Clinical trial results:
A Double-Masked, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy of Oral AKST4290 with Loading Doses of Aflibercept in Patients with Newly Diagnosed Neovascular Age-Related Macular Degeneration (PHTHALO – 205)

Summary

EudraCT number	2019-002738-36
Trial protocol	HU DE
Global end of trial date	16 September 2021

Results information

Result version number	v1 (current)
This version publication date	28 March 2023
First version publication date	28 March 2023

Trial information

Trial identification

Sponsor protocol code	AKST4290-205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04331730
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 650801-0474, trials@alkahest.com
Scientific contact	Head of Communications, Alkahest, Inc. , +1 6508801-0474, trials@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	22 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 September 2021
Global end of trial reached?	Yes
Global end of trial date	16 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the potential therapeutic effects of a 36-week, b.i.d. oral dosing regimen of AKST4290, with loading doses of IAI, by assessing the improvement in best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) method. Mean Change From Baseline in Best Corrected Visual Acuity (BCVA) Per the Early Treatment Diabetic Retinopathy Study (ETDRS) Testing Method [Time Frame: Baseline to
Week 36]

Protection of trial subjects:

Subject information obtained during the conduct of the study was regarded as confidential. The collection and processing of personal data from subjects enrolled in this study was limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. Prior to initiation of any study-specific procedures, subjects received a copy of the IEC/IRB approved updated version 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 studybefore informed consent was obtained. The date the ICF was signed was recorded, and the investigator retained a copy of the signed ICF.

Background therapy:

Subjects will receive 400 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment
Or
800 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment
Or
placebo for 36 weeks, in combination with intravitreal aflibercept injection treatment

Evidence for comparator: -

Actual start date of recruitment	19 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	Poland: 87
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Hungary: 13

Worldwide total number of subjects	107
EEA total number of subjects	100

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)	12
From 65 to 84 years	80
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

Men and women with newly diagnosed active Choroidal Neovascularization (CNV) secondary to Age Related Macular Degeneration (AMD), diagnosed by a retinal specialist with all the following characteristics and ophthalmic inclusion criteria applied to the study eye, as assessed by a central reader:

Pre-assignment

Screening details:

Central subfield thickness (CST) thickness ≥ 250 microns on SD-OCT (spectral domain OCT) (exclusive of subretinal pigment epithelial fluid, inclusive of SRF). Presence of SRF (subretinal fluid) and/or IRF (intraretinal fluid) on SD-OCT. Total lesion size not greater than 12 disc areas (30.48 mm2) (1 disc area = 2.54 mm2) on FA

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AKST4290 (800 mg) + Aflibercept

Arm description:

Subjects will receive 400 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment

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

Dosage and administration details:

Subjects will receive 400 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment

Arm title	AKST4290 (1600 mg) + Aflibercept

Arm description:

Subjects will receive 800 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment

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

Dosage and administration details:

Subjects will receive 800 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment

Arm title	Placebo + Aflibercept

Arm description:

Subjects will receive Placebo twice daily for 36 weeks, in combination with intravitreal aflibercept

injection treatment

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

Dosage and administration details:

Subjects will receive Placebo twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment

Number of subjects in period 1	AKST4290 (800 mg) + Aflibercept	AKST4290 (1600 mg) + Aflibercept	Placebo + Aflibercept
Started	36	35	36
Completed	36	29	34
Not completed	0	6	2
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	-	5	-

Baseline characteristics

Reporting groups	
Reporting group title	AKST4290 (800 mg) + Aflibercept
Reporting group description:	
Subjects will receive 400 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment	
Reporting group title	AKST4290 (1600 mg) + Aflibercept
Reporting group description:	
Subjects will receive 800 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment	
Reporting group title	Placebo + Aflibercept
Reporting group description:	
Subjects will receive Placebo twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment	

Reporting group values	AKST4290 (800 mg) + Aflibercept	AKST4290 (1600 mg) + Aflibercept	Placebo + Aflibercept
Number of subjects	36	35	36
Age categorical			
Subjects 50 years of age or older at screening (Visit 1).			
Units: Subjects			
Adults (18-64 years)	4	3	5
From 65-84 years	24	29	27
85 years and over	8	3	4
Gender categorical Units: Subjects			
Female	22	25	21
Male	14	10	15

Reporting group values	Total		
Number of subjects	107		
Age categorical			
Subjects 50 years of age or older at screening (Visit 1).			
Units: Subjects			
Adults (18-64 years)	12		
From 65-84 years	80		
85 years and over	15		
Gender categorical Units: Subjects			
Female	68		
Male	39		

End points

End points reporting groups

Reporting group title	AKST4290 (800 mg) + Aflibercept
Reporting group description:	
Subjects will receive 400 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment	
Reporting group title	AKST4290 (1600 mg) + Aflibercept
Reporting group description:	
Subjects will receive 800 mg AKST4290 twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment	
Reporting group title	Placebo + Aflibercept
Reporting group description:	
Subjects will receive Placebo twice daily for 36 weeks, in combination with intravitreal aflibercept injection treatment	

Primary: Mean Change From Baseline in Best Corrected Visual Acuity (BCVA)Per the Early Treatment Diabetic Retinopathy Study (ETDRS) TestingMethod

End point title	Mean Change From Baseline in Best Corrected Visual Acuity (BCVA)Per the Early Treatment Diabetic Retinopathy Study (ETDRS) TestingMethod[1]
End point description:	
Mean change from baseline in Best Corrected Visual Acuity (BCVA)per the Early Treatment Diabetic Retinopathy Study (ETDRS) testingmethod. BCVA will be assessed using ETDRS charts at 4 meters initialtesting distance and assessed in both eyes. Score range is 0 to 93. A higher score indicates better vision.	
End point type	Primary
End point timeframe:	
Baseline to Week 36	

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 study was not powered for detecting clinically meaningful statistically significant differences. This study was conducted to identify trends and reinforce previous study results prior to conducting a study of longer treatment duration with a bigger sample size.

End point values	AKST4290 (800 mg) + Aflibercept	AKST4290 (1600 mg) + Aflibercept	Placebo + Aflibercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	35	36	
Units: score				
arithmetic mean (standard deviation)	10.4 (± 10.26)	6.7 (± 7.89)	13.7 (± 7.60)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were captured beginning at time of informed consent through EOS. AE status was followed by the investigator until resolved or considered stable, unless the subject was lost to follow up

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	treatment-emergent AE (TEAEs) AKST4290 (800 mg) + Aflibercept

Reporting group description:

Number of Subjects Reporting at Least One TEAE

Reporting group title	treatment-emergent AE (TEAEs) AKST4290 (1600 mg) + Aflibercept

Reporting group description: -

Reporting group title	treatment-emergent AE (TEAEs) Placebo + Aflibercept

Reporting group description: -

Serious adverse events	treatment-emergent AE (TEAEs) AKST4290 (800 mg) + Aflibercept	treatment-emergent AE (TEAEs) AKST4290 (1600 mg) + Aflibercept	treatment-emergent AE (TEAEs) Placebo + Aflibercept
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 36 (8.33%)	3 / 35 (8.57%)	0 / 36 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Investigations			
Endophthalmitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular failure			

subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supra ventricular tachycardia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	treatment-emergent AE (TEAEs) AKST4290 (800 mg) + Aflibercept	treatment-emergent AE (TEAEs) AKST4290 (1600 mg) + Aflibercept	treatment-emergent AE (TEAEs) Placebo + Aflibercept
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 36 (72.22%)	26 / 35 (74.29%)	20 / 36 (55.56%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Aspartate aminotransterase increase			

subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Blood pressure increased			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 36 (13.89%)	3 / 35 (8.57%)	3 / 36 (8.33%)
occurrences (all)	5	3	3
Glomerular filtration rate decreased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 36 (0.00%)	3 / 35 (8.57%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Liver function test abnormal			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Product residue present			
subjects affected / exposed	3 / 36 (8.33%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences (all)	3	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 36 (8.33%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences (all)	3	1	0
Headache			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	1	2	2
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Eye pain			

subjects affected / exposed	3 / 36 (8.33%)	2 / 35 (5.71%)	5 / 36 (13.89%)
occurrences (all)	3	2	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 36 (2.78%)	3 / 35 (8.57%)	1 / 36 (2.78%)
occurrences (all)	1	3	1
Diarrhoea			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	3 / 36 (8.33%)
occurrences (all)	2	0	3
Nausea			
subjects affected / exposed	0 / 36 (0.00%)	4 / 35 (11.43%)	0 / 36 (0.00%)
occurrences (all)	0	4	0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 36 (8.33%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	3	2	0
Back pain			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Osteoarthritis			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 36 (0.00%)	4 / 35 (11.43%)	2 / 36 (5.56%)
occurrences (all)	0	4	2
Urinary tract infection			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	2	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2020	Main changes 1.Study extended with a final visit at 40 weeks to gather further data related to safety and efficacy. 2. FAF was added to FP as it's a noninvasive technique which assists in delineation of changes in retinal structures; FP/FAF testing was added at week 40 (Visit 12) to gather further data related to efficacy 3. Revised to accommodate expansion of global study sites. 4. PRN Criteria were revised for alignment with recent research findings and to be consistent with other recent global clinical trials in nAMD. 5. Some Inclusion Criteria were updated to align with global regulatory standards 6. Some Exclusion Criteria were updated to align with global regulatory standards 7. Clarification of participant replacement when withdrawn due to AEs or adverse reactions based on study procedures. 8.Content added/revised related to prohibited medications as well as medications that should be administered with caution. 9. Revised the Schedule of Events to reduce burden on subjects and sites 10.Added acquisition of biomarker to new Visit 12 to align with collection timepoint of other exploratory endpoints
12 June 2020	The main changes 1. Study endpoints were updated (primary , secondary and exploratory) - updates required for alignment with revised statistical approach and analyses (e.g., examining treatment arms separately) as well as clarity/consistency. In addition, FAF is not available at every site; therefore, it will be performed, as available. 2. Study population was updated to include 120 enrolled subjects (previously 150) with the intent of obtaining approximately 100 evaluable subjects (previously 129) to provide approximately 33 subjects in each study arm (previously 43) 3.Randomization remains 1:1:1, but will now also be stratified by site and baseline BCVA group (< 55 letters read or ≥ 55 letters read). 4.The statistical analyses were extensively updated. Key revisions include examination of each treatment arm separately (previously pooled) 5.PRN Criterion #3 was revised to provide clarity and for alignment with study visit procedures 6.Clarification of terminology and inclusion of assessment in visit schedule 7 As the study sites may be located in EU or US; therefore, appropriate manufacturing and labelling information was added for each. 8. Additional PK assessments added to better understand and characterize the bioavailability of AKST4290 9. New content added to account for potential protocol deviations related to COVID-19. 10. Additional updates to Section 15 Schedule of Events to facilitate study operations and decrease the burden on subjects. 11.Reduction in listings of prohibited medications by removing entries for conditions that are excluded in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported