Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AKST4290 in Subjects with Parkinson's Disease on Stable Dopaminergic Treatment

Summary

EudraCT number	2019-001657-42
Trial protocol	DE SK
Global end of trial date	10 March 2021

Results information

Result version number	v1 (current)
This version publication date	29 July 2022
First version publication date	29 July 2022

Trial information

Trial identification

Sponsor protocol code	AKST4290-211

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04369430
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alkahest, Inc.
Sponsor organisation address	125 Shoreway Rd, Suite D, San Carlos, United States, 94070
Public contact	Regulatory Affairs, Alkahest, Inc., +1 6508010474, trials@alkahest.com
Scientific contact	Clinical Development, Alkahest, Inc., +1 6508010474, 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	08 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2021
Global end of trial reached?	Yes
Global end of trial date	10 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the efficacy and safety of AKST4290 in subjects with Parkinson’s Disease who are currently on stable dopaminergic treatment.

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:

Stable dopaminergic therapy (e.g., levodopa, dopamine agonists, monoamine oxidase inhibitors, catechol-O-methyl transferase inhibitors, amantadine), for a least 8 weeks prior to enrollment and remain on stable dose during the 12-week treatment period.

Evidence for comparator: -

Actual start date of recruitment	16 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	United States: 14
Country: Number of subjects enrolled	Poland: 32
Country: Number of subjects enrolled	Slovakia: 29
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Germany: 27
Worldwide total number of subjects	107
EEA total number of subjects	93

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)	62
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled 107 subjects, randomized in a 1:1 ratio to active treatment in Arm 1 (52 subjects) or placebo in Arm 2 (55 subjects). The recruitment occurred at 22 clinical sites in United States, Germany, Estonia, Poland, and Slovakia from 16-Jan-2020 (First Patient First Visit - FPFV) to 5-Nov-2020 (Last Patient First Visit - LPFV).

Pre-assignment

Screening details:

130 subjects were screened for the study. Eligible subjects were randomly assigned in a 1:1 ratio to AKST4290 or placebo. Study treatment was administered to 52 subjects in AKST4290 arm and 55 subjects in placebo arm. There were 3 subjects who were randomized but not treated.

Period 1

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

Blinding implementation details:

1:1 ratio AKST4290 (Active):Placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	AKST4290

Arm description:

Subjects will receive AKST4290, 400 mg twice daily, for 12 weeks.

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

Dosage and administration details:

AKST4290 is a small molecule antagonist of human CCR3. The study treatment was self-administered orally twice daily (b.i.d.) (2 × 200 mg per dose), approximately 12 hours apart, for a total daily dose of 800 mg. Subjects received the study treatment for a total of 12 weeks, followed by 4 weeks of follow-up.

Arm title	Placebo

Arm description:

Subjects will receive placebo, 400 mg twice daily, for 12 weeks.

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

Dosage and administration details:

Placebo was self-administered orally twice daily (b.i.d.) (2 × 200 mg per dose), approximately 12 hours apart, for a total daily dose of 800 mg. Subjects received placebo for a total of 12 weeks, followed by 4 weeks of follow-up.

Number of subjects in period 1	AKST4290	Placebo
Started	52	55
Completed	46	48
Not completed	6	7
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	2
COVID concern, Sponsor’s decision	2	1
Adverse event, non-fatal	1	1
Lost to follow-up	-	1
Sponsor decision	-	2

Baseline characteristics

Reporting groups	
Reporting group title	AKST4290
Reporting group description:	
Subjects will receive AKST4290, 400 mg twice daily, for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects will receive placebo, 400 mg twice daily, for 12 weeks.	

Reporting group values	AKST4290	Placebo	Total
Number of subjects	52	55	107
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)	32	30	62
From 65-84 years	20	25	45
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.1	64.9	
standard deviation	± 8.07	± 6.74	-
Gender categorical Units: Subjects			
Female	20	21	41
Male	32	34	66
Modified Hoehn and Yahr Units: Subjects			
No signs of disease	0	0	0
Unilateral disease	5	5	10
Unilateral plus axial involvement	5	6	11
Bilateral disease, without impairment of balance	30	32	62
Mild bilateral disease, with recovery on pull test	12	12	24
Disease Duration Units: year			
arithmetic mean	5.71	7.62	
standard deviation	± 3.138	± 5.467	-
Movement Disorder Society's Unified PD Rating Scale (MDS-UPDRS) Part 3 in the off-medication state			
Sum of the corresponding items for Part 3 of the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (33 scores based on 18 questions with several right, left, or both			

body distribution scores) in the off-medication state. Each Parkinsonian sign or symptom is rated on a 5 # point Likert # type scale (ranging from 0 to 4), with higher scores indicating more severe impairment. The minimum score on the MDS-UPDRS Part 3 is 0 and the maximum is 132.			
Units: Score on a scale			
arithmetic mean	35.2	38.5	
standard deviation	± 14.17	± 12.44	-

End points

End points reporting groups

Reporting group title	AKST4290
Reporting group description:	
Subjects will receive AKST4290, 400 mg twice daily, for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects will receive placebo, 400 mg twice daily, for 12 weeks.	
Subject analysis set title	Modified Intent-to-Treat/Evaluable
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects with non-missing Baseline and primary endpoint data	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of the study medication	

Primary: Change in Motor Function During Levodopa Withdrawal

End point title	Change in Motor Function During Levodopa Withdrawal
End point description:	
Change from Baseline in motor function during the practically defined off-medication state, defined as at least 12 hours off levodopa, at Week 12 as measured by Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part 3 Motor Examination (33 scores based on 18 questions with several right, left, or both body distribution scores). Each Parkinsonian sign or symptom is rated on a 5point Likerttype scale (ranging from 0 to 4), with higher scores indicating more severe impairment. The minimum score on the MDS-UPDRS Part 3 is 0 and the maximum is 132.	
End point type	Primary
End point timeframe:	
Baseline to 12 weeks	

End point values	AKST4290	Placebo	Modified Intent-to-Treat/Evaluable	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	45	45	90	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change in Motor Function During Levodopa Withdrawa	-4.0 (± 8.16)	-5.3 (± 7.58)	-4.7 (± 7.86)	

Statistical analyses

Statistical analysis title	Change from baseline at Week 12 (Day 84)

Statistical analysis description:

The main analysis for the primary efficacy variable will be analyzed using modified Intent-to-Treat subjects.

Comparison groups	AKST4290 v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to Week 14	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	AKST4290
Reporting group description:	
Subjects will receive AKST4290, 400 mg twice daily, for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects will receive placebo, twice daily, for 12 weeks.	

Serious adverse events	AKST4290	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 52 (1.92%)	3 / 55 (5.45%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Neuropsychiatric syndrome			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Clostridium difficile colitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AKST4290	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 52 (15.38%)	11 / 55 (20.00%)	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 52 (1.92%)	4 / 55 (7.27%)	
occurrences (all)	1	4	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 52 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 52 (5.77%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 52 (5.77%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 52 (1.92%)	4 / 55 (7.27%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2019	Expanded to Germany and updated US site number, update eligibility criteria to provide clarity and reflect global regulatory requirements, update schedule of events
17 May 2019	Provide justification of dose selection, add exploratory endpoint and assessment
24 July 2019	Expand geographic range to support timely recruitment and additional geographic representation, update eligibility criteria to aid investigators in determining eligibility and reflect global regulatory requirements
02 December 2019	Update eligibility criteria and prohibited medications based on findings from a clinical drug-drug interaction study
06 January 2020	Germany and US version of amendment 3.0
22 May 2020	Update content to provide clarification on the order of assessments, add new optional sample collections, and new content added to account for potential protocol deviations related to COVID-19.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: