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 Newly Diagnosed Wet Age-Related Macular Degeneration (wAMD).

Summary

EudraCT number	2017-004227-75
Trial protocol	HU PL
Global end of trial date	18 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	ALK4290-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03558061
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	18 November 2018
Global end of trial reached?	Yes
Global end of trial date	18 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 therapeutic effects of a 6-week, twice daily oral dosing regimen of ALK4290 on best corrected visual acuity (BCVA) in newly diagnosed subjects with wAMD who were treatment-naïve (i.e., no previous treatment 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.
Subject Information and Consent
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	04 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: 22
Country: Number of subjects enrolled	Hungary: 8
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	4
From 65 to 84 years	24
85 years and over	2

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), End of Treatment (EOT) visit, and Follow-up visits.

Pre-assignment

Screening details:

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

Period 1

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

Arms

Arm title	baseline

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 ±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 ±1).

Number of subjects in period 1[1]	baseline
Started	29
Completed	29

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 patient has resigned and was not included in the beseline group

Baseline characteristics

Reporting groups

Reporting group title	baseline

Reporting group description:

Subjects with BCVA between 24 and 70

Reporting group values	baseline	Total	
Number of subjects	29	29	
Age categorical			
Ages ranged from 51 to 87 years. All the subjects were Caucasian and none were of Hispanic or Latino ethnicity.			
Units: Subjects			
Adults (18-64 years)	4	4	
From 65-84 years	23	23	
85 years and over	2	2	
Age continuous			
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 dataset. BCVA was measured at the beginning of every study visit and change			
Units: days			
arithmetic mean	100		
standard deviation	± 0.05	-	
Gender categorical			
Units: Subjects			
Female	18	18	
Male	11	11	
newly diagnosed wAMD			
newly diagnosed subjects with wAMD who were treatment-naïve (i.e., no previous treatment in the study eye).			
Units: Subjects			
BCVA	29	29	

Subject analysis sets

Subject analysis set title	• Primary Efficacy Analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The primary endpoint was the mean change from baseline (V 2/Day 1) to EOT (V 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 Study 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 0 .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 letters

Reporting group values	• Primary Efficacy Analysis		
Number of subjects	29		
Age categorical			
Ages ranged from 51 to 87 years. All the subjects were Caucasian and none were of Hispanic or Latino ethnicity.			
Units: Subjects			
Adults (18-64 years)	4		
From 65-84 years	23		
85 years and over	2		
Age continuous			
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 dataset. BCVA was measured at the beginning of every study visit and change			
Units: days			
arithmetic mean	100		
standard deviation	±		
Gender categorical			
Units: Subjects			
Female	18		
Male	11		
newly diagnosed wAMD			
newly diagnosed subjects with wAMD who were treatment-naïve (i.e., no previous treatment in the study eye).			
Units: Subjects			
BCVA	29		

End points

End points reporting groups

Reporting group title	baseline

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	Sub-group analysis

Subject analysis set description:

The primary endpoint was the mean change from baseline (V 2/Day 1) to EOT (V 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 Study 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 0 .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 letters

Primary: Baseline mean BCVA

End point title	Baseline mean BCVA

End point description:

The primary efficacy analysis was evaluated at a two-sided significance level of 0.20. The mean (SD) BCVA score at Baseline was 56.8 (10.22) letters and at EOT was 63.7 (16.42) letters. The mean (SD) BCVA score improved by 7.0 (12.51) (95% confidence interval [CI] 2.2, 11.7; p=0.0056) from Baseline to EOT. The least square mean was 7.8 (95% CI 2.3, 13.2; p=0.0065).
Mean changes in BCVA from Baseline to EOT were as follows: ≥0 letters gained in 24 (82.8%) subjects; ≥15 letters gained in 6 (20.7%) subjects; <15 and ≥10 letters gained in 6 (20.7%) subjects; <10 and ≥5 letters gained in 4 (13.8%) subjects; and <5 and ≥0 letters gained in 8 (27.6%) subjects. Five (17.2%) subjects lost BCVA letters.

End point type	Primary

End point timeframe:

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

End point values	baseline	• Primary Efficacy Analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	29		
Units: BCVA measured in letters	29	29		

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

Statistical analyses

Statistical analysis title	mean change in BCVA letter score
Comparison groups	baseline v • Primary Efficacy Analysis
Number of subjects included in analysis	58
Analysis specification	Pre-specified
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 presentation of baseline characteristics was based on the Intent-to-Treat (ITT) dataset.
A mixed model accounting for repeated measures was used to analyze BCVA. This model included the change from Baseline in BCVA letter score as the response variable and Baseline BCVA letter score, smoking status, and visit as explanatory variables for adjustment. Least squares (LS) means for each visit was calculated along with corresponding 95% CIs and p-values.

[2] - The mean (SD) BCVA score improved by 7.0 (12.51) (95% confidence interval [CI] 2.2, 11.7; p=0.0056) from Baseline to EOT. The least square mean was 7.8 (95% CI 2.3, 13.2; p=0.0065).

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.

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 frequently reported non-ocular TEAEs occurred in the SOCs of musculoskeletal and connective tissue disorders (8 [26.7%] subjects), followed by infections and infestations (4 [13.3%] subjects), and general disorders and administration site conditions and investigations (3 [10.0%] subjects each). The most frequent non-ocular TEAE by PT was arthralgia (5 [16.7%] subjects), back pain (3 [10.0%] subjects), and cystitis and headache (2 [6.7%] subjects each).

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

Reporting group description:

The most frequently reported related non-ocular TEAEs occurred in the SOCs of musculoskeletal and connective tissue disorders (5 [16.7%] subjects), followed by general disorders and administration site conditions (3 [10.0%] subjects), and investigations and nervous system disorders (2 [6.7%] subjects each). The most frequent related non-ocular TEAEs by PT were arthralgia (4 [13.3%] subjects) and headache (2 [6.7%] subjects).

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 / 30 (0.00%)	0 / 30 (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	5 / 30 (16.67%)	9 / 30 (30.00%)	

Eye disorders visual acuity reduction subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2	 2 / 30 (6.67%) 2	
Musculoskeletal and connective tissue disorders arthralgia subjects affected / exposed occurrences (all)	 5 / 30 (16.67%) 7	 9 / 30 (30.00%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2018	The Protocol Version 2.0 (Amendment 1) dated 19 March 2018 replaced Protocol Version 1.0 dated 27 October 2017. Revised inclusion criteria, as requested by the Polish Department of Clinical Trials for Medicinal Products, added the following sentence to bullet 5: "Women of childbearing potential must have a negative serum pregnancy test at Screening/Visit 1, the first treatment visit, and the last treatment visit. Women of childbearing potential and men must agree to use highly effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. A woman was considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause)." Revised number of categories of relatedness of AE in the previous version incorrectly stated there were four categories of relatedness which was revised to state there are three categories of relatedness. Per request from the Polish Department of Clinical Trials for Medicinal Products, added the "serum pregnancy test (in women of childbearing potential)" to Visit 1, Visit 2, Visit 8; and added pregnancy test at Screening/Visit 1 (as applicable per Inclusion Criteria), first treatment visit, and final treatment visit. Added reference to define "highly effective" contraception as per the Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. Throughout the protocol, where appropriate, updated terminology of "patient" to "subject" for clarity and standardization, as a "patient" becomes a "subject" following study enrollment.
15 May 2018	The Protocol Version 3.0 (Amendment 2.0) dated 15 May 2018 replaced Protocol Version 1.0 dated 27 October 2017 (for Hungary) and Protocol Version 2.0 (Amendment 1) dated 19 March 2018 (for Poland). 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. The exploratory endpoint of CRT was changed to CST. Similar change made in inclusion criteria in bullet 1/sub-bullet 2. Due to staffing assignment changes within Alkahest, the Authorized Representative (Signatory) / Responsible Party has been changed. The email address has also been updated to reflect this change. Inclusion Criteria in bullet 5 was revised to include requirements related to pregnancy and pregnancy testing for Hungary and Poland. The requirements have not changed in either country from V1.0/V2.0 to V3.0 other than being combined to create a single protocol. Per request from the Polish Department of Clinical Trials for Medicinal Products, added the "serum pregnancy test (in women of childbearing potential)" to Visit 1, Visit 2, Visit 8 in Visit Procedures; and added pregnancy test at Screening/Visit 1 (as applicable per Inclusion Criteria), first treatment visit, and final treatment visit in Schedule of events (amendment to Hungary protocol). Added the word- for Poland only in all these changes (amendment to both Poland and Hungary protocol).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported