



Clinical trial results:

A Single Arm Open-Label Study to Evaluate the Therapeutic Effects and Safety of a 6-Week Treatment Regimen of ALK4290 in Patients with Refractory Wet Age-Related Macular Degeneration (wAMD)

Summary

EudraCT number	2017-004228-31
Trial protocol	HU PL
Global end of trial date	29 November 2018

Results information

Result version number	v1 (current)
This version publication date	24 December 2021
First version publication date	24 December 2021

Trial information

Trial identification

Sponsor protocol code	ALK4290-202
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03558074
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., 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	31 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2018
Global end of trial reached?	Yes
Global end of trial date	29 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to investigate the potential therapeutic effects of a 6 week, twice daily oral dosing regimen of ALK4290 on best corrected visual acuity (BCVA) in subjects with refractory wAMD (i.e., following 3 consecutive [approximately 4 to 6 weeks apart] intravitreal [IVT] anti-vascular endothelial growth factor [VEGF] injections in the study eye).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with International Conference on Harmonization Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those providing greater protection to the safety of study participants.

Written informed consent was obtained prior to the subject entering the study (before initiation of protocol-specific procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Each informed consent was appropriately signed and dated by the subject and/or their legally authorized representative and the person obtaining consent (Appendix 16.1.3). A copy of the signed consent form was provided to the subject and/or their legally authorized representative. By signing the informed consent form, all parties agreed they will complete the evaluations required by the study, unless they withdrew voluntarily or were terminated from the study for any reason.

Background therapy:

ALK4290 was self-administered orally twice daily for a total daily dose of 800 mg from Visit 2 (Day 1) to Visit 8 (Day 43 ±1). At each study visit, all ophthalmic examinations and safety assessments were performed before administration of ALK4290.

Evidence for comparator: -

Actual start date of recruitment	19 April 2018
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: 20
Country: Number of subjects enrolled	Hungary: 6
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	1
From 65 to 84 years	20
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The subject participation period, inclusive of Screening, was approximately 11 weeks (up to 1 week for Screening, a 6-week treatment period, and 4 weeks of follow-up), unless prematurely discontinued. All subjects underwent a Screening visit, Baseline/Treatment visit(s), an End of Treatment (EOT) visit, and Follow-up visits.

Pre-assignment

Screening details:

Men and women with refractory active CNV secondary to AMD, diagnosed by a retinal specialist that met the characteristics and ophthalmic inclusion criteria applied to the study eye

Period 1

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

Arms

Arm title	ALK4290
-----------	---------

Arm description:

ALK4290 was self-administered orally twice daily for a total daily dose of 800 mg from Visit 2 (Day 1) to Visit 8 (Day 43 \pm 1).

Arm type	active treatment
Investigational medicinal product name	ALK4290
Investigational medicinal product code	ALK4290
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Gastroenteral use

Dosage and administration details:

ALK4290 was self-administered orally twice daily for a total daily dose of 800 mg from Visit 2 (Day 1) to Visit 8 (Day 43 \pm 1).

Number of subjects in period 1^[1]	ALK4290
Started	24
Completed	24

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: 2 subjects discontinued the study

Baseline characteristics

Reporting groups

Reporting group title	overall trial
Reporting group description: -	

Reporting group values	overall trial	Total	
Number of subjects	24	24	
Age categorical			
Of the 26 subjects enrolled, 16 (61.5%) were female and 10 (38.5%) were male. Their ages ranged from 61 to 92 years. All the subjects were Caucasian and none were of Hispanic or Latino ethnicity			
Units: Subjects			
From 65-84 years	20	20	
85 years and over	4	4	
Age continuous			
Units: years			
arithmetic mean	76.3		
standard deviation	± 7.73	-	
Gender categorical			
Of the 26 subjects enrolled, 16 (61.5%) were female and 10 (38.5%) were male.			
Units: Subjects			
Female	15	15	
Male	9	9	

Subject analysis sets

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

Subject analysis set description:

The primary endpoint was the mean change from baseline (Visit 2/Day 1) to EOT (Visit 8/Day 43) in BCVA letter score of the study eye as measured by the ETDRS testing method using the Evaluable set. BCVA was measured at the beginning of every study visit and change from Baseline for each subject was calculated as Follow-up visit minus Baseline visit. Quantitative summary statistics were used to summarize the BCVA letter score and change from Baseline at each visit. A two-tailed, one-sample t-test was used to assess the mean change from Baseline in BVCA letter score at each visit, in which the change from baseline BCVA letter score was compared to a reference value of zero.

Additionally, the number of subjects with change from Baseline in BCVA letter score for the following categories summarized with counts and percentages:

- ≥15 letters
- <15 and ≥10 letters
- <10 and ≥5 letters
- <5 and ≥ 0 letters
- <0 and >-5 letters
- ≤-5 and >-10 letters
- ≤-10 and >-15 letters
- ≤-15 let

Reporting group values	Primary Efficacy Analysis		
Number of subjects	24		
Age categorical			
Of the 26 subjects enrolled, 16 (61.5%) were female and 10 (38.5%) were male. Their ages ranged from 61 to 92 years. All the subjects were Caucasian and none were of Hispanic or Latino ethnicity			
Units: Subjects			

From 65-84 years	20		
85 years and over	4		

Age continuous			
Units: years			
arithmetic mean	76.3		
standard deviation	± 7.73		
Gender categorical			
Of the 26 subjects enrolled, 16 (61.5%) were female and 10 (38.5%) were male.			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	ALK4290
Reporting group description: ALK4290 was self-administered orally twice daily for a total daily dose of 800 mg from Visit 2 (Day 1) to Visit 8 (Day 43 ±1).	
Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description: The primary endpoint was the mean change from baseline (Visit 2/Day 1) to EOT (Visit 8/Day 43) in BCVA letter score of the study eye as measured by the ETDRS testing method using the Evaluable set. BCVA was measured at the beginning of every study visit and change from Baseline for each subject was calculated as Follow-up visit minus Baseline visit. Quantitative summary statistics were used to summarize the BCVA letter score and change from Baseline at each visit. A two-tailed, one-sample t-test was used to assess the mean change from Baseline in BVCA letter score at each visit, in which the change from baseline BCVA letter score was compared to a reference value of zero. Additionally, the number of subjects with change from Baseline in BCVA letter score for the following categories summarized with counts and percentages: <ul style="list-style-type: none">• ≥15 letters• <15 and ≥10 letters• <10 and ≥5 letters• <5 and ≥ 0 letters• <0 and >-5 letters• ≤-5 and >-10 letters• ≤-10 and >-15 letters• ≤-15 let	

Primary: Baseline mean BCVA

End point title	Baseline mean BCVA
End point description: The primary objective of this study was to investigate the potential therapeutic effects of a 6 week, twice daily oral dosing regimen of ALK4290 on best corrected visual acuity (BCVA) in subjects with refractory wAMD (i.e., following 3 consecutive [approximately 4 to 6 weeks apart] intravitreal [IVT] anti-vascular endothelial growth factor [VEGF] injections in the study eye).	
End point type	Primary
End point timeframe: ALK4290 was self-administered orally twice daily for a total daily dose of 800 mg from Visit 2 (Day 1) to Visit 8 (Day 43 ±1)	

End point values	ALK4290	Primary Efficacy Analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	24		
Units: letters				
arithmetic mean (standard deviation)				
all	100 (± 0.05)	100 (± 0.05)		

Attachments (see zip file)	Categorical Summary of Study Eye BCVA Letter
----------------------------	--

Statistical analyses

Statistical analysis title	mean change in BCVA letter score
Statistical analysis description: mean change in BCVA letter score	
Comparison groups	ALK4290 v Primary Efficacy Analysis
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	other ^[1]
P-value	≥ 0.05 ^[2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	100
Variability estimate	Standard deviation
Dispersion value	7

Notes:

[1] - The mean (SD) BCVA letter score at Baseline (Visit 2) was 53.4 (12.37) and at EOT was 55.5 (14.81). The mean (SD) BCVA letter score improved by 2.0 (6.96) (95% CI -0.8, 4.9; $p=0.1558$) from Baseline to EOT. The least square mean was 2.8 (95% CI 0.0, 5.7; $p=0.0535$)

[2] - mean change in BCVA letter score

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent through the Follow-up period) were collected, documented, and reported to the sponsor by the investigator on the appropriate eCRF

Adverse event reporting additional description:

An AE occurring during the treatment period was based on changes in the patient's physical examination, test results, and/or signs and symptoms. The severity of each AE was summarized according to the CTCAE version 4.03. Adverse Events were coded using the MedDRA, v. 21.0

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

Dictionary used

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

Dictionary version	21.0
--------------------	------

Reporting groups

Reporting group title	treatment-emergent AE (TEAEs)
-----------------------	-------------------------------

Reporting group description:

The most frequent non-ocular TEAEs by SOCs reported were 'musculoskeletal and connective tissue disorders' in 3 (11.5%) subjects, followed by ear and labyrinth disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, nervous system disorders, and renal and urinary disorders SOC in 1 (3.8%) each. A total of 4 subjects reported 6 ocular TEAEs in the study. A total of 3 (11.5%) subjects reported TEAEs of visual acuity reduced, 1 (3.8%) subject reported retinal thickening and, 1 (3.8%) subject reported vision blurred

Reporting group title	ALK4290-related (includes definitely and possibly related) AE
-----------------------	---

Reporting group description:

A total of 6 (23.1%) subjects reported non-ocular TEAEs and 3 (11.5%) subjects reported ALK4290 related (includes definitely and possibly related) non-ocular TEAEs. None of the subjects had Grade 3/4/5 non-ocular TEAEs, serious non-ocular TEAEs, or non-ocular TEAEs leading to discontinuation of ALK

Serious adverse events	treatment-emergent AE (TEAEs)	ALK4290-related (includes definitely and possibly related) AE	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	treatment-emergent AE (TEAEs)	ALK4290-related (includes definitely and possibly related) AE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)	3 / 26 (11.54%)	

Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	0 / 26 (0.00%) 0	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0 1 / 26 (3.85%) 1	1 / 26 (3.85%) 1 0 / 26 (0.00%) 0	
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Eye disorders Visual acuity reduced subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 26 (0.00%) 0	
Gastrointestinal disorders Dysphagia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Spinal pain subjects affected / exposed occurrences (all) Synovial cyst subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1	0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0	
Infections and infestations Cystitis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2018	<p>The Protocol Version 3.0 (Amendment 2.0) dated 15 May 2018 replaced Protocol Version 2.0 (Amendment 1) dated 22 Jan 2018 (for Hungary) and Protocol Version 2.0 (Amendment 1) dated 19 March 2018 (for Poland).</p> <p>In Version 3.0, the two former country-specific protocols were combined into a single protocol for global standardization and compliance. Unless otherwise specified, the following changes were applicable for both Hungary and Poland.</p> <p>The exploratory endpoint of CRT was changed to CST. Similar change made in inclusion criteria in bullet 1/sub-bullet 2.</p> <p>List of abbreviations was updated by adding "CST: Central Subfield Thickness".</p> <p>Abbreviation added to accommodate clarified exploratory endpoint measurement.</p> <p>Abbreviation removed – not required in Protocol. The abbreviation "OPU: Operative Unit" was removed.</p> <p>Inclusion Criteria in bullet 1/sub-bullet 1: was updated to read as follows: "Persistent exudation of SRF and IRF as documented by SD-OCT and absence of improvement in visual acuity following 3 consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections, subject must have received their last injection 30 to 90 days prior to the initial Screening visit". The term "monthly" was lacking specificity and was to be regarded as a period of 4 to 6 weeks between each IVT injection for the purposes of the protocol. In addition to Section 5.1, the statement "monthly IVT anti-VEGF therapy" was also used throughout the protocol. Per the revision, this statement was interpreted as "consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections."</p> <p>Inclusion Criteria in bullet 1/sub-bullet 2: Changed "Central subfield retinal thickness to CST." This change was made to standardized nomenclature to align with clarified abbreviation. Removed superscript "5" from "Pharmacokinetics blood sample (for plasma extraction)" at Visit 9 because no treatment was administered at Visit 9.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported