



Clinical trial results:

The Effect of AKST4290 on Choroidal Blood Flow in Patients with Neovascular Age-Related Macular Degeneration

Summary

EudraCT number	2019-002821-31
Trial protocol	AT
Global end of trial date	27 April 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	AKST4290-206
-----------------------	--------------

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	Department of Clinical Pharmacology, Medical University of Vienna, +43 14040029810, klin-pharmakologie@meduniwien.ac.at
Scientific contact	Department of Clinical Pharmacology, Medical University of Vienna, +43 14040029810, klin-pharmakologie@meduniwien.ac.at
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., 001 650-801-0474,
Scientific contact	Head of Communications, Alkahest, Inc., 001 650-801-0474,

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	06 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2020
Global end of trial reached?	Yes
Global end of trial date	27 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effects of a 4-week, oral b.i.d. dosing regimen of AKST4290 on choroidal blood flow (ChBF) in the contralateral eye in subjects with unilateral neovascular age-related macular degeneration (nAMD)

Protection of trial subjects:

The study was conducted in accordance with the following:

- GCP guidelines.
- The Declaration of Helsinki including all revisions.
- Applicable national and local regulatory requirements.

The Sponsor and Principal Investigator (PI) understood that by signing the Protocol Investigator Signature Page they provided their commitment to comply with applicable Good Clinical Practice (GCP) regulation and guidances and to conduct the study in accordance with the protocol and GCP standards. In obtaining and documenting informed consent, the PI complied with the applicable regulatory requirement(s) and adhered to the International Conference on Harmonisation (ICH) guideline for GCP and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the PI gave the subject oral and written information about the trial expressed in the appropriate local language and form that the person giving consent could read and/ or understand. The measures taken to safeguard the subject's privacy and the protection of personnel data were described. This included information on how the identity of the subject and any recorded data was coded, stored and protected. Information was given about the person(s) who will have access to the code list data, where the list was kept and for how long and who was responsible for keeping and destroying it.

A voluntary, signed and dated Subject Information Sheet/ Informed Consent Form (SIS/ICF) was obtained from the subject prior to any trial-related activity. The subject was given a copy of the signed SIS/ICF.

Background therapy:

The study agent was self-administered orally in the clinic under supervision of study personnel during every visit of the treatment period (Visits 2-3) after any pre-dose assessments, and then self-administered at home between study visits at dose of 400 mg b.i.d. (800 mg/day).

Evidence for comparator: -

Actual start date of recruitment	23 September 2019
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	Austria: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	5
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Men and women with active CNV secondary to AMD in 1 eye, as diagnosed by a retinal specialist, with all the following characteristics and ophthalmic inclusion criteria applied to the contralateral eye (study eye), as assessed by a reader

- No active CNV secondary to AMD
- No geographic atrophy
- No previous treatment for AMD
- Ametropy < or = 6 diopter

Pre-assignment

Screening details:

Males and females 50 years of age or older with unilateral active CNV secondary to AMD were eligible to participate.

Body mass index (BMI) between 18 and ≤ 40 at Screening (Visit 1)

Signed informed consent consistent with ICH-GCP guidelines and local legislation prior to participation in the trial, which includes medication washout and restric

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open label study

Arms

Arm title	AKST4290
-----------	----------

Arm description:

active treatment

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 was self-administered orally in the clinic under supervision of study personnel during every visit of the treatment period (Visits 2-3) after any pre-dose assessments, and then self-administered at home between study visits at dose of 400 mg b.i.d. (800 mg/day). Subjects were instructed to take the study agent at approximately the same time every day, once in the morning and once in the evening (every 12 hours). In addition, the study agent was taken approximately 1 hour before a meal or 2 hours after a meal. Training on study agent administration was conducted prior to the initial study agent administration at Visit 2.

Number of subjects in period 1^[1]	AKST4290
Started	14
Completed	14

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject discontinued the study and was not included in the analyzed per protocol population.

Baseline characteristics

Reporting groups

Reporting group title	Baseline
Reporting group description: -	

Reporting group values	Baseline	Total	
Number of subjects	14	14	
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)	5	5	
From 65-84 years	9	9	
85 years and over	0	0	
Gender categorical			
Of the 14 subjects included in the analysis population, 8 were female and 6 were male. None of the female subjects (8 subjects) were of childbearing potential. The mean (SD) age of the study population was 72 (± 9) years and all subjects were white and non-hispanic. Mean (SD) duration of nAMD in the non-study eye was 2.5 (± 3) years. In 6 subjects the right eye (oculus dexter [OD]) served as the study eye and in 8 subjects the left eye (oculus sinister [OS]) was the study eye.			
Units: Subjects			
Female	8	8	
Male	6	6	

Subject analysis sets

Subject analysis set title	Primary
Subject analysis set type	Per protocol
Subject analysis set description:	
Mean change in ChBF in the contralateral eye measured using LDF	

Reporting group values	Primary		
Number of subjects	14		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	5		

From 65-84 years	9		
85 years and over	0		

Gender categorical			
Of the 14 subjects included in the analysis population, 8 were female and 6 were male. None of the female subjects (8 subjects) were of childbearing potential. The mean (SD) age of the study population was 72 (± 9) years and all subjects were white and non-hispanic. Mean (SD) duration of nAMD in the non-study eye was 2.5 (± 3) years. In 6 subjects the right eye (oculus dexter [OD]) served as the study eye and in 8 subjects the left eye (oculus sinister [OS]) was the study eye.			
Units: Subjects			
Female	8		
Male	6		

End points

End points reporting groups

Reporting group title	AKST4290
Reporting group description: active treatment	
Subject analysis set title	Primary
Subject analysis set type	Per protocol
Subject analysis set description: Mean change in ChBF in the contralateral eye measured using LDF	

Primary: Mean change in ChBF in the contralateral eye measured using LDF

End point title	Mean change in ChBF in the contralateral eye measured using LDF ^[1]
-----------------	--

End point description:

Choroidal blood flow significantly increased over time ($p = 0.037$, ANOVA). A numerical increase from Visit 2 to Visit 3 as well as from Visit 3 to Visit 4 was observed in 90% of subjects. Mean (SEM) BCVA improved by 2.5 (1.3) letters at Visit 3 and by 4.4 (1.7) letters at Visit 4 in the nAMD non-study eye, while in the study eye no statistically significant change occurred. No clinically relevant changes in retinal vascular calibers, oxygen saturation or RNFLT were observed during the course of the study in neither eye. In the nAMD non-study eye, macular SD-OCT parameters such as macular thickness, central subfield thickness and macular volume trended toward improvement. Intraocular pressure decreased during the course of the study.

End point type	Primary
----------------	---------

End point timeframe:

In the study eye, a decrease in the mean central retinal arterial equivalent (CRAE) and mean central retinal venous equivalent (CRVE) from Visit 2/baseline to Visit 4/Follow-up was observed over time, which was statistically significant for CRVE

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: This is study with 1 arm - it means that no comparative statistical analysis

End point values	AKST4290	Primary		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	14		
Units: au				
arithmetic mean (standard deviation)	100 (± 0.05)	100 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were reviewed, documented, and reported as required at each visit, beginning at Screening.

Adverse event reporting additional description:

TEAEs were defined as AEs that were reported or worsened on or after the start of study drug dosing and up to and including the end of the follow-up.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	21.1
--------------------	------

Reporting groups

Reporting group title	Treatment Emergent Adverse Events TEAEs
-----------------------	---

Reporting group description:

All Subjects who received at least one dose of study drug. TEAEs were defined as AEs that were reported or worsened on or after the start of study drug dosing and up to and including the end of the follow-up.

Serious adverse events	Treatment Emergent Adverse Events TEAEs		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Treatment Emergent Adverse Events TEAEs		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
Vascular disorders			
Headache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Gouty arthritis			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2019	<p>1) Added content/references to support the inclusion requirement for unilateral nAMD as a known risk factor for the development of CNV in the fellow eye</p> <p>2) Removed Inclusion Criterion #4 ("Female subjects must not be pregnancy or breast feeding. Women of childbearing potential...") and renumbered subsequent inclusion criteria.</p> <p>3) Updated Exclusion Criteria as follows:</p> <ul style="list-style-type: none">- Added Exclusion Criterion #2 Exclusion of women of childbearing potential.- Exclusion Criterion #10f: changed to : Current, active liver disease: > 3-fold elevation of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] over upper limit of normal).- Exclusion Criterion #10g: changed to Uncontrolled high blood pressure (systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 100 mmHg or higher) despite adequate treatment during the 3 months prior to dosing.- Exclusion Criterion #12: changed to: Planned concomitant use of CYP3A4/5 and/or P-gp substrates that have a narrow therapeutic index (e.g., digoxin, warfarin, factor Xa inhibitors).- Exclusion Criterion #15: changed to: Planned concomitant use of organic anion transporter 1 (OAT1) and OAT3 sensitive substrates (e.g., methotrexate and pravastatin).- Added Exclusion Criterion #17: Exclusion of patients with impaired renal function.- Exclusion Criterion #20: changed to: Patients with clinically relevant, abnormal screening hematology, blood chemistry, or urinalysis, if the abnormality defines a significant disease as defined in other exclusion criteria (e.g., (AST) or (ALT) > 3.0-fold the upper limit of normal; total bilirubin (TBR) or prothrombin time > 1.5 times the upper limit of normal). Laboratory testing may be repeated once during the screening phase. <p>4) Updated statistical hypothesis.</p> <p>Previously read:</p> <ul style="list-style-type: none">• H1: Change from baseline in ChBF \neq 0 with $\alpha=0.05$ <p>Now reads:</p> <ul style="list-style-type: none">• H1: Change from baseline in ChBF \neq 0 <p>5) Updated content for standardization with Investigator's Brochure.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported