocol Amendment v3.0** was completed to clarify aspects of protocol version 2.0 as well as to incorporate feedback from global Regulatory bodies. Substantial changes to this version include:

- Discontinuation of study drug (KPL-301 or placebo) in the event of a GCA Flare
- [redacted]
- Clarification of individual patient and study stopping criteria
- Correction of the US Safety contact number

Please see the below summary of changes for more details on the changes incorporated into this version. Bold indicates addition, underline indicates removal.

Change ID	Section(s)	Current Text	Revised Text	Rationale
1	Title Page (pg 1) Header throughout	Date of Protocol: 15 Oct 2018 Version of Protocol: 2.0	Date of Protocol: 15 **Nov** 2018 Version of Protocol: **3**.0	Administrative
2	Section 2 (pg 2) Section 13.6 (pg 55)	US 24 Hour Safety Hotline: 1 888-483-77729	**US 24 Hour Safety Hotline: 1 888-483-7729**	Administrative correction
3	Synopsis (pg 7) Section 8.4.1 (pg 32)	Cases of flare should be treated according to the Investigator's judgment and standard of care (SoC) to ensure the best possible care of the subject. In general: • The subject should continue to receive the assigned KPL-301 or placebo and should also receive an increased dose of coadministered prednisone, as determined by the Investigator, generally of up to 60 mg/day. The dosages of all concomitant medications used to treat the GCA flare must be entered into the eCRF. • If a flare, particularly a major flare, should require a dose of corticosteroid higher than prednisone 60 mg/day, in the judgment of the Investigator, steroid escape therapy is allowed (i.e., doses of prednisone > 60 mg/day or equivalent, or intravenous (IV) corticosteroids) until clinical remission is achieved. If the clinical response is positive, after an appropriate period of clinical stabilization, as determined by the Investigator, the subject may resume the protocol-defined steroid taper, starting at the dose at which remission was achieved or prednisone 60 mg/day, whichever is lower. Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed to receive a more gradual Investigator-defined steroid taper and will continue to receive the assigned KPL-301 or placebo. These subjects will be considered to have met the primary endpoint if a flare has occurred prior to Week 26.	**Subjects who experience a** flare **or subjects who cannot adhere to the protocol-defined steroid taper due to a flare** should be **managed** to ensure the best possible care of the subject: • The subject **must dis**continue the assigned **study drug (**KPL-301 or placebo**)** and should receive **escape therapy in accordance with local SoC**, as determined by the Investigator, **which may include, for example, dose modifications of corticosteroids, other immunomodulatory agents, and/or approved therapies (e.g., tocilizumab)**. The dosages of all concomitant medications used to treat the GCA flare must be entered into the eCRF. • **Escape corticosteroid therapy can be escalated immediately. Due to possible safety and pharmacologic effects resulting from overlapping exposures to immunomodulatory agents on top of co-administered corticosteroids, the investigator should consider a washout period of at least 35 days (based on elimination half-lives) after the last dose of study drug if deemed clinically appropriate.**	Text updated per regulatory feedback

4	Synopsis (pg 11)	Subjects will receive SC KPL-301 or placebo as well as coadministered study-supplied oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Subjects will receive KPL-301 or placebo for 26 weeks (unless a subject discontinues study drug treatment prematurely). Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12-week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion. Thus, the total study duration will be up to approximately 38-44 weeks (including 6-week Screening Period).	Subjects will receive SC KPL-301 or placebo as well as coadministered study-supplied oral prednisone, which will be tapered over a period of up to 26 weeks, unless the subject experiences a flare of GCA. Upon completion of the 26-week double-blind period subjects will discontinue KPL-301 or placebo and enter the 12-week Washout Safety Follow-up period in which they may receive study-supplied oral prednisone per the Investigator's discretion. Thus, the total study duration will be up to approximately 38-44 weeks (including 6-week Screening Period).	Removed redundant text
5	Synopsis (pg 7) Section 8.4.2 (pg 35) Section 9.3 (pg 40)	…The prednisone dose can then be tapered or maintained throughout the remainder of the 12-week Washout Safety Follow-up Period as per Investigator discretion…	…The prednisone dose can then be tapered, **increased** or maintained throughout the remainder of the 12-week Washout Safety Follow-up Period as per Investigator discretion...	Text added for clarity
6	Table 1 Schedule of Activities (pgs 15- 16)	[redacted]	[redacted]	[redacted]
7	Section 8.3 (pg 32)	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will follow a different Investigator-defined steroid therapy/taper but will continue to receive the assigned KPL-301 or placebo. Subjects are not allowed to receive biologic DMARDs other than KPL-301 during the study to mitigate potential safety risks of administering KPL-301 concomitantly with other biologics…	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse **must** discontinue the assigned **study drug** (KPL-301 or placebo) **and should receive escape therapy in accordance with local SoC**. Subjects are not allowed to receive biologic DMARDs **while receiving** KPL-301 during the study to mitigate potential safety risks of administering KPL-301 concomitantly with other biologics...	Text updated per regulatory feedback

8	Section 8.8 (pgs 38-39)	Subjects may withdraw from the study drug treatment or from the study as a whole at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with and withdraw subjects from the study for any of the following reasons: Adverse event Life threatening or other unacceptable toxicity Subject requires use of a prohibited concomitant medication or therapy General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion Severe noncompliance Lost to follow-up Subject withdrawal of consent A decision to modify or discontinue development of the drug	Subjects may withdraw from the study drug treatment or from the study as a whole at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with and withdraw subjects from the study for any of the following reasons: Adverse event or Life threatening or other unacceptable toxicity, for example: Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN, assessed as related to investigational product CTCAE Grade 4 (life-threatening) anaphylaxis or hypersensitivity reactions CTCAE Grade 4 (life-threatening) serious infection or opportunistic infection (including septic shock). In addition, subjects with a diagnosis or reactivation of TB, hepatitis B, or hepatitis C will not receive any further investigational product. CTCAE Grade 4 (life-threatening) neutropenia Adverse events of malignancy of any grade; except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured. Subject requires use of a prohibited concomitant medication or therapy General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion Severe noncompliance Lost to follow-up Pregnancy or a decision to become pregnant Subjects who request to be permanently discontinued from further receipt of investigational product, regardless of the reason (Subject withdrawal of consent) A decision to modify or discontinue development of the drug	Text updated per regulatory feedback
9	Section 9.3 (pg 40)	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed steroid escape therapy per the Investigator <u>such as prednisone or similar > 60 mg/day or IV corticosteroids but will continue to receive the KPL-301 or placebo</u>…	…Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed escape therapy per the Investigator….	Text removed per regulatory feedback

10	Section 10.2 (pg 43)	The introduction of the following medications is not permitted from initiation of screening through the end of the study.	The introduction of the following medications is not permitted from initiation of screening through the end of the study **unless indicated for escape therapy**.	Text add for clarity
11	Section 10.3 (pg 43)	Subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed steroid escape therapy per the Investigator, such as prednisone or similar > 60mg/day or IV corticosteroids and will continue to receive the assigned study drug treatment (KPL-301 or placebo). These subjects are considered to have met the primary endpoint provided the flare occurs prior to Week 26.	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). These subjects are considered to have met the primary endpoint provided the flare occurs prior to Week 26. Escape corticosteroid therapy can be escalated immediately. Due to unknown possible safety and pharmacological effects from overlapping exposures to immunomodulatory agents on top of co-administered corticosteroids, the investigator should consider a washout period of at least 35 days (based on elimination half-lives) after the last dose of study drug (KPL-301 or placebo) if deemed clinically appropriate.	Text updated per regulatory feedback
12	Section 11.2 (pg 45)	In cases of flare, the prednisone dose may be increased. Any subject who cannot adhere to the protocol-defined steroid taper due to flare/relapse will be allowed to receive a more gradual Investigator-defined steroid taper and will continue to receive the assigned KPL-301 or placebo. These subjects will be considered to have met the primary endpoint if a flare has occurred prior to Week 26.	**Subjects who experience a flare or** who cannot adhere to the protocol-defined steroid taper due to flare/relapse **must dis**continue the assigned **study drug (**KPL-301 or placebo**) and should receive escape therapy in accordance with local SoC.** These subjects will be considered to have met the primary endpoint if a flare has occurred prior to Week 26.	Text updated per regulatory feedback
13	Section 12.6.7 (pg 49)	For women of child bearing potential a serum pregnancy test should be performed prior to enrolment at the site. Urine pregnancy tests should be performed at Day 0, Week 12, Week 26 and the Final Washout Safety Follow-up Visit. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	For women of child bearing potential a serum pregnancy test should be performed prior to **randomization** at the site. Urine pregnancy tests should be performed at Day 0, Week 12, Week 26 and the Final Washout Safety Follow-up Visit. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).	Text changed for clarification

14	Section 17.1 (pg 63)	-	17.1 Study Stopping Criteria If the sponsor receives a report of an event consistent with any one of the following, the medical monitor or designee will immediately assess the event by gathering all available information including, where possible, direct telephone contact with the reporter. A prompt review of the data will be initiated by the sponsor, and the information will be referred to the DMC within 1 business day of the receipt of the initial report by the Sponsor. Any CTCAE grade 5 (death) assessed as related to the investigational product Any CTCAE grade 4 (life-threatening) assessed as related to the investigational product Any CTCAE grade 4 (life-threatening) of anaphylaxis Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN, assessed as related to investigational product Any unforeseen events that, in the opinion of the DMC and the Sponsor, may contraindicate further dosing Clinically-significant pulmonary abnormalities that in the opinion of the DMC and the Sponsor may contraindicate further dosing If any above-listed events occur, the Sponsor will promptly conduct a cumulative review of safety data, including the DMC assessment of the event, and the circumstances of the event in question to determine whether the study should be modified, suspended or terminated.	Text added per regulatory feedback

20.3.3 Protocol Amendment v4.0

Rationale for Amendment – **Protocol Amendment v4.0** was completed to clarify aspects of protocol version 3.0 as well as to incorporate feedback from global Regulatory bodies. Substantial changes to this version include:

- Updated secondary endpoints and analysis; and inserted study endpoints into the Synopsis Objective section.
- The planned number of subjects to be enrolled in the study was updated from approximately 60 to approximately 70 subjects (42 subjects planned to be assigned to the KPL-301 arm and 28 subjects planned to be assigned to the placebo arm) to align with the updated sample size estimation.
- Added clarification that SAEs will be recorded in the eCRF within 24 hours of discovery.

Please see the below summary of changes for more details on the changes incorporated into this version. Bold indicates addition, underline indicates removal.

Change ID	Section(s)	Current Text	Revised Text	Rationale
1	Cover page, Header throughout	Date of Protocol: 15 Nov 2018 Version of Protocol: 3.0	Date of Protocol: **30 Mar 2020** Version of Protocol: **4.0**	Updated to reflect Amendment date and versioning
2	1. Protocol Approval	Sponsor Signatory: [redacted] Chief Medical Officer Kiniksa Pharmaceuticals Ltd. 100 Hayden Ave Lexington, MA 02421 USA	[redacted] **Senior Vice President** **Clinical Development** Kiniksa Pharmaceuticals Ltd. 100 Hayden Ave Lexington, MA 02421 USA	Change in Sponsor Signatory
3	Throughout document	-	-	Minor administrative editing and formatting changes for ease of reading
4	Synopsis: Objective(s) Section	**Objective(s):** Primary: The primary objective of the study is to evaluate the efficacy of KPL-301 versus placebo, coadministered with a 26-week steroid taper, for maintaining sustained remission for 26 weeks in subjects with new-onset or relapsing/refractory giant cell arteritis (GCA). Secondary: The secondary objectives of the study, in subjects with new-onset and relapsing/refractory GCA, are: a.) To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose. [redacted] c.) To evaluate the safety and tolerability of KPL-301. [redacted]	**Objective(s):** Primary: The primary objective of the study is to evaluate the efficacy of KPL-301 versus placebo, coadministered with a 26-week steroid taper, for maintaining sustained remission for 26 weeks in subjects with new-onset or relapsing/refractory giant cell arteritis (GCA). Secondary: The secondary objectives of the study, in subjects with new-onset and relapsing/refractory GCA, are: a.) To evaluate the effect of KPL-301 vs placebo on cumulative corticosteroid dose. [redacted] c.) To evaluate the safety and tolerability of KPL-301. [redacted]	Added endpoints to synopsis.

Change ID	Section(s)	Current Text	Revised Text	Rationale
		[redacted]	[redacted] **Efficacy Endpoints:** **Primary Endpoint:** • **Time to flare by Week 26 defined as time from randomization to the first flare occurring within the treatment period** **Secondary Endpoints:** • **Sustained remission rate 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 have completed the corticosteroid taper and who have neither signs/symptoms of GCA nor new or worsening vasculitis by imaging by 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 by imaging by Week 26** • **Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up Period** [redacted]	

Change ID	Section(s)	Current Text	Revised Text	Rationale

			[redacted]
			Safety Endpoints:
			• **Incidence of treatment emergent adverse events**
			• **Change in physical exam results**
			• **Change in vital signs**
			• **Change in clinical laboratory parameters**
			  ○ **Serum chemistry**
			  ○ **Hematology**
			  ○ **Urinalysis**	

5	Synopsis: Number of Subjects and Overview of Trial Design Figure	Approximately 60 subjects will be randomized at a 3:2 allocation ratio. Approximately 36 subjects will be assigned to KPL-301, and approximately 24 subjects will be assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	Approximately **70** subjects will be randomized at a 3:2 allocation ratio. Approximately **42** subjects will be assigned to KPL-301, and approximately **28** subjects will be assigned to placebo. Of the study population, the aim is to have 50% with new-onset disease and 50% with relapsing disease.	Updated the planned number of subjects to address potential early dropout.
6	Synopsis: Statistical Methods	General Methods All statistical analyses will be performed using SAS® Version 9.3 or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding. Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and at least have 1 assessment in the double blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment. Safety Analysis Set All randomized subjects who take at least 1 dose of 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.	General Methods All statistical analyses will be performed using SAS® Version 9.**4** or higher. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. The preliminary SAP is presented here, with the final SAP to be confirmed in a separate document (SAP) prior to study unblinding. Modified Intent-to-Treat Analysis Set All randomized subjects who receive at least 1 dose of KPL-301 or placebo and at least have 1 assessment in the double blind treatment period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment **assignment.** Safety Analysis Set All randomized subjects who take at least 1 dose of 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.	Updated text to allow use of SAS Version 9.4 or higher Updated text in Endpoint Analysis subsection for clarification and new statistical assumptions. Sustained remission rate at Week 26 was added as a standalone secondary efficacy endpoint. Time to elevated ESR and CRP by Week 26 and time to sign/symptoms of GCA or new or worsening vasculitis by imaging by Week 26 were added as secondary efficacy endpoints in response to request from the FDA.

Change ID	Section(s)	Current Text	Revised Text	Rationale
		Per Protocol Analysis Set All mITT subjects without protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) set. Primary Efficacy Endpoint Analysis The primary efficacy endpoint is time to flare by Week 26 defined as time from randomization to the date of first flare occurring within the 26-week period. Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit. The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare by Week 26. Kaplan-Meier estimates of remission rate at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate. As a key secondary efficacy endpoint, time to flare by week 26 in the per protocol population will be analyzed using the same methods described above. Subjects who do not experience flare during double-blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow-up prior to experiencing a flare at any time during double-blind treatment will be censored at the time of their last available visit. Additional secondary efficacy endpoints include the following endpoints that will be analyzed. Treatment comparisons will be performed using Cochran-Mantel-Haenszel test controlling for the randomized stratum. • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal ESR • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal CRP by Week 26	Per Protocol Analysis Set All mITT subjects without **important** protocol deviations deemed to impact efficacy or ethical conduct will be included in the per-protocol (PP) **analysis** set. Primary Efficacy Endpoint Analysis The primary efficacy endpoint is time to flare by Week 26 defined as time from randomization to the first flare occurring within the **treatment** period. **Detailed censoring rules** will be **provided in** the **SAP**. The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the **treatment** period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare by Week 26. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as **a** covariate **and stratified by the randomization strata.** **The protocol definition of flare includes multiple components. Supportive analyses will be performed based on each individual component. The details will be described in the SAP. In addition, a sensitivity analysis will be performed using the same method described above for the per-protocol analysis set.** **Secondary Efficacy Endpoint Analysis** **Sustained remission rate at Week 26 will be estimated and compared using the Kaplan-Meier method** **The following endpoints will be analysed using the Cochran-Mantel-Haenszel test, stratified by the randomized stratum:** • 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 have completed the corticosteroid taper and who have **neither** signs/symptoms of GCA **nor new or**	The key secondary endpoint time to flare by Week 26 in the Per Protocol population was deleted as it will be handled as a sensitivity analysis. Deleted time to corticosteroid dose of zero mg/day as a secondary efficacy endpoint because patients enter the study with varying doses of steroids. Updated the planned number of subjects to address potential early dropout. Updated statistical assumptions based on review of Phase 3 Tocilizumab data.

Change ID	Section(s)	Current Text	Revised Text	Rationale
		• Percentage of subjects who have completed the 26-week corticosteroid taper and who have no signs/symptoms of GCA The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate: • Time to corticosteroid dose of zero mg/day • Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted] Safety Analyses Descriptive statistics will be used to summarize all safety endpoints, by treatment group and study visit. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed parameters such as incidence of adverse events (AEs), clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, PFT and diffusing capacity for carbon monoxide (DLCO) parameters, and physical exam, where available. [redacted] Sample Size Estimation Assuming that time to flare follows an exponential distribution and the proportion of subjects without a flare by Week 26 will be 20% in placebo and 57.5% in KPL-301, the median time to flare would be estimated to be approximately 11.20 weeks in placebo and 32.57 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) would be estimated to be approximately 0.3438. With a 2-sided significance level of 0.05 and a 3:2 randomization ratio for KPL-301 vs. placebo, it would require approximately 34 events to achieve 86% power using a two-sided log rank test.	**worsening vasculitis by imaging by Week 26** **The following time to event endpoints will be analyzed using the same methods used for the primary efficacy endpoint:** • **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 by imaging by Week 26** The following continuous secondary efficacy endpoints will be analyzed. The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate. **Details will be described in the SAP:** • Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted] Safety Analyses Descriptive statistics will be used to summarize all safety endpoints, by treatment group and study visit. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed parameters such as incidence of adverse events (AEs), clinical laboratory variables, vital signs, body weight and body mass index, ECG parameters, PFT and diffusing capacity for carbon monoxide (DLCO) parameters, and physical exam, where available. [redacted] Sample Size Estimation Assuming 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 is estimated to be	

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		Approximately 60 subjects will be randomized by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo at a 3:2 allocation ratio. Subject disposition and the flare event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion. If there is a high dropout rate and/or the event accrual rate is significantly slower than anticipated, up to 10 additional subjects may be randomized to obtain the target number of events required for the analysis of primary efficacy endpoint.	approximately **26** weeks in placebo and **111** weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) **is** estimated to 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.	
7	Section 8.6	Approximately 60 patients with GCA will be randomized as study subjects. For the primary endpoint analysis, the aim is to have 36 subjects assigned to KPL-301 and 24 subjects assigned to placebo, with balanced randomization in the two randomization cohorts.	Approximately **70 patients** with GCA will be randomized as study subjects. For the primary endpoint analysis, the aim is to have 42 subjects assigned to KPL-301 and 28 subjects assigned to placebo, with balanced randomization in the two randomization cohorts.	Updated the planned number of subjects to address potential early dropout.
8	Section 12.5.4	The modified Borg scale (Borg, 1982) 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 10 (maximal). A validated version of the Borg scale in local language will be provided.	The modified Borg scale (Borg **and 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 10 (maximal). A validated version of the Borg scale in local language will be provided.	Updated citation for modified Borg scale.
9	Section 13.6	All SAEs, whether or not considered causally related to study drug or to the study procedure(s), have to be reported. All SAEs will be recorded in the eCRF. The Investigator must report all SAEs to the Safety Department and Sponsor within 24 hours of discovery via the SAE reporting form to: **24 Hour Safety Hotline: +44 1223 374 240** **24 Hour Safety Hotline Fax: +44 1223 374 102** **US 24 Hour Safety Hotline: 1 888-483-7729** **US 24 Hour Safety Hotline Fax: 1 888-529-3580**	All SAEs, whether or not considered causally related to study drug or to the study procedure(s), have to be reported. SAEs will be recorded in the eCRF **within 24 hours of discovery.** **In case the eCRF is inaccessible,** the Investigator must report all SAEs to the Safety Department and Sponsor within 24 hours of discovery via the SAE reporting form to: **24 Hour Safety Hotline: +44 1223 374 240** **24 Hour Safety Hotline Fax: +44 1223 374 102** **US 24 Hour Safety Hotline: 1 888-483-7729** **US 24 Hour Safety Hotline Fax: 1 888-529-3580**	Updated text upon request from Slovenian Inspection.
10	Section 14.1	All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.3 or later. A statistical analysis plan (SAP) will be written and approved prior to performing the first review of the data.	All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.**4** or later. A statistical analysis plan (SAP) will be written and approved prior to performing the first review of the data.	Updated text to allow use of SAS Version 9.4 or higher

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11	Section 14.1.2	14.1.2 Multiple Comparisons/Multiplicity Multiplicity with respect to the primary efficacy endpoint and the key secondary efficacy endpoints will be managed via the gated hierarchical testing procedure. If and only if the primary comparison results in a statistically significant difference between KPL-301 and placebo at 0.05 level of significance, the key secondary comparison will be conducted at alpha 0.05 as well. All other secondary endpoints are considered exploratory, and no adjustment for multiple testing of secondary efficacy endpoints will be performed.	14 1 2 Multiplicity **Adjustment** Multiplicity **adjustment** with respect to the primary efficacy **and secondary efficacy endpoints will be performed using** the **gate-keeping** hierarchical testing procedure. **The order of the secondary endpoints will be described in the SAP. 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 ≤0.05 and the test statistic shows KPL-301 is superior than placebo, 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.**	Clarified language in response to request from the FDA.
12	Section 14.2	Approximately 60 subjects will be randomized 3:2 by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo. Assuming that time to flare follows an exponential distribution and the proportion of subjects without a flare by week 26 will be 20% in placebo and 57.5% in KPL-301, the median time to flare would be estimated to be approximately 11.20 weeks in placebo and 32.57 weeks in KPL-301. The hazard ratio (KPL-301 vs. placebo) would be estimated to be approximately 0.3438. With a 2-sided significance level of 0.05 and a 3:2 randomization ratio for KPL-301 vs. placebo, it would require approximately 34 events to achieve 86% power using a two- sided log rank test. Approximately 60 subjects will be randomized by disease stratum (new-onset or relapsing/refractory) to receive KPL-301 or placebo at a 3:2 allocation ratio. Subject disposition and the flare event accrual will be closely monitored during the study. The monitoring activities will be done in a blinded fashion. If there is a high dropout rate and/or the event accrual rate is significantly slower than anticipated, up to 10 additional subjects may be randomized to obtain the target number of events required for the analysis of primary efficacy endpoint.	Assuming 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 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.	Updated the planned number of subjects to address potential early dropout. Updated statistical assumptions based on review of Phase 3 Tocilizumab data.
13	Section 14.4	Efficacy Endpoints: Primary Endpoint: • Time to flare by Week 26 defined as time from randomization to the first flare occurring within the first 26-weeks of the double-blind period Key secondary endpoint:	Efficacy Endpoints: Primary Endpoint: • Time to flare by Week 26 defined as time from randomization to the first flare occurring within the **treatment** period Secondary Endpoints:	Updated text in Efficacy Endpoints for clarification. Sustained remission rate at Week 26 was added as a standalone secondary efficacy endpoint.

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		• Time to flare by week 26 from randomization to first flare occurring within the first 26 weeks of the double-blind period in the per protocol population Additional Secondary Endpoints: • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal ESR • Percentage of subjects who have completed the 26-week corticosteroid taper and who have a normal CRP • Percentage of subjects who completed the 26-week corticosteroid taper and who have no signs/symptoms of GCA • Time to corticosteroid dose of zero mg/day • Cumulative steroid dose at Week 26 and at the end of the Washout Safety Follow-up Period [redacted] Safety Endpoints • Incidence of treatment emergent adverse events • Change in physical exam results • Change in vital signs • Change in clinical laboratory parameters o Serum chemistry o Hematology o Urinalysis	• **Sustained remission rate 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** • **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 and at the end of the Washout Safety Follow-up Period [redacted] Safety Endpoints • Incidence of treatment emergent adverse events • Change in physical exam results • Change in vital signs • • Change in clinical laboratory parameters o Serum chemistry o Hematology	Time to elevated ESR and CRP by Week 26 and time to sign/symptoms of GCA or new or worsening vasculitis by imaging by Week 26 were added as secondary efficacy endpoints in response to request from the FDA. The key secondary endpoint time to flare by Week 26 in the Per Protocol population was deleted as it will be handled as a sensitivity analysis. Deleted time to corticosteroid dose of zero mg/day as a secondary efficacy endpoint because patients enter the study with varying doses of steroids.

Change ID	Section(s)	Current Text	Revised Text	Rationale
			o Urinalysis	
14	Section 14.5	14.5 Analysis of Efficacy All efficacy analyses will be performed on the mITT analysis set. The primary and key secondary efficacy Analyses will be repeated using the PP set to assess the sensitivity of the results to major deviations/violations of the protocol. All efficacy data including those collected during the open label extension will be listed by subject. 14.5.1 Primary Efficacy Analysis The primary efficacy endpoint is time to flare by Week 26 defined in 14.1 Subjects who do not experience a flare during this period will be censored at the Week 26 visit. Subjects who drop out or are lost to follow-up prior to experiencing a flare during the 26-week double-blind period will be censored at the time of their last available visit. The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the 26-week double-blind period will be summarized for each treatment group. Time to flare by week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare. The Kaplan-Meier estimates of remission rate at 26 weeks will be presented with the corresponding 95% CI by treatment group. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as covariate. 14.5.2 Key Secondary Efficacy Analysis The key secondary efficacy endpoint is time to flare by week 26 in the per protocol population and will be analyzed using the same methods as described above. Subjects who do not experience flare during double blind treatment will be censored at their last visit of the double-blind treatment period. Subjects who drop out or are lost to follow up prior to experiencing a flare at any time during double blind treatment will be censored at the time of their last available visit. 14.5.3 Additional Secondary Efficacy Analysis The number and percentage of subjects with normal ESR at Week 26 as well as the number and percentage of subjects with normal CRP at Week 26 will be analyzed. Treatment groups will be compared using a Cochran-Mantel-Haenszel test controlling for the randomized strata. Confidence	14 5 Analysis of Efficacy All efficacy analyses will be performed on the mITT analysis set. Analyses will be repeated using the PP set to assess the sensitivity of the results to **important** deviations of the protocol. 14 5 1 Primary Efficacy **Endpoint** Analysis The primary efficacy endpoint is time to flare by Week 26 defined **as time from randomization to the first** flare **occurring within the treatment** period. **Detailed censoring rules will be provided in the SAP.** The number and percentage of subjects who remain in remission (no flare), who flare, and who are lost to follow-up prior to a flare during the **treatment** period will be summarized for each treatment group. Time to flare by Week 26 will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. A log-rank test stratified by randomization strata will be used to compare KPL-301 and placebo with respect to time to flare **by Week 26**. To describe the magnitude of treatment effect, the hazard ratio for KPL-301 compared to placebo and the corresponding 95% CI will be calculated based on a Cox proportional-hazards model with treatment as **a** covariate **and stratified by randomization strata.** **The protocol definition of flare includes multiple components. Supportive analyses will be performed based on each individual component. The details will be described in the SAP. In addition, a sensitivity analysis will be performed using the same method described above for the PP analysis set.** **14 5 2** Secondary Efficacy **Endpoint** Analysis **Sustained remission rate** at Week 26 will be **estimated and** compared using **the Kaplan-Meier method.** **The following endpoints will be analyzed using the** Cochran-Mantel-Haenszel test **stratified by the randomization strata.** • **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**	Updated text for clarification and new statistical assumptions. Sustained remission rate at Week 26 was added as a standalone secondary efficacy endpoint. Time to elevated ESR and CRP by Week 26 and time to sign/symptoms of GCA or new or worsening vasculitis by imaging by Week 26 were added as secondary efficacy endpoints in response to request from the FDA. The key secondary endpoint time to flare by Week 26 in the Per Protocol population was deleted as it will be handled as a sensitivity analysis. Deleted time to corticosteroid dose of zero mg/day as a secondary efficacy endpoint because patients enter the study with varying doses of steroids. Updated the planned number of subjects to address potential early drop-out. Updated statistical assumptions based on review of Phase 3

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		intervals for the difference of proportions between treatment groups will be displayed.with normal ESR at Week 26 as well as the number and with normal CRP at Week 26. Time to steroid dose of zero will be summarized by the 25th, 50th (median), and 75th percentiles calculated using the Kaplan-Meier method to estimate the survival functions for each treatment group. The 95% confidence interval (CI) for the percentiles will also be calculated. The following continuous secondary efficacy endpoints will be analyzed. The details will be provided in the SAP. • Cumulative corticosteroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted]	• **Percentage of subjects who have completed the corticosteroid taper and who have neither signs/symptoms of GCA or new or worsening vasculitis by imaging by Week 26** **The following time-to event endpoints will be analyzed using the same method for the primary efficacy endpoint.** • **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 by imaging by Week 26** The following continuous secondary efficacy endpoints will be analyzed. **The analyses will include two-sided 95% CIs for the difference of treatment means, as appropriate. Details will be** provided in the SAP. • Cumulative corticosteroid dose at Week 26 and at the end of the Washout Safety Follow-up period [redacted]	Tocilizumab data.
15	Section 19	Borg GAJ. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982:14:37781.	**Borg G, Borg E. The Borg CR Scales® Folder. Hasselby, Sweden: Borg Perception; 2010.**	Updated reference for the modified Borg scale.