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

Summary

EudraCT number	2019-001059-37
Trial protocol	DE BG
Global end of trial date	14 April 2021

Results information

Result version number	v1 (current)
This version publication date	13 May 2022
First version publication date	13 May 2022

Trial information

Trial identification

Sponsor protocol code	AKST4290-221

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkahest, Inc.
Sponsor organisation address	125 Shoreway Road, Suite D, San Carlos, United States, CA 94070
Public contact	Head of Communications, Alkahest, Inc., +1 650-801-0474, info@alkahest.com
Scientific contact	Head of Communications, Alkahest, Inc., +1 650-801-0474, info@alkahest.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2021
Global end of trial reached?	Yes
Global end of trial date	14 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the proportion of subjects who achieved disease control (defined as ≤ 3 new blisters/eczematous lesions/urticarial plaques/day and healing of existing blisters/eczematous lesions/urticarial plaques) without the use of rescue therapy.

Protection of trial subjects:

Prior to initiation of any study-specific procedures, subjects received a copy of the Informed Consent Form (ICF) that summarized, in non-technical terms, the purpose of the study, the procedures to be carried out, and the potential hazards. The PI or authorized representative explained the nature of the study to the subjects, in non-technical terms, and answered all questions regarding the study. Subjects reviewed, signed, and dated the ICF. Subjects received a copy of the fully signed ICF. The subject was given adequate time to read the ICF and the opportunity to ask questions and consider the statement before signing and dating the form. They were also given a copy of the signed document. No subject entered the study before informed consent or assent with parental consent was obtained. The date the ICF was signed was recorded, and the investigator retained a copy of the signed ICF.

Background therapy:

AKST4290, 400 mg manufactured by Alkahest, Inc. One batch (lot number 17-0148) was used. 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 were delivered to the site, and the drug products were labeled for investigational use only according to applicable local regulatory requirements for clinical studies.

Evidence for comparator:

Placebo. Three batches of Placebo were produced for the study: lot numbers 18-0097, 19-0101, and 19-0175. However, only one batch was administered to a subject (lot 19-0175).

Actual start date of recruitment	30 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	6
EEA total number of subjects	6

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The planned enrollment was approximately 30 subjects. A total of 6 subjects were enrolled in the study, and all subjects completed the study. All 6 subjects were included in intent-to-treat (ITT) and safety analyses.

Pre-assignment

Screening details:

1. Age 60-95 years, inclusive at screening.
2. Clinical diagnosis of mild to moderate BP at screening:
- Mild BP was defined as BPDAI ≤ 10 OR < 10% affected body surface
- Moderate BP was 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

Pre-assignment period milestones

Number of subjects started	6
Number of subjects completed	6

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

To minimize the potential bias at the time of randomization, the study was double-blinded and randomized in a 1:1 ratio (AKST4290:placebo). Randomization codes were generated by a statistician who had no involvement in the study other than generation and maintenance of the randomization codes. When changes to the randomization scheme were implemented on 17 Jun 2020, it was possible to minimize bias by retaining the blind. Blinded staff were only informed about removal of stratification by sites.

Arms

Are arms mutually exclusive?	Yes
Arm title	AKST4290

Arm description:

Subjects received whole-body topical mometasone furoate cream (MFC) therapy (dose and dosing interval dependent upon severity of disease at the time of enrollment, as assessed by the investigator) concurrently with study agent - AKST4290 400 mg twice daily [bid]) in an inpatient setting until disease control was reached (duration of inpatient stay was dependent upon individual disease course – estimated between 1-3 weeks).

Arm type	Experimental
Investigational medicinal product name	AKST4290
Investigational medicinal product code	AKST4290
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

The study agent AKST4290, 400 mg was administered orally bid. During the course of the study, in all the patients, administration of study agent wasperformed at the study site under the direct supervision of the study and/or hospital personnel for documentation of precise administration time.

Arm title	Placebo

Arm description:

Subjects received whole-body topical mometasone furoate cream (MFC) therapy (dose and dosing interval dependent upon severity of disease at the time of enrollment, as assessed by the investigator) concurrently with placebo twice daily [bid]) in an inpatient setting until disease control was reached (duration of inpatient stay was dependent upon individual disease course – estimated between 1-3 weeks).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	Placebo
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered orally bid during the course of the study. All study agent and placebo administration were performed at the study site under the direct supervision of the study and/or hospital personnel for documentation of precise administration times.

Number of subjects in period 1	AKST4290	Placebo
Started	5	1
Completed	5	1

Baseline characteristics

Reporting groups	
Reporting group title	AKST4290
Reporting group description:	
Subjects received whole-body topical mometasone furoate cream (MFC) therapy (dose and dosing interval dependent upon severity of disease at the time of enrollment, as assessed by the investigator) concurrently with study agent - AKST4290 400 mg twice daily [bid]) in an inpatient setting until disease control was reached (duration of inpatient stay was dependent upon individual disease course – estimated between 1-3 weeks).	
Reporting group title	Placebo
Reporting group description:	
Subjects received whole-body topical mometasone furoate cream (MFC) therapy (dose and dosing interval dependent upon severity of disease at the time of enrollment, as assessed by the investigator) concurrently with placebo twice daily [bid]) in an inpatient setting until disease control was reached (duration of inpatient stay was dependent upon individual disease course – estimated between 1-3 weeks).	

Reporting group values	AKST4290	Placebo	Total
Number of subjects	5	1	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	1	3
From 65-84 years	3	0	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	66	60	
standard deviation	± 7.78	± 0	-
Gender categorical			
In the AKST4290 group, of 5 subjects, 3 (60.0%) were males and 2 (40.0%) were females. The mean (SD) age at randomization was 66.0 (7.78) years. The mean (SD) weight was 81.54 (16.55) kg. All 5 (100%) subjects belonged to White race and were not of Hispanic or Latino ethnicity. Of the 5 subjects, 2 (40.0%) had an Occupational Associate and Master's Degree each, while the remaining 1 (20.0%) had an Academic Associate Degree. In the Placebo group, only 1 subject was enrolled. The subject was a male, aged 60.0 years, with a weight of 150.00 kg.			
Units: Subjects			
Female	2	0	2
Male	3	1	4
Disease Control Without Rescue Medication			
presented by treatment group; additionally, the number and percent of subjects who achieved disease control without the need for rescue therapy as well as the number and percent of subjects who required rescue therapy were reported by treatment group. The same analysis was assessed stratifying by those subjects who fulfilled all eligibility criteria and those who did not as determined by the Inclusion/Exclusion criteria CRF			
Units: Subjects			

BP Severity Moderate	5	1	6

Subject analysis sets

Subject analysis set title	Primary Efficacy Analysis AKST4290
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The full analysis set (FAS) includes the set of subjects that is as close as possible to the ideal implied by the Intention-to-treat principle. It is derived from the set of all randomized subjects by minimal and justified elimination of subjects.

Subject analysis set title	Primary Efficacy Analysis Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The full analysis set (FAS) includes the set of subjects that is as close as possible to the ideal implied by the Intention-to-treat principle. It is derived from the set of all randomized subjects by minimal and justified elimination of subjects.

Reporting group values	Primary Efficacy Analysis AKST4290	Primary Efficacy Analysis Placebo	
Number of subjects	5	1	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	1	
From 65-84 years	3	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66	60	
standard deviation	± 7.78	± 0	
Gender categorical			
In the AKST4290 group, of 5 subjects, 3 (60.0%) were males and 2 (40.0%) were females. The mean (SD) age at randomization was 66.0 (7.78) years. The mean (SD) weight was 81.54 (16.55) kg. All 5 (100%) subjects belonged to White race and were not of Hispanic or Latino ethnicity. Of the 5 subjects, 2 (40.0%) had an Occupational Associate and Master's Degree each, while the remaining 1 (20.0%) had an Academic Associate Degree. In the Placebo group, only 1 subject was enrolled. The subject was a male, aged 60.0 years, with a weight of 150.00 kg.			
Units: Subjects			
Female	2	0	
Male	3	1	
Disease Control Without Rescue Medication			
presented by treatment group; additionally, the number and percent of subjects who achieved disease control without the need for rescue therapy as well as the number and percent of subjects who required rescue therapy were reported by treatment group. The same analysis was assessed stratifying by those subjects who fulfilled all eligibility criteria and those who did not as determined by the Inclusion/Exclusion criteria CRF			

Units: Subjects			
BP Severity Moderate	5	1	

End points

End points reporting groups

Reporting group title	AKST4290

Reporting group description:

Subjects received whole-body topical mometasone furoate cream (MFC) therapy (dose and dosing interval dependent upon severity of disease at the time of enrollment, as assessed by the investigator) concurrently with study agent - AKST4290 400 mg twice daily [bid]) in an inpatient setting until disease control was reached (duration of inpatient stay was dependent upon individual disease course – estimated between 1-3 weeks).

Reporting group title	Placebo

Reporting group description:

Subjects received whole-body topical mometasone furoate cream (MFC) therapy (dose and dosing interval dependent upon severity of disease at the time of enrollment, as assessed by the investigator) concurrently with placebo twice daily [bid]) in an inpatient setting until disease control was reached (duration of inpatient stay was dependent upon individual disease course – estimated between 1-3 weeks).

Subject analysis set title	Primary Efficacy Analysis AKST4290
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The full analysis set (FAS) includes the set of subjects that is as close as possible to the ideal implied by the Intention-to-treat principle. It is derived from the set of all randomized subjects by minimal and justified elimination of subjects.

Subject analysis set title	Primary Efficacy Analysis Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The full analysis set (FAS) includes the set of subjects that is as close as possible to the ideal implied by the Intention-to-treat principle. It is derived from the set of all randomized subjects by minimal and justified elimination of subjects.

Primary: achieved disease control without rescue therapy,

End point title	achieved disease control without rescue therapy,[1]

End point description:

In the AKST4290 group, all 5 (100.0%) subjects achieved disease control. Of these 5 subjects, 3 (60.0%) achieved disease control with rescue therapy, while 2 (40.0%) achieved disease control without rescue therapy. In the Placebo group, the single enrolled subject (100.0%) achieved disease control without rescue therapy. Thus, a greater proportion of subjects in the Placebo group achieved disease control without rescue therapy.

End point type	Primary

End point timeframe:

1 to 3 weeks of inpatient treatment to achieve disease control

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the limited data-set, formal hypothesis testing was not undertaken. Limited analyses were performed, and descriptive statistics were provided.
Analysis datasets of the clinical study protocol included a PP analysis set defined as "a subset of ITT subjects. This analysis set was not utilized in the SAP due to the limited enrollment noted previously and the restriction to descriptive analysis of study endpoints.

End point values	AKST4290	Placebo	Primary Efficacy Analysis AKST4290	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	1	6	
Units: patients	2	1	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All subjects who provided informed consent were evaluated for AEs. All 6 subjects received at least one dose of the study drug and were included in safety analysis. Of 6 subjects, 5 received AKST4290 and 1 received Placebo.

Adverse event reporting additional description:

Treatment emergent AEs (TEAEs) were summarized by Medical Dictionary for Regulatory Activities (MedDRA) coding terms, and separate tabulations were produced for treatment-related AEs, SAEs, and discontinuations due to AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	treatment-emergent AE (TEAEs)

Reporting group description:

All 6 subjects received at least one dose of the study drug and were included in safety analysis. Of 6 subjects, 5 received AKST4290 and 1 received Placebo.

Serious adverse events	treatment-emergent AE (TEAEs)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Infections and infestations			
COVID-19 pneumonia	Additional description: In the Placebo group, a patient developed SAE of COVID-19 that resulted in death 18 days after completing treatment. On investigation the event was found to be unrelated to the study treatment.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 5		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	treatment-emergent AE (TEAEs)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)		
Investigations			
Blood potassium decreased	Additional description: By SOC and PT, in the AKST4290 group, 1 subject reported TEAE - decreased blood potassium. This TEAE was found to be possibly related to the study treatment.		

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2019	Updates to definitions, assessments, and Inclusion/Exclusion criteria for clarity and accuracy of content; additional rationale for conduct of trial and justification of dose selection
31 January 2020	Updates to study procedures and Inclusion/Exclusion criteria for feasibility and clarity, and content revised to align with updated AKST4290 IB V4.0.
15 May 2020	Updates to Schedule of Events and study procedures due to removal of follow-on, open-label study; updates to exclusion criteria based on findings from clinical drug-drug interaction study; additional content for clarity on study procedures; optional time points added to improve evaluation of PK.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 April 2021	The study was terminated prematurely by the Sponsor due to operational challenges stemming from the coronavirus disease 2019 (COVID-19), treatment limitations, rarity of the disease, and drug supply considerations	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrolling 6 of the planned 30 subjects making data interpretation difficult.

Notes: