Double-Blind, Randomized, Placebo-Controlled Trial of AKST4290 for Adjunctive Treatment of Mild to Moderate Bullous Pemphigoid

Protocol Number:	AKST4290-221
EudraCT Number:	2019-001059-37
Clinical Phase:	2
Sponsor:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070
Study Agent:	AKST4290
Indications:	Mild to Moderate Bullous Pemphigoid
Authorized Representative:	[redacted]
Version Number:	V4.0
Version Date:	15MAY2020
Replaces Version(s):	V3.0, 31JAN2020

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LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
AESI	Adverse Events of Special Interest
ALT	Alanine Amino Transferase
ALP	Alkaline Phosphatase
AST	Aspartate Amino Transferase
AUC	Area under the Curve
b.i.d.	Twice Daily
BP	Bullous Pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
BPDAI-VAS	Bullous Pemphigoid Disease Area Index Visual Analog Scale
BLQ	Below the Limit of Quantification
CBC	Complete Blood Count
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI(s)	Confidence Interval(s)
C_{max}	Maximum Plasma Concentration
CMP	Clinical Monitoring Plan
CPC	Clobetasol Propionate Cream
CRF	Case Report Form
CRO(s)	Contract Research Organization(s)
CS(s)	Corticosteroid(s)
[redacted]	[redacted]
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DSUR	Development Safety Update Report
ECG	Electrocardiogram
[redacted]	[redacted]
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicine Agency
EOT	End of Treatment
[redacted]	[redacted]
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
ICH E6 R2	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidance for Industry, Good Clinical Practice: Consolidated Guidance, Revision 2

IEC	Independent Ethics Committee
IFN-g	Interferon-gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
MCI	Mild Cognitive Impairment
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
MFC	Mometasone Furoate Cream
MoCA	Montreal Cognitive Assessment
NOA	Not Analyzed
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample Available
NTI	Narrow Therapeutic Index
OVA	Ovalbumin
P-gp	Permeability Glycoprotein
PK	Pharmacokinetic(s)
PP	Per Protocol
QA	Quality Assurance
QT	QT Interval on ECG
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analytical Plan
SOC	Standard of Care
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
ULN	Upper Limit of Normal
VCA	Vascularized Composite Allotransplantation

PROTOCOL APPROVAL PAGE

Study Title:	Double-Blind, Randomized, Placebo-Controlled Trial of AKST4290 for Adjunctive Treatment of Mild to Moderate Bullous Pemphigoid
Protocol Number:	AKST4290-221
Version/Date:	V4.0 15MAY2020
Sponsor Name and Address:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and applicable legal and regulatory requirements.

Approved by:

[redacted]

STATEMENT OF COMPLIANCE

Protocol Title:	Double-Blind, Randomized, Placebo-Controlled Trial of AKST4290 for Adjunctive Treatment of Mild to Moderate Bullous Pemphigoid
Protocol Number:	AKST4290-221
Version/Date:	V4.0 15MAY2020

By my signature, I:

- Confirm that my staff and I have carefully read and understand this protocol or protocol amendment, have received the Investigator Brochure, and are thoroughly familiar with the appropriate use of the investigational agent described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by the Sponsor, Alkahest, Inc., or their designee.
- Agree to assume responsibility for the proper conduct of the study at this site, including complying with current relevant versions of the US Food and Drug Administration (FDA) regulations, European Medicines Agency (EMA), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of all source documents by Alkahest, Inc. or designee and to onsite inspection of source documents by appropriate regulatory authorities, including but not limited to the FDA, EMA, local governing regulatory bodies, and IRB/IEC inspectors.

_____ _____

Investigator's Signature Date

_____

Print Name

PROTOCOL SUMMARY

Title: Double-Blind, Randomized, Placebo-Controlled Trial of AKST4290 for Adjunctive Treatment of Mild to Moderate Bullous Pemphigoid

Précis: This is a randomized, double-blind, placebo-controlled phase 2 trial to be conducted at up to 8 sites in approximately 30 subjects to assess the therapeutic effect and safety of adjunctive AKST4290 in subjects with bullous pemphigoid (BP). Subjects will receive whole-body topical mometasone furoate cream (MFC) therapy (dose and dosing interval dependent upon severity of disease at time of enrollment, as assessed by the investigator) concurrently with study agent (placebo or AKST4290 400 mg twice daily [b.i.d.]) in an inpatient setting until disease control is reached (duration of inpatient stay is dependent upon individual disease course – estimated between 1-3 weeks). Study agent dosing will commence upon clinical BP diagnosis and may occur up to 7 days after initial whole-body topical steroid therapy (clobetasol propionate class). Following clinical diagnosis, histological diagnosis of BP will subsequently be confirmed per the S2k Guideline for the Diagnosis of Pemphigus Vulgaris/Foliaceus and Bullous Pemphigoid (Schmidt 2015). Subjects will receive rescue therapy at any time if their clinical condition worsens or if their clinical condition fails to improve by the completion of Week 1 on study treatment, as assessed by the investigator. Rescue therapy will consist of whole-body clobetasol propionate cream (CPC) (15-50 g) and/or oral prednisone (0.5 mg/kg per day), as determined by the investigator. Subjects who receive rescue therapy will remain in the study until disease control, unless they are withdrawn or withdraw from participation. For a complete listing of study events, please see Section 15.

Objectives: **Primary Objective:** To investigate the proportion of subjects who achieve disease control (defined as ≤ 3 new blisters/day and healing of existing blisters) following topical steroid treatment with adjunctive AKST4290 without receiving rescue therapy.

Secondary Objectives: To assess treatment safety of the proposed dosing regimen. Additional secondary endpoints include assessment of time to disease control; time to rescue therapy; change in BP Disease Area Index (BPDAI) score; and change in pruritis as assessed by the BPDAI-Visual Analog Scale (BPDAI-VAS). In addition, change in skin (biopsy) [redacted] and overall steroid use required to achieve disease control will be assessed.

Exploratory Objectives: Blister fluid protein levels [redacted] anti-BP180 Immunoglobulin G [IgG] serum levels, serum protein levels [redacted] and blood chemistry will be evaluated. Pharmacokinetic (PK) studies will also be conducted to determine AKST4290 plasma levels. Cognitive assessments will be conducted using the Montreal Cognitive Assessment (MoCA). Quality of life will be assessed by the Dermatology Life Quality Index

(DLQI). Additional biomarker evaluations may be conducted on plasma samples.

Endpoints:

Primary Endpoints:

- The proportion of subjects who achieve disease control (≤ 3 new blisters/day and healing of existing blisters) without requiring rescue therapy.

Secondary Endpoints:

- Safety as assessed by the incidence, seriousness, and severity of adverse events (AEs).
- Time to disease control by treatment day/week.
- Time to rescue therapy by treatment day/week.
- Change from baseline in BPDAI score by treatment week and at disease control.
- Change from baseline in pruritus as evaluated by the BPDAI-VAS by treatment week and at disease control.
- Change from baseline in skin biopsy [redacted] at disease control.
- Evaluation of total cumulative steroid exposure at baseline, by treatment week and at disease control.
- Evaluation of maximum daily steroid dose at baseline, by treatment week and at disease control.

Exploratory Endpoints:

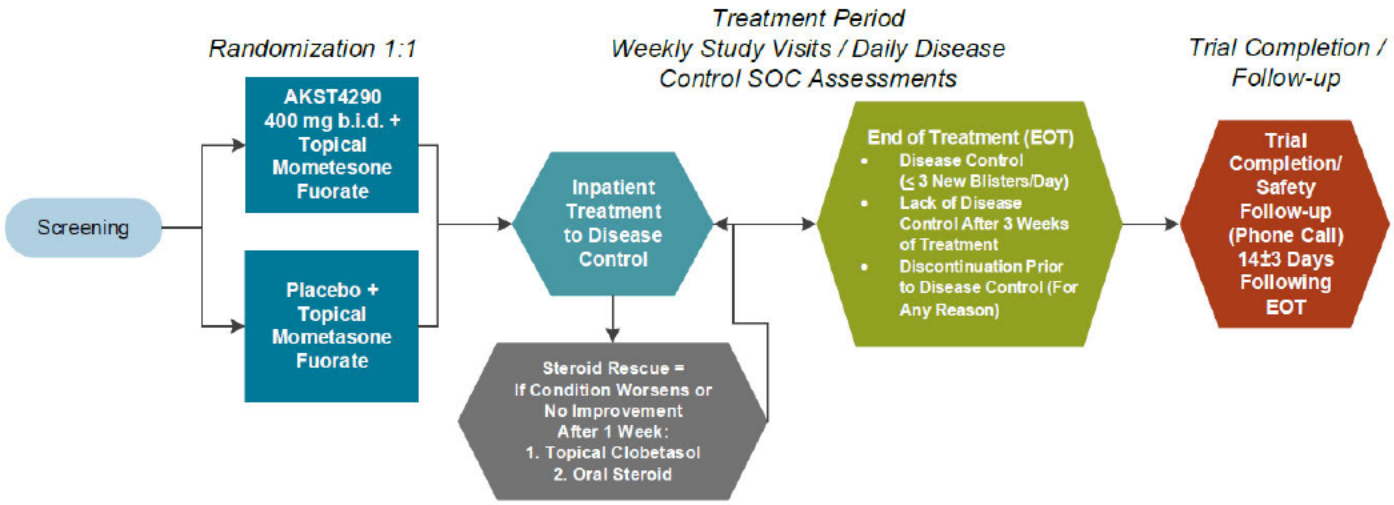
- Change from baseline in blister fluid protein levels [redacted] at treatment Week 1.
- Change from baseline in blood [redacted] levels by treatment week and at disease control.
- Change from baseline in Anti-BP180 IgG levels by treatment week and at disease control.
- Evaluations of complete blood count (CBC), blood chemistry, and serum protein levels [redacted] at baseline, by treatment week and at disease control.
- Changes in AKST4290 plasma concentrations at various timepoints.
- Change from baseline in cognitive assessments using the MoCA at disease control.
- Change from baseline in quality of life, as assessed by the DLQI at disease control.
- Evaluation of exploratory biomarkers in plasma samples at various timepoints.

Population:

Approximately 30 subjects, between 60 to 95 years of age (inclusive), with a baseline diagnosis of mild to moderate BP.

Phase:	2
Number of Sites:	Up to 8 sites
Description of Study Agent:	AKST4290: [redacted]
Study Duration:	15 months
Subject Participation:	Approximately 1 to 5 weeks (inclusive of the Safety Follow-up call).

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

1.1 AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY

[redacted]

1.2 STUDY ORGANIZATION

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), Sponsor's medical expert and study monitor, Sponsor's representative(s), laboratories, steering committees, and oversight committees (including IECs and IRBs, as applicable) will be maintained by the Sponsor, or their designee, and provided to the investigator.

2 INTRODUCTION

[redacted]

[redacted]

[redacted]

[redacted]

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to investigate the proportion of subjects who achieve disease control (defined as ≤ 3 new blisters/day and healing of existing blisters) following topical steroid treatment with adjunctive AKST4290 without receiving rescue therapy.

Secondary objectives include the assessment of treatment safety (incidence and severity of AEs), time to disease control, time to rescue therapy, change in BPDAI score; steroid dose required to achieve disease control; and change in pruritus as assessed by the BPDAI-Visual Analog Scale (BPDAI-VAS). Skin (biopsy) [redacted] levels will also be evaluated.

Exploratory objectives include the evaluation of blister fluid [redacted] levels [redacted] blood [redacted] levels, Anti-BP180 immunoglobulin G (IgG) serum levels, serum protein levels [redacted], and blood chemistry. PK studies will also be conducted to assess AKST4290 plasma concentrations at various required and optional timepoints. Cognitive assessments will be performed using the MoCA. Quality of life will be assessed by the DLQI. Additional biomarker evaluations may be conducted on plasma samples.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, phase 2 trial to be conducted at up to 8 sites in approximately 30 subjects to assess the therapeutic effect and safety of adjunctive AKST4290 in subjects with mild to moderate BP in an inpatient hospital setting. Subjects will receive whole-body topical steroid therapy, MFC, with the dose and frequency dependent upon severity of disease at the time of enrollment, as assessed by the investigator, concurrently with study agent (placebo or AKST4290 400 mg b.i.d.) in an inpatient setting until time of disease control (estimated time to disease control is approximately 1 to 3 weeks). Study agent dosing will commence upon clinical BP diagnosis and may occur up to 7 days after initial whole-body topical steroid therapy (clobetasol propionate class). Following clinical diagnosis, histological diagnosis of BP will subsequently be confirmed per the S2k Guideline for the Diagnosis of Pemphigus Vulgaris/Foliaceus and Bullous Pemphigoid (Schmidt 2015). Subjects will receive a rescue therapy if their clinical condition worsens or if their clinical condition fails to improve after 1 week of treatment (as assessed by the investigator). Rescue therapy will consist of whole-body clobetasol propionate cream (CPC), 15-50 g per day (dose and frequency per investigator discretion), and/or oral prednisone, 0.5 mg/kg per day, as per investigator discretion.
Safety and treatment tolerability will be assessed at every visit. At specified visits, BPDAI, BPDAI–VAS, skin biopsies, and [redacted] levels will be evaluated. See Section 15 for a complete schedule of study events.

The overall duration of the study is approximately 15 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit) with a targeted recruitment of 30 subjects over the accrual period. The planned duration of subject participation is approximately 5 weeks, which includes 1 to 3 weeks of inpatient treatment to achieve disease control followed by a 14-day [2 weeks] outpatient period to the Safety Follow-up call, or until withdrawal from the study for any reason.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Primary Endpoint:

- The proportion of subjects who achieve disease control (≤ 3 new blisters/day and healing of existing blisters) without requiring rescue therapy.

4.2.2 SECONDARY ENDPOINTS

Secondary Endpoints:

- Safety as assessed by the incidence, seriousness, and severity of AEs.
- Time to disease control by treatment day/week.
- Time to rescue therapy by treatment day/week.
- Change from baseline in BPDAI score by treatment week and at disease control.
- Change from baseline in pruritus as evaluated by the BPDAI-VAS by treatment week and at disease control.
- Change from baseline in skin biopsy [redacted] levels at disease control.
- Evaluation of total cumulative steroid exposure at baseline, by treatment week and at disease control.
- Evaluation of maximum daily steroid dose at baseline, by treatment week and at disease control.

4.2.3 EXPLORATORY ENDPOINTS

Exploratory Endpoints:

- Change from baseline in blister fluid protein levels [redacted] at treatment Week 1.
- Change from baseline in blood [redacted] levels by treatment week and at disease control.
- Change from baseline in Anti-BP180 IgG serum levels by treatment week and at disease control.
- Evaluations of complete blood count [CBC], blood chemistry, and serum protein levels [redacted] at baseline, by study week and at disease control.
- Changes in AKST4290 plasma concentrations at various timepoints.
- Change from baseline in cognitive assessments using the MoCA at disease control.
- Change from baseline in quality of life, as assessed by the Dermatology Life Quality Index (DLQI) at disease control.
- Evaluation of exploratory biomarkers in plasma samples at various timepoint.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

In order to be eligible for inclusion, all subjects must meet the following criteria:

1. Age 60-95 years, inclusive at screening.

2. Clinical diagnosis of mild to moderate BP at screening:
    - Mild BP is defined as BPDAI ≤ 10 **OR** < 10% affected body surface
    - Moderate BP is defined as BPDAI ≥ 10 and ≤ 55 **OR** 10%-30% affected body surface
3. Treatment naïve or initiation of whole-body high potency topical steroid treatment ≤ 7 days of screening (lesion-only treatment for any amount of time with any topical steroids prior to screening is allowed without restriction).
4. Female subjects must not be pregnant or breastfeeding. Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening. WOCBP and men must agree to use highly effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 1 year without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately. Male subjects must be willing to use a barrier method contraception while participating in the study.
5. The subject must be able to follow the study procedures, receive the treatment in the established timeframe, and agree to remain an inpatient until the end of treatment (EOT)/disease control.
6. The subject must be able to understand the procedures and agree to complete the required assessments.
7. Provide signed and dated informed consent form in accordance with local regulations and/or IRB/IEC guidelines.

5.2 EXCLUSION CRITERIA

An individual will not be eligible for inclusion if any of the following criteria apply:

1. Severe BP (BPDAI score ≥ 56 OR > 30 new blisters per day OR > 30% affected body surface).
2. Initiation of gliptins and other treatments (e.g., etanercept, sulfasalazine, furosemide, penicillin) that can trigger BP if this treatment was started within 4 weeks prior to screening and is considered possibly related to the onset of BP.
3. Initiation of any concomitant medication in the last 3 months prior to screening and assessed by the investigator as possibly related to the development of BP.
4. Planned use of intravenous immunoglobulin or other concomitant treatments for BP (i.e., doxycycline, dapsone) during the study period.
5. Life expectancy of < 6 months (as assessed by the investigator).
6. Use of systemic immunosuppressants (i.e., mycophenolate, azathioprine, methotrexate) within 4 weeks prior to screening.
7. Treatment with rituximab within 1 year prior to screening.
8. Medical history of:
    - Myocardial infarction or stroke within 6 months of screening
    - Active bleeding disorder
    - Major surgery within 1 month of screening or planned within the study period
    - Active liver disease
    - Positive screening test result for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), or tuberculosis (TB)(by QuantiFERON testing)
9. [redacted]
10. [redacted]
11. Subjects taking warfarin (see Section 17.6.1).
12. Renal function as defined by estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 using the

Modification of Diet in Renal Disease (MDRD) study equation (see Section 17.5).

13. Use of systemic steroids (>10 mg prednisone or equivalent/day) within 14 days of first dose of study agent or known diseases (other than BP) that could require the use of systemic steroids within the study period. Subjects who have received a single high-dose of steroids (intravenous or oral) 14 days or more before the administration of the first dose of study drug are eligible for enrollment.
14. Clinically relevant abnormal laboratory value at screening, including hematology, blood chemistry, or urinalysis (laboratory testing may be repeated once during the screening phase).
15. Significant alcohol or drug abuse within past 2 years.
16. Based on ECG reading, subjects with a risk of QT prolongation including:
    - A baseline prolongation of QTc (using Fridericia's formula: ≥ 450 ms in men and ≥ 470 ms in women) with confirmation on a repeat ECG.
    - A history of additional risk factors for Torsades de pointes arrhythmia (e.g., heart failure, hypokalemia, family history of Long QT Syndrome, etc.).
17. The use of concomitant medications known to prolong the QT/QTc interval.
18. Significant medical conditions (as determined by medical history, examination, and clinical investigations at screening) that may, in the opinion of the investigator, result in the any of the following:
    - Put the subject at risk because of participation in the study.
    - Influence the results of the study.
    - Cause concern regarding the subject's ability to participate in the study.
19. Malignancy for which the subject is currently undergoing resection, radiation, or chemotherapy.
20. Participation in studies of investigational drugs must have been discontinued within 30 days or 5 half-lives of the drug (whichever was longer) prior to screening.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The Sponsor does not anticipate any specific challenges in meeting recruitment goals of enrolling and retaining a total of 30 subjects in this study. Subjects will be recruited continuously until the planned sample size is achieved. Subjects who withdraw or are withdrawn during screening, as well as subjects who discontinue, may be replaced (see Section 5.4.2).

The expected length of participation in the study of approximately 5 weeks, which includes 1 to 3 weeks of inpatient treatment to achieve disease control followed by a 14-day [2 weeks] outpatient period to the Safety Follow-up call, is not expected to be challenging to subjects. Financial support for meal and miscellaneous expenses will be available during the study, as appropriate and based on local regulations and guidelines. The study will be entered into local clinical trial registries, as required.

5.4 SUBJECT WITHDRAWAL

5.4.1 REASONS FOR WITHDRAWAL

A subject may be withdrawn from the study for the following medical or administrative reasons:

- Occurrence of an AE that represents an unacceptable risk to the subject and when continued participation in the investigational study is not warranted, in the judgment of the investigator, Sponsor, or medical monitor. The investigator must follow the subject until the AE resolves or is stable, unless the subject is lost to follow up.
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator.

- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures.
- At the request of the subject (e.g., subject withdraws consent), investigator, Sponsor, or regulatory authority.
- Pregnancy.
- Subject did not achieve disease control (as defined per protocol) following 3 weeks of treatment with study agent (please see Schematic of Study Design for more information).

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS

Subjects will be encouraged to complete the study and all assessments. Subjects may voluntarily withdraw at any time, and the investigator may discontinue individual subjects from the study at any time.

Approximately 30 subjects will be enrolled in the study with the intent of obtaining 27 evaluable subjects, assuming a 10% dropout rate. Subjects who discontinue or are unblinded prior to treatment Week 1 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced.

Subjects who have received at least 1 dose (400 mg) but are withdrawn or withdraw from the study will be encouraged to complete the EOT visit procedures and the Safety Follow-up call. The primary reason for study discontinuation will be documented on the case report form (CRF).

Subjects that are withdrawn at the end of Week 3 of treatment due to lack of disease control will perform all EOT visit procedures and the Safety Follow-up call. The primary reason for withdrawal will be documented on the CRF.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor and/or their representatives will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the investigator will continue to protect the subjects' privacy and identity as required by relevant statues and regulations.

Alkahest, Inc. has the right to terminate a study site from participating in the study at any time. Reasons for study or site termination may include, but are not limited to:

- (Immediate) risk to subject safety.
- Unsatisfactory subject enrollment.
- Unacceptable protocol deviations/violations as assessed by the medical monitor.
- Inaccurate or incomplete data entry and recording/fabricated data.
- Investigational site noncompliance with ICH GCP.
- Unacceptable emergent safety profile.

6 STUDY AGENTS

6.1 STUDY AGENT AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The study agent (AKST4290) and placebo will be manufactured, labeled, packaged, and distributed by Alkahest, Inc. The co-administered agent, MFC, will be supplied by the study sites. Likewise, if rescue

therapy is required, including CPC and/or oral prednisone, study sites will supply these treatments. At the conclusion of the study, sites may be reimbursed by Alkahest for MFC, CPC, and oral prednisone administered to subjects during the course of the study (see Section 6.2), as applicable.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

AKST4290 is a film-coated pink, oblong tablet manufactured by Alkahest, Inc., with a unit strength of 400 mg. The study agent and matching placebo will be delivered to the site, and the drug products will be labeled for investigational use only according to applicable local regulatory requirements for clinical studies.

For further details and information on AKST4290 and placebo, including packaging and labeling, see the Investigator's Brochure.

6.1.3 PRODUCT STORAGE AND STABILITY

The study agent and placebo will be kept in its original packaging in a secure limited access storage area at 15° C - 30° C. A temperature log must be maintained to make certain the study agent and placebo are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the site must immediately notify the sponsor or designee.

Co-administered steroids and rescue treatments should be stored according the product labels and study site/institutional policies.

6.1.4 DOSING AND ADMINISTRATION

The study agent or placebo will be administered orally twice daily (b.i.d.).During the course of the study, all study agent and placebo administration will be performed at the study site under the direct supervision of the study personnel for documentation of precise administration times.

During the study, topical whole-body MFC will be co-administered. The baseline dose will be dependent upon disease severity as assessed by the investigator and will remain unchanged until disease control or until rescue is indicated, per protocol guidelines. The guidelines for baseline dose of MFC is once a day application for mild BP subjects and b.i.d. application for moderate BP subjects, per investigator discretion.

Subjects requiring rescue therapy will receive whole-body CPC, 15-50 g per day (dose and frequency per investigator discretion) and/or oral prednisone (0.5 mg/kg per day), as determined by the investigator if their condition worsens at any time during the study or fails to improve after Week 1 on treatment.

6.2 STUDY AGENT ACCOUNTABILITY

The investigator and/or pharmacist will receive the study agent/placebo delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical study protocol and Informed Consent by the IRB or IEC
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification of the appropriate regulatory authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical study protocol by principal investigator

The investigator and/or pharmacist must maintain records of the study agent/placebo delivery to the study site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused study agent/placebo. In addition, for purposes of reimbursement of co-administered agents and rescue treatments, the investigator and/or pharmacist must maintain records of the use by each subject. At the conclusion of the study, reimbursement for co-administered agents and rescue treatments will be distributed on the basis of these records.

For the study agent/placebo, records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the study agent/placebo and subjects. The investigator/pharmacist will maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all study agent/placebo received from the sponsor. At the time of final study agent/placebo reconciliation, the investigator/pharmacist must verify that all unused or partially used portions of study agent/placebo have been returned and that no remaining study agent/placebo is retained by the investigator.

Accountability records must be maintained and readily available for inspection/audits by representatives of Alkahest, Inc. or their designee and are open to inspections by regulatory authorities at any time. The accounts of any study agent/placebo accidentally wasted or intentionally disposed of must be maintained.

The disposal of used, partially used, or wasted study agent/placebo materials must be performed in accordance with the institution's drug disposal policy. At study initiation, the clinical study monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure it complies with study requirements. At the end of the study, following final study agent/placebo reconciliation by the monitor, the study site will be instructed by the sponsor to return or destroy all unused study agent/placebo supplies, including empty containers. In case of destruction according to the site's drug disposal/destruction policy, a certificate of destruction must be issued and provided to the Sponsor. A copy of the institution's drug disposal policy and certificate of destruction, if applicable, should be maintained or referenced in the Investigator Site File (ISF).

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

7.1.1.1 Screening Procedures

Subjects must be admitted to the hospital/site or in the process of being admitted at the time of screening. During screening, the following will be performed:

- Assessment of BP including the following:
  - BPDAI
  - BPDAI-VAS
- Medical history
- Demographics
- Review of medications, including steroids
- Vital signs
- Physical examination
- 12-Lead ECG
- Blood and urine collection for laboratory evaluations
- Skin biopsy for confirmation of BP by immunohistochemistry (IHC) (note: histological confirmation of BP is not required for initial eligibility)

Detailed descriptions of each of these procedures are provided in the sections immediately following. Information pertaining to all study activities performed during screening, and the sequence of events, is provided in Section 7.3.1.

7.1.1.1.1 Assessment of Bullous Pemphigoid/Steroid Dose Determination

At screening and baseline, subjects will be assessed for clinical diagnosis of BP and severity of disease will be assessed. Only subjects with mild (BPDAI ≤ 10 OR < 10% affected body surface) or moderate (BPDAI > 10 and < 55 OR 10%-30% affected body surface) disease are eligible for participation. Investigators will also obtain skin biopsy and draw blood samples to test for antibodies for subsequent histologic confirmation of BP per the S2k Guideline for the Diagnosis of Pemphigus Vulgaris/Foliaceus and Bullous Pemphigoid (Schmidt 2015). Histological confirmation of BP is not required prior to randomization, but is required prior to participation in follow-on open-label, 12-month treatment study.

The investigator will also select the initial dose and frequency of topical MFC, per disease severity and investigator assessment. The guidance for initial frequency of MFC application at baseline is once per day application for mild BP subjects, and twice daily (b.i.d.) application for moderate BP subjects. The dose and frequency selected at baseline will be the same dose used throughout the study, unless rescue therapy is required. Initial whole-body topical steroid therapy (clobetasol propionate class) prior to study entry is allowed for up to and including 7 days prior to enrollment. Additionally, subjects who have received a single high-dose of steroids (intravenous or oral) 14 days or more before the administration of the first dose of study drug are eligible for enrollment. There is no restriction for the number of days of prior lesion-only topical steroid treatment. Total prior steroid dose will be captured in the eCRFs.

7.1.1.1.2 Medical History

The investigator or designee will obtain a detailed medical history through interview with the subject during screening. The medical history should focus on recent history, with an emphasis on the history of symptoms related to BP. Additionally, the medical history should include:

- Current/past illnesses and conditions
- Current symptoms of any active medical condition
- Surgeries and procedures
- Allergies
- Social history (e.g., exercise, smoking, alcohol, illegal substances) and current living situation
- Cause of parental death (if not living)

7.1.1.1.3 Demographics

Demographic information such as the subject's education level, ethnicity, and race will be collected by interview with the subject at screening.

7.1.1.1.4 Review of Medications

The investigator or designee should obtain a complete list of the subject's current medications, including over-the-counter drugs, herbal supplements and/or vitamins, as well as those taken by the subject in the past 12 months. Assessment of eligibility should include a review of permitted and prohibited medications. Any additions, discontinuation, or dosage changes in medication during the course of the study will be recorded.

7.1.1.1.5 Vital Signs

Vital signs will include seated systolic and diastolic blood pressure (mm Hg), heart rate (beats per minute [bpm]), respiration rate (breaths per minute), and body temperature. Vital signs will be measured after the subject has been seated for 5 minutes.

7.1.1.1.6 Physical Examination
A full physical examination will be performed to assess the following organ systems: skin, ENT (ears, nose, and throat), head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, neurologic and lymphatic systems. Height will be measured at screening and weight will be monitored during the trial.

7.1.1.1.7 12-Lead ECG
Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph. A 12-lead ECG will be performed after the subject has rested quietly for at least 5 minutes in a supine position. In some cases, it may be appropriate to repeat abnormal ECGs to rule out technical factors contributing to ECG artifacts or abnormality. It is important that leads are placed in the same positions each time for consistency. The overall conclusion with the interpretation of the ECGs will be recorded on the appropriate CRF. The interpretation of the ECGs will be recorded as normal, abnormal but not clinically significant, or abnormal and clinically significant. QTc intervals will be calculated using Fridericia's correction formula and entered into the CRF.

7.1.1.1.8 Screening Biological Specimen Collection
For screening evaluation, blood will be drawn by a qualified medical provider, and urine specimens will also be collected (also see Section 7.1.1.2.6 and Schedule of Events).

7.1.1.1.9 Skin Biopsy
For disease confirmation, a skin biopsy will be obtained for IHC. Instructions on biopsy sampling and processing through a separate Laboratory Manual.

7.1.1.2 Procedures to Assess Safety
Subjects enrolled in the trial will be monitored closely to assess safety and tolerability of the study agent and intervention. Study specific procedures that will be used for this purpose are summarized below. Information regarding the timing and frequency of these procedures is provided in Section 7.3.

- Review of AEs
- Review of medications
- Review of daily SOC disease assessments
- Vital signs
- Targeted physical examinations and weight
- EOT (or Withdrawal) physical examination
- Blood and urine collection for laboratory evaluations

7.1.1.2.1 Review of Adverse Events
AEs will be reviewed, documented, and reported as required at each visit, beginning at screening. For definitions, guidance, and additional information regarding AEs, refer to Section 8.

7.1.1.2.2 Review of Medications
The investigator or designee should review the subject's current medications, including over-the-counter drugs, herbal supplements and/or vitamins, as well as those taken by the subject since the last visit. Changes to the subject's list of medications should be reviewed and recorded. Review of medications should occur at every visit.

7.1.1.2.3 Review of Daily Standard of Care Disease Assessments

Per SOC, disease assessment will be performed on a daily basis to assess safety and disease control. At each schedule study visit, SOC disease assessments will be reviewed and documented in the CRF per the Schedule of Events. If disease control is indicated at any point during the study, the EOT visit should be performed and the date of disease control will be recorded in the CRF.

7.1.1.2.4 Vital Signs

Refer to Section 7.1.1.1.5 for a description of vital signs and weight measurements. Vital signs will be collected at every visit (see the Schedule of Events).

7.1.1.2.5 Targeted Physical Examination

During the study period, a targeted physical examination, including auscultation of the heart and body weight, will be performed per the Schedule of Events.

7.1.1.2.6 Blood and Urine Collection for Laboratory Evaluations

Blood samples and urine will be collected according to the Schedule of Events. All safety laboratory measurements will be performed by a Clinical Laboratory Improvement Amendments-certified laboratory. Investigators will receive guidance and instructions on laboratory sampling and processing through a separate Laboratory Manual provided by the central laboratory.

Laboratory tests collected will include the following per the Schedule of Events:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential [redacted], platelets
- Chemistry: glucose, sodium, potassium, calcium, inorganic phosphate, chloride, bicarbonate, magnesium, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase, direct and indirect bilirubin, blood urea nitrogen, total protein, albumin
- Serology: HBV, HCV, HIV, and QuantiFERON testing for TB.
- Coagulation: activated partial thromboplastin time, prothrombin time/international normalized ratio (INR)
- Urinalysis: pH, glucose, erythrocytes, leukocytes, protein, nitrite
- Serum Proteins (exploratory): [redacted]
- Blister fluid proteins: ECP, IL-5, IL-6 (only at screening and Week 1)
- Anti-BP180 Antibodies: Anti-BP180 IgG serum levels
- Pregnancy test in WOCBP (only at screening and EOT)

Additional laboratory parameters may be reported, as detailed in the laboratory manual. Glomerular filtration rate (GFR) will be estimated by the MDRD formula utilizing serum creatinine (see Section 17.5).

Serology will only be conducted at screening. Potential subjects with positive screening test result for HBV, HCV, or HIV will not be eligible for study participation. Any subjects with active signs of TB will be excluded from the study. All subjects will be tested for TB at screening. Subjects meeting all other eligibility requirements will be randomized for study participation while awaiting TB tests results (QuantiFERON) which may require several days for processing. If the TB test results are positive, the subject will be discontinued from the study.

The investigator is responsible for determining and documenting if out of range laboratory values are clinically significant. All clinically significant values will be recorded as AEs in the eCRF and followed until

resolution. Once resolved, the appropriate eCRF page(s) will be updated.

Samples may be used for re-testing, further evaluation of an AE and/or assessment, and follow up of other exploratory endpoints. Samples that remain after study testing is complete will be stored in the event additional testing (e.g., further evaluation of an AE or assessment of effect) is required. Samples will be stored in a deidentified coded form. Subjects can opt out of storage of samples for future analysis.

7.1.1.3 Procedures to Assess Efficacy

The assessment of disease control (≤ 3 new blisters/day and healing of existing blisters) following topical steroid treatment with adjunctive AKST4290 will be performed. During the treatment period, daily SOC assessments of disease will be performed between scheduled study visits and will be reviewed by the site staff and recorded in the study source documentation and in the clinical study database, as available. Time to disease control will be assessed and compared across treatment groups. Change in BPDAI score will be assessed following treatment until disease control. Change in pruritus as evaluated by the BPDAI-VAS will be assessed until disease control. The steroid regimen and total dose used during the study period will be evaluated. Change in skin biopsy [redacted] levels and change in blister fluid protein levels will also be evaluated. Change in cognition (as assessed by MoCA) and change in quality of life (as a by DLQI) will be evaluated.

Descriptions of each assessment are provided below.

7.1.1.3.1 Bullous Pemphigoid Disease Area Index Tool

The BPDAI tool (Murrell 2012) computes 2 scores: total BPDAI activity and total BPDAI damage. The total BPDAI activity score is the arithmetic sum of the 3 subcomponents – cutaneous blisters/erosions, cutaneous urticaria/erythema, and mucosal blisters/erosions. The total BPDAI damage score is the arithmetic sum of the items rated regionally for damage caused by more permanent features such as post-inflammatory hyperpigmentation, scarring, and other. The BPDAI quantifies lesion number and size thresholds, and lesions are rated based on the regions affected. Additional weighting is given to areas of the skin primarily affected in BP, such as the limbs, and less emphasis to scalp and face, to better differentiate clinical response in BP. Scores can range from 0 to 360 for BPDAI total activity (maximum 240 for total skin activity and 120 for mucosal activity), and 0 to 12 for BPDAI damage, with higher scores indicating greater disease activity or damage. An example of the BPDAI tool is provided in Section 17.1.

7.1.1.3.2 Bullous Pemphigoid Disease Area Index Tool Visual Analog Scale (BPDAI-VAS)

Pruritus, a major symptom of the onset or recurrence of BP, is measured using a separate subjective component of the BPDAI (Murrell 2012). The intensity of pruritus is assessed using a visual analog scale to answer the question, ‘‘How severe is your itching today?’’ and the subject marks an ‘‘x’’ on the 0- to 10-cm line where 0 is no itch and 10 is maximal itching. The degree of itching is measured as the distance in centimeters from 0, out of 10. This is repeated for the severity overall of itching in the past week and month. A total score is calculated from this out of 30. An example of the BPDAI-VAS is provided in Section 17.2.

7.1.1.3.3 Dermatology Life Quality Index

The DLQI is a 10 question tool designed to assess the impact of skin diseases on a subject’s quality of life (Finley 1994). The questionnaire was structured with each question having 4 alternative responses: 'not at all', 'a little', 'a lot' or 'very much' with corresponding scores of 0, 1, 2 and 3, respectively. The answer 'not relevant', is scored as '0'. The DLQI is calculated by summing the score of each question, resulting in a maximum of 30 and minimum of 0. The higher the score, the greater the impairment of quality of life. The DLQI can also be expressed as a percentage of the maximum possible score of 30. An example of the DLQI is provided in Section 17.3.

7.1.1.3.4 Skin Biopsy and Blister Fluid Assessments

A skin biopsy will be required to confirm the histological diagnosis of BP by IHC and to assess skin [redacted] levels. Skin biopsies will be collected at screening and will be requested at disease control (optional). Skin biopsies will be performed only if blisters are present and at the margin of the blister.

Blister fluid protein levels [redacted] will be assessed at baseline and Week 1. Blister fluid will be collected directly from the blisters that have not been drained and/or ruptured by using a sterile hypodermic needle and syringe. The blister fluid will be aliquoted and stored frozen at the site until shipped to the lab. Blister fluid assessment will not be performed if there is no detectable fluid or active blister present at time of scheduled assessment.

7.1.1.3.5 Montreal Cognitive Assessment

The MoCA has been designed as a rapid screening instrument to detect mild cognitive impairment (MCI) (Nasreddine 2005). It is a commonly used screening test easily administered by nonspecialist staff. It assesses the domains of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points with a score of 26 or more considered normal. Time to administer the MoCA is approximately 15 minutes. The total possible score is 30 points. An example of this tool is provided in Section 17.4.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Biological samples (e.g. whole blood, serum, plasma, urine) will be collected for laboratory evaluations in accordance with the Schedule of Events. Refer to the study's Laboratory Manual for complete information regarding all laboratory evaluations to be performed, sample collection procedures, and related requirements.

The investigator is responsible for determining and documenting whether out of range laboratory values are clinically significant. All clinically significant values will be recorded as AEs in the CRF and followed until determined to be stable or resolved, unless the subject is lost to follow up. Once resolved, the appropriate CRF page(s) will be updated.

7.2.2 OTHER TESTS OR PROCEDURES

7.2.2.1 Study Agent Concentration and Pharmacokinetics

Plasma concentration measurements of AKST4290 and its major metabolites will be assessed to determine systemic exposure to the study agent. For required and optional sampling time points and further details, please refer to Section 17.8.1.

7.2.2.1.1 Pharmacokinetic Endpoints

As far as feasible, the following PK parameter will be summarized descriptively:

- $C_{pre,ss,N}$ Pre-dose concentration of AKST4290 in plasma immediately before administration of the Nth dose

7.2.2.1.2 Methods of Sample Collections

Details regarding collection, sample handling, and shipment instructions will be provided in the Laboratory Manual.

7.2.2.1.3 Analytical Determinations

Concentrations of AKST4290 and metabolites (if feasible) in plasma samples will be determined by a validated high-performance liquid chromatography, tandem mass spectrometry assay. Leftover samples will be used for exploratory biomarker assessment (see Section 7.2.2.2).

7.2.2.2 Plasma Biomarkers

Measurement of biomarkers is exploratory. Investigations might include mechanism related markers [redacted] which could identify subsets of subjects who may benefit most from the treatment with AKST4290. Other disease related markers may include inflammatory mediators or markers of oxidative stress. Biomarkers will be measured in plasma samples to investigate any change in response to treatment. After completion of the study, leftover samples may be used for further methodological and/or other, non-genetic biomarker investigations either by the Sponsor, or designee. The study samples will be discarded after completion of the additional investigations, but not later than 3 years after the final study report has been archived. The exploratory biomarker measurements will be conducted either at the Sponsor's labs or at external Contract Research Organizations (CROs) using appropriate methodology (e.g., immunoassays, multiplex technology). Details regarding collection, sample handling, and shipment instructions will be provided in the Laboratory Manual.

7.2.2.3 Serum Protein Evaluation

Evaluation of serum proteins is exploratory. Details regarding collection, sample handling, and shipment instructions will be provided in the Laboratory Manual.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

7.3.1.1 Visit 1, Screening Visit (Day -3 to 0)

The following procedures will be performed during the Screening Visit, as per the Schedule of Events:

- Signing of all applicable informed consents must be completed prior to any study-related assessments
- Verify clinical diagnosis of BP and perform specified assessments:
  - BPDAI (see Section 7.1.1.3.1)
  - BPDAI-VAS (see Section 7.1.1.3.2)
  - Skin biopsy (see Section 7.1.1.3.4)
- Obtain medical history, including medical records and test results to support BP diagnosis, if available
- Collect demographic information
- Review subject's current and prior medications
- Review prohibited medications and substances with the subject
- Collect vital signs
- Collect clinical laboratory tests (see Section 7.1.1.2.6)
  - Hematology
  - Chemistry
  - Serology
  - Coagulation
  - Urinalysis
  - Serum Proteins

  - Anti-BP180 antibodies
  - Pregnancy test in WOCBP
- Perform full physical examination (including height)
- Perform 12-lead ECG
- Verify the subject fulfills all the inclusion criteria and none of the exclusion criteria
- AE reporting and evaluation

7.3.2 BASELINE

7.3.2.1 Visit 2, Baseline (Day 1)

To be enrolled, the subjects must be inpatient and remain inpatient until disease control/EOT. All baseline procedures will be performed following admission, unless already admitted.

- Following confirmation of eligibility, subject will be randomized to AKST4290 or placebo
- Perform Specified assessments:
  - BPDAI (see Section 7.1.1.3.1)
  - BPDAI-VAS (see Section 7.1.1.3.2)
  - DLQI (see Section 7.1.1.3.3)
  - MoCA (see Section 7.1.1.3.5)
  - Topical steroid MFC dose and frequency assignment
- Review concomitant medications
- AE reporting and evaluation
- Perform targeted physical examination
- Collect vital signs
- Collect clinical laboratory tests (see Section 7.1.1.2.6)
  - Hematology
  - Chemistry
  - Coagulation
  - Urinalysis
  - Serum Proteins
  - Anti-BP180 antibodies
  - Blister fluid
- PK (required and optional) samples and biomarker samples (see Section 7.2.2.1 and Section 7.2.2.2)
- Study agent and topical steroid dispensing/administration
- Study agent accountability

7.3.3 TREATMENT

The examinations of each visit are specified in Section 15. In addition, please see Section 17.8 for detailed information regarding PK evaluations. Weekly study visits will be performed up until the time of disease control/EOT. Important note: To ensure accuracy of PK sampling, study drug (AKST4290/placebo) should be administered during the study visit to enable appropriate timing of PK sample acquisition.

7.3.3.1 Visit 3/Week 1 (Day 7 ± 2)

- Collect PK samples (see Section 7.2.2.1) (pre-dose)
- Perform specified assessments:
  - BPDAI (see Section 7.1.1.3.1)

  - BPDAI-VAS (see Section 7.1.1.3.2)
  - Assessment of disease control (see Section 7.1.1.3)
  - Assessment of need for rescue therapy
- Perform targeted physical examination
- Collect vital signs
- Collect clinical laboratory tests (see Section 7.1.1.2.6)
  - Hematology
  - Chemistry
  - Coagulation
  - Urinalysis
  - Serum Proteins
  - Anti-BP180 antibodies
  - Blister fluid
- Review concomitant medications
- AE reporting and evaluation
- Study agent and topical steroid dispensing/administration
- Study agent accountability
- Review and document daily SOC disease assessments performed since the previous study visit, as available

7.3.3.2 Visit 4/Week 2 (Day 14 ± 2)

The following assessments will be performed at study Week 2, and until disease control, regardless of rescue therapy administration.

- Collect PK samples (see Section 7.2.2.1) (pre-dose)
- Perform specified assessments:
  - BPDAI (see Section 7.1.1.3.1)
  - BPDAI-VAS (see Section 7.1.1.3.2)
  - Assessment of disease control (see Section 7.1.1.3)
  - Assessment of need for rescue therapy
- Perform targeted physical examination
- Collect vital signs
- Collect clinical laboratory tests (see Section 7.1.1.2.6)
  - Hematology
  - Chemistry
  - Coagulation
  - Urinalysis
  - Serum Proteins
  - Anti-BP180 antibodies
- Review concomitant medications
- AE reporting and evaluation
- Study agent and topical steroid dispensing/administration
- Study agent accountability
- Review and document daily SOC disease assessments performed since the previous study visit, as available

7.3.3.3 Unscheduled Visits

Unscheduled visits may be conducted in between scheduled study visits for assessment of AEs, concomitant

medications, or disease control, but must not take the place of a scheduled weekly visit or EOT visit.

- Review concomitant medications
- AE reporting and evaluation
- Assessment of disease control (see Section 7.1.1.3)
- Assessment of need for rescue therapy
- Topical steroid assessment
- Study agent and topical steroid dispensing/administration
- Study agent accountability

7.3.3.4 End of Treatment Visit/Visit 5/Week 3 (Day 21 ± 2)

The EOT visit should be conducted at any time during the study once the subject has achieved disease control, as assessed by the investigator or at the time of withdrawal (see Section 5.4.1). This visit can be performed outside the weekly visit and in place of the next scheduled visit. If a previously completed weekly visit was performed within 2 days of the EOT visit, then only the procedures unique to the EOT visit must be performed.

Subjects that do not reach disease control by treatment Visit 5/Week 3 (Day 21 ± 2) (see Section 5.4.1) will be discontinued and required to perform all EOT procedures.

- Collect PK and biomarker samples (see Section 17.8.1)
- Perform specified assessments:
  - BPDAI (see Section 7.1.1.3.1)
  - BPDAI-VAS (see Section 7.1.1.3.2)
  - DLQI (see Section 7.1.1.3.3)
  - Assessment of disease control (see Section 7.1.1.3)
  - Skin biopsy (optional) (see Section 7.1.1.3.4)
  - MoCA (see Section 7.1.1.3.5)
- Collect clinical laboratory tests (see Section 7.1.1.2.6)
  - Hematology
  - Chemistry
  - Coagulation
  - Urinalysis
  - Serum Proteins
  - Anti-BP180 antibodies
  - Pregnancy test in WOCBP
- Perform full physical examination
- Perform 12-lead ECG
- Collect vital signs
- Review concomitant medications
- AE reporting and evaluation
- Study agent and topical steroid dispensing/administration
- Study agent accountability
- Review and document daily SOC disease assessments performed since the previous study visit, as available
- Documentation of confirmation of histological BP diagnosis per the S2k Guideline for the Diagnosis of Pemphigus Vulgaris/Foliaceus and Bullous Pemphigoid (Schmidt 2015) for potential participation in the follow-on open-label, 12-month treatment study

7.3.4 FOLLOW-UP

7.3.4.1 Fourteen (14)-Day Safety Follow-Up: (Day 14 ± 3) Following Discontinuation of Study Agent

All subjects will be contacted via telephone 14 days ±3 days after EOT visit to assess safety. A review of all ongoing AEs and concomitant medications will be performed.

7.3.5 EARLY WITHDRAWAL

In cases of early withdrawal, if a subject has received at least 1 dose (400 mg) of AKST4290 or placebo, the site should try to perform all assessments scheduled at the EOT visit unless the subject has withdrawn consent (also see Section 5.4.1).

7.3.6 TRIAL COMPLETION AND END OF TRIAL

Trial completion is defined as the end of participation for each enrolled subject. A Safety Follow-up call will be performed (see Section 7.3.4.1) and trial completion will occur after the follow-up call. The Safety Follow-up call should occur 14 ± 3 days following the EOT visit, independent of the actual study day number. If a subject has withdrawn consent, trial completion will be at the time of consent withdrawal and no further procedures will be performed (also see the Schematic of Study Design for additional information).

The end of the trial will occur following the last subject's last visit. The approximate duration to conduct the trial to support full recruitment is approximately 15 months.

7.3.7 SCHEDULE OF EVENTS TABLE

A tabular summary of all procedures that will be accomplished at each study visit can be found in Section 15.

7.4 CONCOMITANT MEDICATIONS

All prescription, over-the-counter, and non-prescription medications (including herbal therapies and supplements) must be documented in the source documents and electronic CRFs (eCRFs). All subjects should be maintained on the same medications at the same dosage and administration throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. Any changes in medications should be documented in the eCRF with reason for change (e.g., AE).

[redacted]

[redacted]

8 ASSESSMENT OF SAFETY

Assessment of safety will be conducted by blinded study personnel except in extraordinary circumstances where knowledge of whether AKST4290 or placebo was received by a subject is essential. Any instances of unblinding will be managed as indicated in Section 10.6.3.

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS

Per 21 Code of Federal Regulations (CFR) 312.32(a), an AE is any untoward (unfavorable, harmful, or pathologic) medical occurrence in a subject administered a pharmaceutical (investigational) product even if the event does not necessarily have a causal relationship with this treatment.

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

An AE does include any:

- Exacerbation of a pre-existing illness.
- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study (unless it can be demonstrated by medical record review that the onset of the event preceded the date/time of Informed Consent).
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Symptoms associated with disease not previously reported by the subject.
- Untoward medical occurrences considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments (e.g., change on physical examination, ECG findings), if they represent a clinically significant finding, that were not present at baseline or worsened during the course of the study.

- Laboratory test abnormalities, if they represent a clinically significant finding, symptomatic or not, which were not present at baseline or worsened during the course of the study.

An AE DOES NOT include a/an:

- Elective medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion).
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions).
- Overdose of either study drug or concurrent medication without any signs or symptoms.
- Pregnancy.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Note: if either the investigator or the Sponsor believes that the event is serious, the event must be considered serious and evaluated for expedited reporting.

Note: the terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE. “Serious” is a regulatory definition.
An SAE (experience) or reaction is an untoward medical occurrence that, at any dose, fulfills one or more of the following criteria:

a. Results in death (i.e., the AE actually causes or leads to death).
b. Is life threatening.
    - An AE is considered “life threatening” if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death; it does not include AEs which, had it occurred in a more severe form, might have caused death.
c. Results in inpatient hospitalization or prolongation of existing hospitalization.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE; hospitalization for participating in this study is not considered an AE.
    - Complications that occur during hospitalization are AEs; if a complication prolongs hospitalization, the event is an SAE.
    - “Inpatient” hospitalization means the subject has been formally admitted to a hospital for medical reasons that may or may not be overnight; it does not include presentation at a casualty or emergency room unless the event meets the definition of an Important Medical Event (in the opinion of the investigator or Sponsor).
d. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
    - The term ‘disability’ means a substantial disruption of a person’s ability to conduct normal life functions; this definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Results in a congenital anomaly in the offspring of a subject who received drug.

f. Results in an Important Medical Event. Important medical events are events that may not result in death, be life threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition; examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
    - Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

Each AE or suspected adverse reaction must be assessed for its seriousness and severity. Severity will be assessed by the investigator or designee using the following definitions:

SEVERITY	DEFINITION
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE	Incapacitating with inability to work or do usual activity

Outcome will be assessed using the following categories: recovered/resolved, not recovered/ not resolved, recovered/resolved with sequelae, fatal, or unknown.

8.2.2 RELATIONSHIP TO STUDY AGENT

Investigators are required to assess the causal relationship (i.e., whether there is reasonable possibility that the study drug caused the event) using the following definitions:

- Unrelated: another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the study agent; or a causal relationship is considered biologically implausible.
- Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the study agent, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the study agent is one or several biologically plausible AE causes.
- Definitely Related: The AE is clearly related to use of the study agent.

If either the investigator or the Sponsor considers the event related, then the event will be considered related for reporting purposes.

8.2.3 EXPECTEDNESS

The Sponsor or designee will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the Reference Safety Information described in the Investigator's Brochure.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected" as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's 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. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme inhibitor class and angioedema would be described in the Investigator's Brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes.

This definition of "unexpected" relies entirely on the Reference Safety Information in the Investigator's Brochure as the basis for determining if newly acquired information generated from clinical trials or reported from other sources is unexpected. The suspected adverse reactions listed in the Investigator's Brochure (i.e., "expected") are those observed with the investigational drug and for which a causal relationship between the event and the drug is suspected or confirmed.

Sponsor assessment of expectedness and relationship to study drug/causality will determine the need for expedited reporting of AEs.

8.3 TIME PERIOD/FREQUENCY FOR EVENT ASSESSMENT/FOLLOW-UP

At every clinic visit, subjects who have given informed consent will be assessed for AEs and SAEs. After the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking a non-leading question such as the following:

1. "How are you feeling?"
2. "Have you had any changes since your last assessment/visit?"
3. "Have you taken any new medicines since your last assessment/visit?"

8.3.1 POST-STUDY AE AND SAE

The investigator is not obligated to actively seek SAE information in former study subjects, but the investigator is encouraged to notify Alkahest, Inc. or their designee of any AE or SAE occurring within 30 days after a subject completes the study (or has their last visit) that the investigator judges may be reasonably related to study treatment or study participation.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All subjects who have given informed consent will be evaluated for AEs. All AEs that occur after the time of treatment with the study drug will be considered Treatment Emergent AEs. Subjects with Treatment Emergent AEs must be followed until the AE is resolved or is stable, unless the subject is lost to follow up.

Each AE or suspected adverse reaction must be described as follows: the date of onset, date of resolution, severity (mild, moderate, severe), frequency of the event (single episode, intermittent, continuous), action taken with study treatment (no action taken, treatment held, treatment discontinued), outcome, causality*

(unrelated, possibly related, definitely related), and seriousness criteria. Each AE or suspected adverse reaction must be recorded separately.

***Note**: Causality assessment will be made only when the AE occurs after the subject has initiated at least 1 dose of the study agent. An AE occurring before the subject's exposure to study agent will always be labeled as "unrelated".

Any AE occurring during the study must be documented in the subject's medical records and as an AE in the CRF. Any SAE occurring during the study must be documented in the subject's medical records and as an SAE in the CRF.

A separate set of SAE pages should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE page.

The investigator should attempt to establish a diagnosis of the event (that meets the definition of an AE or SAE) based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs or symptoms. The diagnosis will become the basis for the verbatim term as reported by the investigator. If no diagnosis is known and clinical signs and symptoms are not present, the abnormal finding should be recorded.

In addition to the investigator's own description of the AE, each AE will be encoded according to the MedDRA.

The investigator will take all appropriate and necessary therapeutic measures required for resolution of the AE. Any medication necessary for the treatment of an AE must be recorded on the concomitant medication CRF.

The SAE pages of the CRF should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to the study CRO. It is very important that the investigator provide his/her assessment of causality to study drug as well as an applicable diagnosis at the time of the initial SAE report.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

8.4.2.1 Timeframes for Reporting Serious Adverse Events

Under 21 CFR 312.32(c), the Sponsor is required to notify FDA, EMA, and all participating investigators in a safety report of potentially serious risks from clinical trials (i.e., Suspected Unexpected Serious Adverse Reactions [SUSARS]), as soon as possible after the Sponsor receives the safety information and determines that the information qualifies for reporting:

- No later than 7 calendar days for events that are life threatening (in the opinion of the investigator or the Sponsor) or that involve Death as an outcome.
- No later than 15 calendar days for all other SUSARS.

As such, prompt notification of the Sponsor, and/or the Sponsor's representatives, and promptly providing requested follow up information regarding SAEs is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. Investigators are responsible for reporting SAEs according to the following timeframes:

- All SAEs occurring during the study should be reported immediately.

- The SAE Report Form and relevant source documents, if applicable, must be completed and emailed to the drug safety representative within 24 hours of observation or learning of the event. NOTE: Contact information for the drug safety representative will be provided on the SAE forms and in the ISF.
- Follow up information must be sent to the CRO within 24 hours of receipt of information by the investigational site.

SAEs will be followed until resolution, the condition stabilizes, the event is otherwise explained or is judged by the investigator to be no longer clinically significant, or until the subject is lost to follow up.

8.4.2.2 SAE Information to Report

All information available regarding an SAE must be submitted in the timeframes indicated. At a minimum, SAE reports must contain the subject ID, the SAE verbatim term, onset date, relationship to study drug/causality, and a brief narrative of the event. Please note that **relationship to study drug/causality as well as the reported verbatim term are very important** and should be included in the initial report as it may impact expedited regulatory reporting requirements for the event. The date of SAE discovery by the site staff should be documented in the source documents.

The investigator must record all relevant information regarding an AE/SAE in the applicable sections of the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when copies of medical records for certain cases are requested by the CRO and/or the Sponsor. If medical records are submitted to the CRO then all subject personal identifiers must be completely and thoroughly redacted prior to submission.

A blank SAE Report Form and instructions for SAE reporting will be provided to the site and will be maintained in the investigator's study file. The SAE Report Form must be completed and emailed to the drug safety representative according to the timeframes specified in Section 8.4.2.1. The SAE Report Form should include copies of relevant source documents, if applicable. Reconciliation of any discrepancy noted during monitoring and amending the eCRF is required.

If new information about an SAE is received or corrections to data are needed, the investigator should complete a new SAE Report Form and check the "follow up" box on the form. This follow up SAE Report Form should be submitted within 24 hours of learning of the information, especially if the new information concerns seriousness, relatedness, or the event term of an AE.

Sites acting under their local IRB/EC should submit all applicable events, unanticipated problems, and safety reports to the site's local IRB/EC, if applicable. All safety reporting deviations should also be submitted to their local IRB/EC, if applicable.

[redacted]

8.4.4 REPORTING OF PREGNANCY

While pregnancy itself is not considered an AE, pregnancy occurring in a clinical study must be followed to collect information regarding the experiences of gestation and pregnancy with study agent exposure. The investigator must report any pregnancy that occurs in a female study subject or female partner of a male subject subsequent to first exposure to the study agent until the EOT visit, or 3 months following a subject's last dose in the event of early withdrawal. All pregnancies will be reported to the IRB/IEC, Sponsor, and CRO. In the event of a pregnancy, treatment will be discontinued, and the subject will undergo continued safety follow up through pregnancy outcome. The study blind can be broken for safety reasons if the information is required for the management of pregnancy. Any noted intentional or unintentional breaking of the blind should be reported to the Sponsor's Study Team Lead and Quality Group (see Section 10.6.3).

Any pregnancy must be followed by the investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect(s) observed in the child must be reported as an SAE within 24 hours of the investigator or study personnel's first knowledge.

8.5 STUDY HALTING RULES

If any of the following safety events occur, a Safety Evaluation Meeting (defined below) will be triggered:

- Three or more SAEs in the same system organ class that are assessed as possibly or definitely related to the study agent by the investigator and confirmed as such by the Sponsor (see Section 8.2.2).
- Within or between any of the dosing groups: an overall pattern of symptomatic, clinical, or laboratory events associated with the study agent that the Sponsor's Program Physician or designee consider a serious potential safety concern (e.g., suspicious overall pattern).

Events that are more likely related to a specific study procedure, will not be considered "drug related" and will not contribute to the count of definitely related SAEs that would trigger a Safety Evaluation Meeting.

Safety Evaluation Meeting

If safety events of potential concern occur during the trial (i.e., 3 related events in the same system organ class or a suspicious overall pattern, as defined above) a Safety Evaluation Meeting will be triggered, and dosing may be temporarily halted based on the observations. The Sponsor will inform investigators, the FDA and EMA in the event of any temporary halt in dosing at any time during the conduct of the study. The purpose of the meeting is for investigators, the Sponsor, and the CRO medical monitor(s) to discuss and evaluate the safety of the subjects using available aggregated safety data and without compromising study blinding, unless the Sponsor deems unblinding necessary for safety evaluation.

Attendants at the Safety Evaluation Meeting will include the Program Physician of Alkahest (or his/her designee), the CRO medical monitor(s), and available active investigators participating in the trial. After sufficient data review the Sponsor will choose one of the following courses of action:

1. Continue dosing with no change to protocol.

2. Halt dosing in all groups and stop the study.
3. Continue with a modified protocol design and amend the protocol as appropriate.

8.6 SAFETY OVERSIGHT

Safety oversight will be provided by the Sponsor's Program Physician or his or her designee and the CRO's Medical Monitor(s) in concert with the site investigators. There will be no formal Data Safety Monitoring Board established. As needed, Safety Evaluation Meetings will be convened as described in Section 8.5 to monitor the ongoing safety of the study. The Sponsor's Program Physician or designee is the final authority for safety oversight in the study.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and wellbeing of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the study CRO in accordance with the Clinical Monitoring Plan (CMP).
- A mix of onsite and centralized risk-based monitoring will be performed to ensure the safety of clinical subjects and the accuracy and completeness of study data.
- The Sponsor will be provided with copies of monitoring reports per the timelines specified within the CMP.
- Details of clinical site monitoring tasks and scope are documented in the study's CMP. The CMP describes in detail who will conduct monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted by the Sponsor's Quality Assurance (QA) function or Sponsor contracted QA consultants in accordance with a study specific QA Plan to ensure monitoring practices are performed consistently across all participating sites, that monitors are following the CMP and sites conduct the study according to the protocol, GCP, and applicable regulatory requirements.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL DESIGN MODEL AND ANALYTICAL PLANS

A Statistical Analysis Plan (SAP) with analytical details and assumptions will be developed and finalized before database lock and unblinding of the study data.

10.2 STATISTICAL HYPOTHESES

No formal hypothesis testing is planned for this study. Statistical comparisons will be made between placebo and AKST4290.

10.3 ANALYSIS DATASETS

Study data will be analyzed in one of the following analysis sets:

- **Intent-to-Treat (ITT)** set will include all randomized subjects.

- **Safety Evaluable** set will include all randomized subjects who receive at least 1 dose of the study agent (placebo or AKST4290)
- **Per Protocol (PP)** set is a subset of ITT subjects. A detailed description of the reasons for exclusion from the PP population will be included in the SAP.

Subjects will be analyzed in the treatment arm assigned at randomization for the ITT and PP data sets. For the Safety Evaluable data set, subjects will be grouped according to actual treatment received.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Subject disposition and protocol deviations will be summarized descriptively by treatment arm. The comparability between the treatment arms in demographics and baseline characteristics will be assessed. Prior and concomitant medications will also be summarized by treatment arm.

All summary statistics will be descriptive unless noted otherwise. Descriptive summaries will include mean, standard deviation, median, and range for continuous variables and counts, and percentages for categorical variables. Two-sided 95% confidence intervals (CIs) will be provided for the means and percentages as needed. For key outcome measures, the difference between the treatment arm and the 95% CI of the difference will be computed.

Detailed statistical methods will be outlined in the SAP for the study.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

The primary endpoint is the proportion of subjects who achieve disease control (≤ 3 new blisters/day and healing of existing blisters) without the use of rescue therapy. The proportion of subjects who achieve disease control will be compared between treatment groups on a daily and weekly basis (or other appropriate aggregate methodologies).

The analysis of the primary endpoint will be performed based on the ITT and PP data sets.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Secondary Endpoints include:

- Safety as assessed by the incidence, seriousness, and severity of AEs.
- Time to disease control by treatment day/week.
- Time to rescue therapy by treatment day/week.
- Change from baseline in BPDAI score by treatment week and at disease control.
- Change from baseline in pruritus as evaluated by the BPDAI-VAS by treatment week and at disease control.
- Change from baseline in skin biopsy [redacted] levels at disease control.
- Evaluation of total cumulative steroid exposure at baseline, by treatment week, and at disease control.
- Evaluation of maximum daily steroid dose at baseline, by treatment week, and at disease control.

Safety data will be analyzed using the Safety Evaluable set. Treatment emergent AEs will be summarized by

MedDRA coding terms, and separate tabulations will be produced for treatment-related AEs, SAEs, and discontinuations due to AEs.

Secondary efficacy measures will be analyzed using the ITT data set.

Time to disease control will be compared between treatment groups by treatment day and week using a Kaplan-Meier curve.

Time to rescue therapy will be compared between treatment groups by treatment day and week using a Kaplan-Meier curve.

Change from baseline in BPDAI and BPDAI-VAS scores by treatment week until disease control will be compared between treatment groups using Student's t-test. Missing values will not be estimated.

Change from baseline in skin biopsy [redacted] levels at baseline (i.e., screening) and at disease control will be compared between treatment groups using Student's t-test.

Evaluation of total cumulative steroid exposure at baseline, by treatment week and at disease control will be summarized between treatment groups. A similar summarization for the maximum daily steroid dose until disease control will also be done.

Additional safety data will be analyzed using the safety evaluable data set. Vital sign data and findings from physical examinations will be tabulated for changes over time during the study period. Laboratory parameters will be summarized for changes across the study period using descriptive statistics.

10.4.4 PLANNED INTERIM ANALYSES

There is no planned interim analysis for this study.

10.4.5 MULTIPLE COMPARISON/MULTIPLICITY

No adjustments for multiplicity will be employed.

10.4.6 EXPLORATORY ANALYSES

The exploratory endpoints are:

- Change from baseline in blister fluid protein levels [redacted] at treatment Week 1.
- Change from baseline in blood [redacted] levels by treatment week and at disease control.
- Change from baseline in Anti-BP180 IgG serum levels by treatment week and at disease control.
- Evaluations of CBC, blood chemistry, and serum protein levels [redacted] at baseline, by study week and at disease control.
- Changes in AKST4290 plasma concentrations at various timepoints.
- Change from baseline in cognitive assessments using the MoCA at disease control.
- Change from baseline in quality of life, as assessed by the DLQI at disease control.
- Evaluation of exploratory biomarkers in plasma samples at various timepoints.

Exploratory endpoints will be summarized descriptively. Treatment comparisons may be performed on exploratory endpoints to assist in the generation of hypotheses for future studies.

10.5 SAMPLE SIZE

The sample size of 30 subjects was chosen based on clinical experience.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/RANDOMIZATION/MASKING PROCEDURES

To minimize the potential bias at the time of randomization, the study will be double-blinded and randomized in a 1:1 ratio (AKST4290:placebo). The randomization codes will be generated by a statistician that has no involvement in the study other than generation and maintenance of the randomization codes.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Success of blinding will be assessed based on all occurrences (intentional or unintentional) of unblinding of blinded study subjects or study personnel (e.g., investigators, medical providers, cognitive/motor testing raters, the Sponsor or their representatives). All intentional and unintentional unblinding will be documented and reported to the Sponsor within 24 hours after notification of unblinding.

10.6.3 BREAKING THE STUDY BLIND/SUBJECT CODE

The study blind can only be broken for safety reasons if the information is required for the management of SAEs, severe AEs, or pregnancies. Any noted intentional or unintentional breaking of the blind should be reported to the Sponsor's Study Team Lead and QA function within 24 hours of notification of the unblinding event. If unintentional unblinding occurs during the study, root cause analysis will occur, and corrective and preventative actions will be documented and implemented.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 R2 and regulatory and Institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of regulatory agencies, the IRB/IEC, the Sponsor, or the Sponsor's representatives to examine (and when permitted by applicable law, to copy) clinical records for the purposes of QA reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being attributable, legible, accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

It is not acceptable for the CRF to be the only record of a subject's participation in the study. This is to ensure that anyone who would access the subject's medical record has adequate knowledge that the subject is participating in a clinical trial. Source document templates will be developed for this study.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, ICH E6 R2, 21 CFR part 320, Retention of Bioavailability and Bioequivalence Testing Samples (1993), and the Declaration of Helsinki.

12.2 INSTITUTIONAL REVIEW BOARD

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

Any modifications or amendments to the protocol must also be submitted to the IRB/IEC for approval prior to implementation.

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT FORMS

Consent forms describing in detail the study agent, study procedures, and risks are given to the subject or healthcare power of attorney or equivalent legal representative, and written documentation of informed consent is required prior to any study-related procedures.

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION

It is the responsibility of the investigator or designee to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

Subjects should have the opportunity to discuss the study with their family members or other advisors and the time to consider participation in the trial carefully. The subjects may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The investigator or designee must utilize an IRB/IEC approved consent form that contains the elements required by ICH GCP and applicable regulatory requirements for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person obtaining consent. A copy of the signed consent form will be provided to the subject. By signing the informed consent form, all parties agree they will complete the evaluations required by the study, unless they withdraw

voluntarily or are terminated from the study for any reason.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g., date of screening).

All subjects who provide consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to the study subject. Once a number is assigned to a subject, that number will remain with that study subject and will not be reused.

If an individual's medical chart or results of diagnostic tests performed as part of an individual's regular medical care are going to be used for screening, written informed consent must be obtained prior to review of that information in accordance with Health Insurance Portability and Accountability Act.

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

Subject confidentiality is held in strict trust by the participating investigators, their staff, the Sponsor, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC, or government regulatory agencies may inspect documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. An identification code (i.e., not names) should be recorded on non-local lab samples, requisitions, and any documents submitted to the CRO, Sponsor, and/or IRB/IEC. The investigator must keep a subject log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

12.5 FUTURE USE OF STORED SPECIMENS

With the subject's approval and as approved by local IRB/IECs, de-identified biological samples may be stored at Alkahest, or designee, for future use. These samples could be used for research and to improve treatment. Alkahest will also be provided with a code-link that will allow linking the biological specimens with the specific data from each subject, maintaining the masking of the identity of the study subject. Subjects may choose whether the Sponsor can store and use samples for further research.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research.

When the study is completed, access to study data and/or samples will be managed by Alkahest. In the event Alkahest transfers ownership to another commercial Sponsor, ownership of the samples may be transferred as well.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. The investigator may need to request previous medical records or transfer records, depending on the trial; also, current medical records must be available.

For each subject who receives the study agent or placebo, the eCRF must be completed in a timely manner. The investigator will review and approve the eCRF for each study subject after all data have been entered, the eCRFs have been source document verified, and all queries have been resolved. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

All data collection and recordkeeping procedures must be compliant with applicable ICH GCP.

13.1.1 INVESTIGATOR RESPONSIBILITIES

The investigator will comply with the protocol (which has been approved/given favorable opinion by an IRB/IEC), ICH GCP, and applicable regulatory requirements. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators as listed on Form FDA 1572 or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

13.1.2 STUDY FILES

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories (although not limited to) the following: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the clinical study protocol/amendments, Investigator's Brochure (IB), eCRF, IRB/IEC approval with correspondence, informed consents, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and study specific manuals (e.g., Laboratory Manual).

Subject clinical source documents would include (although are not limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, radiologic imaging, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

13.2 STUDY RECORDS RETENTION

All clinical study documents must be retained by the investigator until 2 years after the study is discontinued and regulatory authorities have been notified. Before the investigator destroys any material related to the clinical study, he/she must obtain approval in writing from the Sponsor.

The investigator should keep a file where the full name and address of the subject and all signed informed consents are included for at least 15 years after completion of the trial. Any original study-related information that permits verification of inclusion and exclusion criteria, including clinical history, a copy of all data collection logs, and documents on the use of the study agent, must be stored for as long a time period as permitted by the center.

Should the investigator wish to move study records to another location, arrangements must be made to store these in sealed containers so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

13.3 PROTOCOL DEVIATIONS

A Protocol Deviation is any noncompliance with the clinical trial protocol or with GCP. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. When deviations occur, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol Deviations will be categorized as either Major or Minor and will be defined in the study specific Protocol Deviation Plan.

Major Protocol Deviations are departures from the approved protocol relating to the conduct of the study which may affect the rights, safety, and/or wellbeing of study participants or the study outcomes or data quality. Major protocol deviations may result in data that are not deemed evaluable for the PP analysis and/or may require that subjects are discontinued from the study. Major protocol deviations are Significant Clinical Issues. *Note: observations categorized as Major may include those situations where there is a pattern of deviation, numerous Minor observations, or other significant deviation.*

Minor Protocol Deviations are departures from the approved protocol relating to the conduct of a study that does not affect the rights, safety, and/or wellbeing of study participants or the study outcomes or data quality. Minor protocol deviations would not generally preclude subject data from the PP analysis population. *Note: persistently missed or incomplete study procedures and/or study evaluations will be considered Major protocol deviations.*

All deviations will be logged and tracked by the site and CRO. Periodic review of Protocol Deviations will serve as an indicator of site performance.

It is the responsibility of the site to use continuous vigilance to identify and report deviations promptly to the study CRO and/or Sponsor. All deviations must be addressed in study source documents. Notification of Protocol Deviations must be sent to the local IRB/IEC per their guidelines. The site investigator/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

13.4 PUBLICATION AND DATA SHARING POLICY

In compliance with The International Committee of Medical Journal Editors clinical trials registration policy and Section 801 of the FDA Amendments Act of 2007, this study will be registered by the Sponsor in ClinicalTrials.gov, a public trials registry which is sponsored by the National Library of Medicine.

Notwithstanding the Sponsor's requirements for registration and data sharing in ClinicalTrials.gov, any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigator(s) and the Sponsor. In the case of multicenter studies, it is mandatory that the first publication be made based on the totality of data obtained from all centers, analyzed as stipulated in the protocol, and presented and interpreted as documented in the final Clinical Study Report. The resulting publication will name investigators according to the policy of the chosen journal. Where it is not permitted for all investigators to be included as authors, the publication will name all investigators within the publication.

Individual investigators may publish data arising from their own subjects. The investigator will provide the Sponsor with copies of written publications (including abstracts and posters) at least 60 days in advance of submission. This review is to permit the Sponsor to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged (including patent protection), to allow adequate input or supplementary information that may not have been available to the investigator, and to allow establishment of co-authorship.

Investigators participating in multicenter studies must agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication unless this has been agreed otherwise by all other investigators and the Sponsor. However, in the event that no publication of the overall results has been submitted after approval of the Clinical Study Report, investigators may publish results of one or more center's subjects to the same review as outlined above. The Sponsor will circulate proposed multicenter publications to all investigators for review.

Data will be reviewed by all participating investigators prior to publication. The study Sponsor will have 90 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

14 FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST POLICY

A separate financial disclosure agreement will be made between each principal investigator and Alkahest, Inc. or its authorized representative before the study agent is shipped. Each investigator will notify Alkahest, Inc. or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed. Alkahest and the study CRO will evaluate any disclosed conflicts of interest and will establish a mechanism for their management.

15 SCHEDULE OF EVENTS

	Screening/ Baseline		Treatment			EOT	Safety Follow-up[6]
Visit Number/Name **Day** **Window (days)** **Week**	**1** **-3 to 0**	**2** **1**	**3[1]** **7** **±2** **1**	**4[2]** **14** **±2** **2**	**Unsched. Visit[4]**	**5[3]/ EOT[5]** **21 or Dis. Control** **±2[3]** **Up to 3**	**Follow-up** **EOT + 14** **±3** **Up to 5**
Informed consent[7]	X						
Demographics	X						
Medical history	X						
Inclusion/exclusion criteria	X	X[8]					
Physical examination	X					X	
Targeted physical examination		X	X	X			
Vital signs	X	X	X	X		X	
12-lead ECG	X					X	
BPDAI	X	X	X	X		X	
BPDAI-VAS	X	X	X	X		X	
Skin biopsy[9]	X					X	
Blister fluid collection		X	X				
Randomization		X					
Topical steroid assessment[10]		X			X		
Administration of study agent		◄———	———	———	———	———►	
Administration of topical steroid therapy		◄———	———	———	———	———►	
Assessment of disease control[11]			X	X	X	X	
Rescue therapy assessment[12]			X	X	X		
MoCA		X				X	
DLQI		X				X	
Laboratory tests[13]	X	X	X	X		X	
Serum protein sample collection	X	X	X	X		X	
Anti-BP180 antibodies sample collection	X	X	X	X		X	
Pregnancy test (in WOCBP only)[14]	X					X	
PK blood sample[15]		X	X	X		X	
Biomarker plasma aliquots[16]		X				X	
Study agent accountability[17]		X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X
Concomitant medications[18]	X	X	X	X	X	X	X
Documentation of confirmation of histological BP diagnosis						X	
Trial completion							X

Notes:

1. At Visit 3/Week 1, all subjects that have not achieved disease control will be assessed for rescue therapy. Rescue therapy is indicated if the subject worsens at any time during the study or fails to improve by the end of Week 1, as assessed by the investigator.
2. After Visit 3/Week 1, subjects will continue to be assessed weekly until disease control/EOT visit.
3. Subjects that do not reach disease control by the end of Week 3/Visit 5 will be discontinued and required to perform all EOT visit procedures. Visit 5 will be the EOT visit for subjects that reach Week 3, and all EOT procedures will be performed. The visit window of ± 2 days is applicable only for subjects that did not yet reach disease control and are being discontinued. Subjects that reach disease control should complete EOT on the same day in which disease control is confirmed.
4. Unscheduled visits can be performed during the study for assessment of AEs, concomitant medications, or disease control, but are not to be conducted in place of a scheduled weekly visit.
5. All EOT visit procedures will be conducted at any point in the study once the subject has achieved disease control. This may be performed outside of the scheduled weekly visits and in place of the next scheduled visit.
6. Trial completion will occur after the completion of the Safety Follow-up call. The Safety Follow-up call should occur 14 days ± 3 days following the EOT visit, independent of the actual study day number.
7. All subjects must sign an informed consent consistent with ICH GCP guidelines prior to any trial related procedures, which includes medication washouts and restrictions.
8. At Visit 2/baseline, confirmation of all inclusion and exclusion will be required prior to enrollment in the study.
9. Skin biopsy at screening is required for subsequent confirmation of diagnosis. Skin biopsies at disease control will be performed only if blisters are present and are optional.
10. At baseline, subjects will be assessed by the investigator to assign the initial dose of topical MFC. The dose selected at baseline will be the same dose used throughout the study, unless the subject requires rescue therapy.
11. Disease control is defined as: ≤ 3 new blisters/day and healing of existing blisters. Assessment of disease control will be performed during scheduled weekly visits by the investigator, as per protocol. Additional assessments performed daily as part of SOC will be reviewed by the site staff at each study visit to monitor disease progression between visits. SOC assessments of disease control will be collected and recorded, as available.
12. Rescue therapy can be provided at any time after enrollment if the subject's clinical condition worsens OR fails to improve after completing 1 week of treatment, as determined by the investigator.
13. Laboratory tests include: hematology; chemistry; serology (HBV, HCV, HIV, and TB); coagulation; urinalysis. Note: serology will only be conducted at screening. See Section 7.1.1.2.6 for more details.
14. Serum pregnancy test will be collected at screening and end of treatment in WOCBP.
15. At Baseline (Visit 2) PK samples will be required to be collected pre-dose and 1 hour (± 15 minutes) after administration of the first dose. Additionally, optional PK samples may be collected at 2 hours (± 30 minutes) after administration of the first dose and 4 hours (± 30 minutes) after administration of the first dose. All PK samples collected during the scheduled weekly visits will be drawn within 1 hour prior to the morning (am) dose. At the EOT visit, the sample will be collected at any time during the visit, and the time of the subject's last dose and the time of the PK sample collection will be recorded.
16. Biomarker aliquots will be taken from the PK samples, as described in the Laboratory Manual.
17. Includes all study agents (AKST4290, MFC, and CPC and /or oral prednisone).
18. [redacted]

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[redacted]

[redacted]

17 APPENDICES

The BP assessments, cognitive assessment and quality of life assessment tools provided in this section and associated information are provided as EXAMPLES ONLY. The actual assessments, related source documents, and instructions for administration and scoring are included in a rater reference manual or equivalent.

17.1 BULLOUS PEMPHIGOID DISEASE AREA INDEX TOOL

BPDAI					
SKIN	ACTIVITY		ACTIVITY		DAMAGE
Anatomical location	Erosions/Blisters	Number of Lesions if <3	Urticaria/ Erythema / Other	Number of Lesions if <3	Pigmentation / Other
	0 absent		0 absent		Absent 0, present 1
	1 1-3 lesions, none > 1 cm diameter		1 1-3 lesions, none >6 cm diameter		
	2 1-3 lesions, at least one > 1 cm diameter		2 1-3 lesions, at least one lesion > 6 cm diameter		
	3 >3 lesions, none > 2 cm diameter		3 >3 lesions, or at least one lesion > 10 cm		
	5 >3 lesions, and at least one >2 cm		5 >3 lesions and at least one lesion > 25 cm		
	10 >3 lesions, and at least one lesion >5 cm diameter or entire area		10 >3 lesions and at least one lesion > 50 cm diameter or entire area		
Head					
Neck					
Chest					
Left arm					
Right arm					
Hands					
Abdomen					
Genitals					
Back/Buttocks					
Left leg					
Right leg					
Feet					
Total skin	/120		/120		
MUCOSA	Erosions/Blisters				
	1 1 lesion				
	2 2-3 lesions				
	5 >3 lesions, or 2 lesions >2cm				
	10 entire area				
Eyes					
Nose					
Buccal mucosa					
Hard palate					
Soft palate					
Upper gingiva					
Lower gingiva					
Tongue					
Floor of Mouth					
Labial Mucosa					
Posterior Pharynx					
Anogenital					
Total Mucosa	/120				

17.2 BULLOUS PEMPHIGOID DISEASE AREA INDEX TOOL - VISUAL ANALOG SCALE

BPDAI PRURITUS COMPONENT - VAS

DATE: ……..

☐**Baseline**
☐**Consolidation phase**
☐**Tapering phase**
☐**Complete remission on minimal therapy**
☐**Complete remission off therapy**
☐ **Beginning Consolidation**
☐**End of Consolidation**
☐**Partial remission on minimal therapy**
☐**Partial remission off therapy**
☐**Flare**

A. How severe has your itching been over the last 24 hours?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

B. How severe has your itching been the past week?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

C. How severe has your itching been in the past month?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

Average INTENSITY SCORE FOR PAST MONTH = (A+B+C) = /30

PRURITIS ASSESSMENT FOR BP PATIENTS WITH IMPAIRED MENTAL FUNCTIONING:

	No evidence of itch (no excoriations)	0
	Mild itch (isolated excoriations up to two body sites)	10
	Moderate itch (excoriations on ≥ 3 body sites, impairment of daily activity	20
	Severe itch (generalized excoriation, sleep impairment)	30
	TOTAL SCORE	/30

17.3 DERMATOLOGY LIFE QUALITY INDEX

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ..... **Date:** .....

Name: ..... **Score:** .....

Address: ..... **Diagnosis:** .....

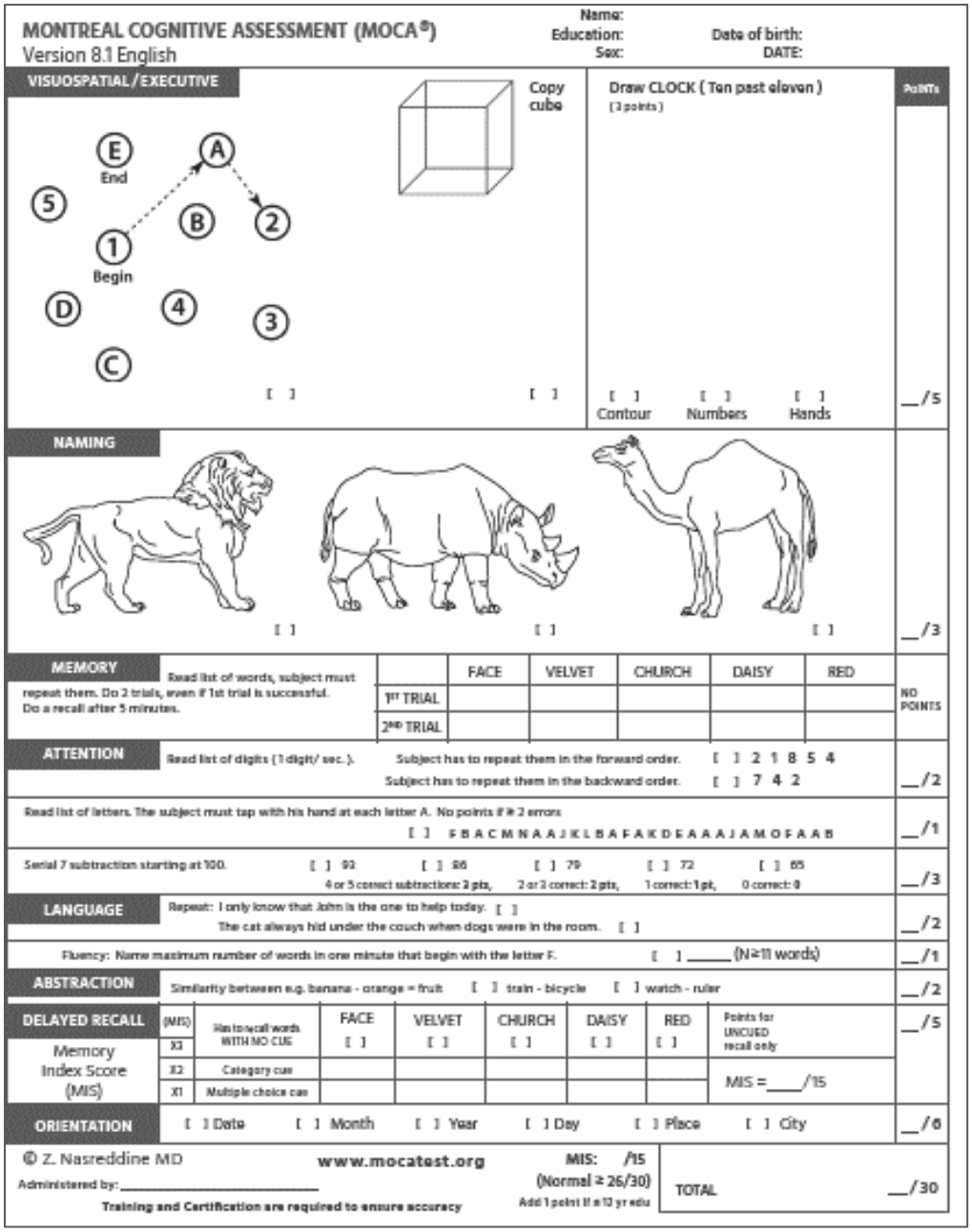
.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒

17.4 MONTREAL COGNITIVE ASSESSMENT

The MoCA (Nasreddine 2005) is a commonly used screening test easily administered by nonspecialist staff. It assesses the domains of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points with a score of 26 or more considered normal. Time to administer the MoCA is approximately 15 minutes. The total possible score is 30 points.



MONTREAL COGNITIVE ASSESSMENT (MOCA®)
Version 8.1 English

Name:
Education: Date of birth:
Sex: DATE:

VISUOSPATIAL / EXECUTIVE — Points

Copy cube

Draw CLOCK (Ten past eleven)
(3 points)

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED	NO POINTS
1ST TRIAL						
2ND TRIAL						

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order. [ ] 2 1 8 5 4

Subject has to repeat them in the backward order. [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0

__/3

LANGUAGE — Repeat: I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency: Name maximum number of words in one minute that begin with the letter F. [ ] _____ (N≥11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler

__/2

DELAYED RECALL

(MIS)	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
X3	Category cue						
X2	Multiple choice cue						MIS = ____/15
X1							

Memory Index Score (MIS)

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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MIS: /15
(Normal ≥ 26/30)
Add 1 point if ≤ 12 yr edu

TOTAL __/30

Administered by: _____
Training and Certification are required to ensure accuracy

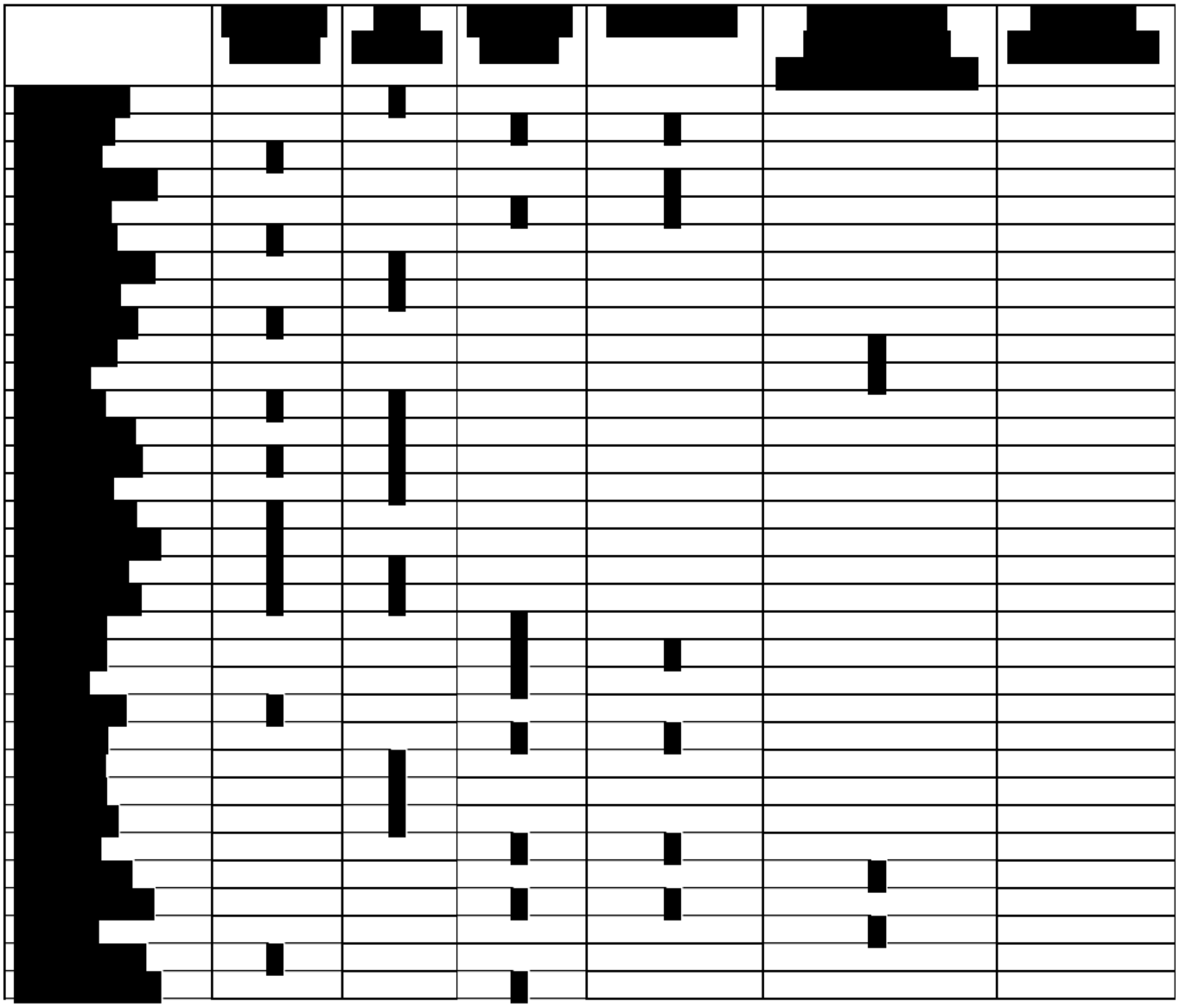
17.5 MODIFICATION OF DIET IN RENAL DISEASE FORMULA

The GFR may be estimated based on the MDRD formula:

$$GFR\ (ml/min/1.73\,m^2) = 186 \times [(P_{cr})/88.4]^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

Units: GFR [ml/min], age [years]

[redacted]



[redacted]

17.7 CLINICAL EVALUATION OF LIVER INJURY

17.7.1 INTRODUCTION

Alterations of liver laboratory parameters [redacted] are to be further evaluated using the procedures described below.

17.7.2 PROCEDURES

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in cases in which the central laboratory is not immediately available (e.g. if the logistics are such that the subject´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by the local laboratory and results will be made available to the investigator and to Alkahest as soon as possible. If ALT and/or AST > 3-fold ULN combined with an elevation of total bilirubin >2-fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to Alkahest as soon as possible.

In addition, the following should be reported in the eCRF:

- Detailed history of current symptoms and concurrent diagnoses and medical history according to the DILI Checklist provided in the ISF
- History of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the DILI Checklist provided in the ISF
- History of exposure to environmental chemical agents (consider home and workplace exposure) according to the DILI Checklist provided in the ISF

17.10.2.1 Clinical Chemistry

- Obtain an ALP, albumin, prothrombin time or INR, creatinine kinase, creatinine kinase-muscle/brain test, ceruloplasmin, α-1 antitrypsin, transferrin amylase, lipase, glucose, cholesterol, triglycerides

17.10.2.2 Serology

- Obtain a hepatitis A (anti-immunoglobulin M [IgM], anti-IGM), hepatitis B (hepatitis B antigen, anti-HBs, DNA), hepatitis C (anti-hepatitis C virus [HCV], RNA if anti-HCV positive), hepatitis D (anti-IgM, anti-immunoglobulin G [IgG]), hepatitis E (anti-hepatitis E virus [HEV], anti-HEV IgM, RNA if anti-HEV IgM positive), anti-smooth muscle antibody (titer), anti-nuclear antibody (titer), anti-liver-kidney microsomes antibody, antimitochondrial antibody, Epstein Barr virus (vascularized composite allotransplantation [VCA] IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM).

17.10.2.3 Hormones

- Thyroid-stimulating hormone

17.10.2.4 Hematology

- Thrombocytes, [redacted]

17.10.2.5 Ultrasound

- Provide an abdominal ultrasound to rule out biliary tract, pancreatic, or intrahepatic pathology (e.g., bile duct stones or neoplasm)

17.10.2.6 Observation/Repeat Testing

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgment and GCP.

17.8 PHARMACOKINETIC AND BIOMARKER SAMPLING

17.8.1 TABLE OF PHARMACOKINETIC AND BIOMARKER SAMPLING

Visit	Time Point	Time for Database Setup	PK Blood	Extra Biomarker Aliquot from PK Blood Sample
2 (Baseline)	Prior to (i.e., within 15 min before study agent administration) REQUIRED SAMPLE	-0:15 h	X	X
	0:00	0:00 h	Study agent administration	
	1:00 hour ± 15 minutes after administration of the first dose REQUIRED SAMPLE	1:00 h	X	
	2 ± 30 minutes after administration of the first dose OPTIONAL SAMPLE	2:00 h	X	
	4 ± 30 minutes after administration of the first dose OPTIONAL SAMPLE	4:00 h	X	
3 – 5 (Study Week 1 and all subsequent weekly visits until EOT)	-00:15 min (i.e., within 15 min before study agent administration)		X	
EOT	Any time during visit – preferably at the end of all visit procedures		X	X

17.9 PHARMACOKINETIC MEASURES AND EVALUATION

17.9.1 TIMING OF PHARMACOKINETIC BLOOD SAMPLING

For the time schedules of PK blood samples, please refer to Section 17.8.1.

17.9.2 PHARMACOKINETIC SAMPLE HANDLING AND SHIPMENT

Methods of PK sample collection are described in Section 7.2.2.1.2. Further instructions for sampling procedures, and for handling, storage and shipment of the samples will be provided in the Laboratory Manual in the ISF.

17.9.3 PHARMACOKINETIC DATA EVALUATION

For PK analysis and displays, concentrations will be presented in the same format as reported in the bioanalytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the calculation of PK parameters.

17.9.4 HANDLING OF MISSING BIOANALYTICAL DATA

In the noncompartmental analysis, concentration data identified as no sample available (NOS), no valid results (NOR), or not analyzed (NOA) will not be considered. Below limit of quantification (BLQ) and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first timepoint with a concentration above the quantification limit. All other BLQ and/or NOP values of the profile will be ignored. Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should be excluded.

Descriptive statistics of concentrations will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the '2/3' rule is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e., BLQ, NOR, NOS, NOA, NOP are included). Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available.

18 REVISION HISTORY

18.1 SUMMARY OF CHANGES

Protocol Version 4.0 dated 15MAY2020
Replaces: Protocol Version 3.0 dated 31JAN2020

The following table describes changes from Version 3.0 (dated 31JAN2020) with justifications provided.

Section	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V3.0_31JAN2020 ***Now reads:*** V4.0_15MAY2020	Version control.
Throughout	Minor grammar and content updates.	Minor grammar/content updates for clarity/accuracy of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
Protocol Summary: Precis; 4.1; 7.3.4.1; 7.3.6; 15	Removal of text indicating that subjects who achieve disease control will be offered participation in a follow on, open-label 12-month treatment study (AKST4290-222).	The Sponsor decided to close AKST4290-222 study; therefore, subjects will now complete EOT procedures and a 14-days Safety Follow-up call.
Protocol Summary: Subject Participation; Schematic of Study Design; 4.1; 5.3	***Previously read***: Approximately 1 to 3 weeks (until disease control). ***Now reads***: Approximately 1 to 5 weeks (inclusive of the Safety Follow-up call).	Subject participation clarified to show all subjects will now complete EOT procedures and a 14-days Safety Follow-up call because study AKST4290-222 was closed by the Sponsor; therefore, rollover to the follow-on study is not possible.
5.2	***Previously read***: [redacted] [redacted] Exclusion Criterion #11: Subjects taking warfarin (see Section 17.6.1).	Updated criteria based on findings from the clinical drug-drug interaction study.
	[redacted] ***Now reads***:	Updated criteria based on findings from the clinical drug-drug interaction study.

	Criterion was removed.	
	[redacted] ***Now reads***: Criterion was removed.	Updated criteria based on findings from the clinical drug-drug interaction study.
	Previously read: [redacted] ***Now reads***: Criterion was removed.	Updated criteria based on findings from the clinical drug-drug interaction study.
	Previously read: [redacted] ***Now reads***: Criterion was removed.	Updated criteria based on findings from the clinical drug-drug interaction study.
	Previously read: [redacted] ***Now reads***: Criterion was removed.	Updated criteria based on findings from the clinical drug-drug interaction study.
	Previously read: [redacted] ***Now reads***: Criterion was removed.	Updated criteria based on findings from the clinical drug-drug interaction study.
	Previously read: [redacted]	Updated criteria based on findings from the clinical drug-drug interaction study.

	[redacted] ***Now reads***: Exclusion Criterion #12: Renal function as defined by estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m2 using the Modification of Diet in Renal Disease (MDRD) study equation (see Section 17.5).	
	Previously read: [redacted] ***Now reads***: Exclusion Criterion #13: Use of systemic steroids (>10 mg prednisone or equivalent/day) within 14 days of first dose of study agent or known diseases (other than BP) that could require the use of systemic steroids within the study period. Subjects who have received a single high-dose of steroids (intravenous or oral) 14 days or more before the administration of the first dose of study drug are eligible for enrollment.	Text added to clarify the window for allowed use of high-dose intravenous or oral steroids
5.4.2	Clarification added that all subjects will have EOT visit procedures and the 14-day Safety Follow-up call completed upon withdrawal.	The Sponsor decided to close AKST4290-222 study; therefore, subjects will now complete EOT procedures and a 14-days Safety Follow-up call.
7.1.1.1	Clarification to show the allowed window of use for high-dose intravenous or oral steroids. "Additionally, subjects who have received a single high-dose of steroids (intravenous or oral) 14 days or more before the administration of the first dose of study drug are eligible for enrollment. "	Text added to clarify the window for allowed use of high-dose intravenous or oral steroids
7.2.2.1, 7.3.2.1	Added "required and optional" to indicate that not all PK sampling timepoints are mandatory.	Modified to correctly describe the PK sampling time points.
7.2.2.1.1	***Previously read***: As far as feasible, the following pharmacokinetic parameter will be derived by noncompartmental methods: • $C_{pre,ss,N}$ Pre-dose concentration of AKST4290 in plasma immediately before administration of the Nth dose In addition, the average pre-dose concentration in plasma at steady state will be calculated as the geometric mean of $C_{pre,ss,N}$ values, as applicable. ***Now reads***: As far as feasible, the following pharmacokinetic parameter will be summarized descriptively: • Cpre,ss,N Pre-dose concentration of AKST4290 in plasma immediately before administration of the Nth dose	Modified to correctly describe the PK parameters based on the available sampling time points.
7.5	***Previously read***: [redacted]	Updated based on findings from the clinical drug-drug interaction study.

[redacted]

***Now reads*:**

[redacted]

	[redacted]	
15	Note #18 ***Previously read***: [redacted] ***Now reads***: [redacted]	Prohibited medications and precautions modified based on findings from clinical drug-drug interaction studies.
17.6	[redacted]	Prohibited medications and precautions modified based on findings from clinical drug-drug interaction studies.

		
15, 17.8.1	At Baseline (Visit 2) PK samples will be required to be collected pre-dose and 1 hour (± 15 minutes) after administration of the first dose. Additionally, optional PK samples may be collected at 2 hours (± 30 minutes) after administration of the first dose and 4 hours (± 30 minutes) after administration of the first dose. All PK samples collected during the scheduled weekly visits will be drawn within 1 hour prior to the morning (am) dose. At the EOT visit, the sample will be collected at any time during the visit and the time of the subject's last dose and the time of the PK sample collection will be recorded.	Optional time points were added to improve the evaluation of PK.