Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo Controlled, Study to Evaluate Multiple Doses of AK001 in Patients With Moderate to Severe Nasal Polyposis

Summary

EudraCT number	2016-000460-42
Trial protocol	BE GB ES NL DE
Global end of trial date	05 January 2018

Results information

Result version number	v1 (current)
This version publication date	20 January 2019
First version publication date	20 January 2019

Trial information

Trial identification

Sponsor protocol code	AK001-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Allakos, Inc.
Sponsor organisation address	975 Island Drive, Suite 201, Redwood City, United States, CA 94065
Public contact	Clinical Trials Information, Allakos, Inc., +1 6505975002, rwinger@allakos.com
Scientific contact	Clinical Trials Information, Allakos, Inc., +1 6505975002, rwinger@allakos.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	05 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2017
Global end of trial reached?	Yes
Global end of trial date	05 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of each of 2 doses of AK001 separately in combination with an intranasal steroid (INS) versus the INS alone on the reduction in size of nasal polyps as evaluated by the change from Baseline to Week 12 after the start of treatment in Total Polyp Score (TPS)

Protection of trial subjects:

A data monitoring committee was available to monitor the safety of patients over the course of the study. The intravenous (IV) infusion could be interrupted for 5 to 30 minutes and the rate could be reduced and gradually increased in 15-minute intervals if a patient experienced infusion-related reactions. Medication to treat mild or moderate infusion-reactions were ready to be used. Signs or symptoms of anaphylaxis were carefully monitored and treated according to standard of care. Emergency crash cart equipment was available at all times during the conduct of the study.

Background therapy:

Eligible patients entered a 4-week Run-In Period to achieve a stable regimen with a common intranasal topical steroid (NASONEX [mometasone furoate monohydrate]) and discontinued any other intranasal topical steroids. Patients were instructed to self-administer 2 nasal inhalations in each nostril twice a day. Patients still eligible after the run-in period were randomized and continued treatment with NASONEX as background therapy throughout the study.

Evidence for comparator: -

Actual start date of recruitment	04 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	European Union: 25
Worldwide total number of subjects	40
EEA total number of subjects	0

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)	38
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with moderate to severe chronic nasal polyposis and whose symptoms were resistant to treatment with intranasal steroids were recruited at a total of 15 sites in the United States and European Union (including sites in Spain, Belgium, The Netherlands, and Germany). The first informed consent form was signed on 04-Apr-2016.

Pre-assignment

Screening details:

After the Screening Period, eligible patients were enrolled and entered the Run-In Period to achieve a stable regimen with Nasonex and discontinued any other intranasal topical steroid. Thereafter, 40 eligible patients were randomized stratified by presence of asthma to 25mg or 250mg AK001 or placebo treatment.

Period 1

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

Blinding implementation details:

To maintain the blind, the prepared test and control IV infusion solutions were identical in appearance. Access to the randomization codes were strictly controlled via the interactive voice or web response system. Throughout the study, the blind remained unbroken until completion of the study and after the study database had been locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	25 mg AK001

Arm description:

25 mg AK001 was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.

Arm type	Experimental
Investigational medicinal product name	AK001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AK001 Drug Product was supplied as a sterile liquid in a single-use glass vial. For dose administration, the assigned amount of AK001 was diluted with 0.9% sodium chloride for IV injection.

Arm title	250 mg AK001

Arm description:

250 mg AK001 was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.

Arm type	Experimental
Investigational medicinal product name	AK001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AK001 Drug Product was supplied as a sterile liquid in a single-use glass vial. For dose administration, the assigned amount of AK001 was diluted with 0.9% sodium chloride for IV injection.

Arm title	Placebo

Arm description:

Placebo was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The placebo was supplied as a sterile liquid in a single-use glass vial. The vial was indistinguishable from the AK001 active product. For dose administration, the assigned amount of placebo was diluted with 0.9% sodium chloride for IV injection.

Number of subjects in period 1[1]	25 mg AK001	250 mg AK001	Placebo
Started	15	14	10
Completed	12	14	9
Not completed	3	0	1
Consent withdrawn by subject	2	-	1
Adverse event, non-fatal	1	-	-

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 was randomized but never received study treatment, because it was noted that the subject did not qualify based on inclusion criteria. The patient was excluded from all analysis sets.

Baseline characteristics

Reporting groups	
Reporting group title	25 mg AK001
Reporting group description:	
25 mg AK001 was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.	
Reporting group title	250 mg AK001
Reporting group description:	
250 mg AK001 was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.	

Reporting group values	25 mg AK001	250 mg AK001	Placebo
Number of subjects	15	14	10
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)	13	14	10
From 65-84 years	2	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	48.0	46.5	45.0
full range (min-max)	24 to 71	27 to 63	29 to 60
Gender categorical Units: Subjects			
Female	5	8	5
Male	10	6	5

Reporting group values	Total		
Number of subjects	39		
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)	37		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	18		
Male	21		

End points

End points reporting groups

Reporting group title	25 mg AK001
Reporting group description:	
25 mg AK001 was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.	
Reporting group title	250 mg AK001
Reporting group description:	
250 mg AK001 was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered as a single IV infusion through a peripheral vein on Days 0, 21, and 49.	

Primary: Change in total polyp score (TPS)

End point title	Change in total polyp score (TPS)[1]
End point description:	

End point type	Primary
End point timeframe:	
Change in TPS from Baseline (prior to the first dose) to Week 12 (Day 84).	

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: The study was terminated early because the Sponsor decided not to pursue further development of AK001 and was, consequently, underpowered for the endpoint comparison. Statistical analyses of the primary endpoint did not show statistically significant results for either the comparison of the 25 mg or the 250 mg group with placebo.

End point values	25 mg AK001	250 mg AK001	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	14	10	
Units: score				
least squares mean (confidence interval 95%)	-0.5 (-1.3 to 0.3)	-0.3 (-1.1 to 0.5)	-0.2 (-1.1 to 0.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of study drug administration until completion of the last study-related procedure.

Adverse event reporting additional description:

If a patient completed the study with an ongoing adverse event (AE), investigational site personnel continued to follow-up until AE resolution and the documentation thereof. If, after 30 days from the study completion date, the AE was still continuing but not assessed as serious, the outcome was recorded as ongoing.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	25 mg AX001

Reporting group description:

25 mg AX001 will be administered as a single intravenous infusion over about 1 hour through a peripheral vein on Day 0, 21, and 49.

Reporting group title	250 mg AX001

Reporting group description:

250 mg AX001 will be administered as a single intravenous infusion over about 1 hour through a peripheral vein on Day 0, 21, and 49.

Reporting group title	Placebo

Reporting group description:

Placebo will be administered as a single intravenous infusion over about 1 hour through a peripheral vein on Day 0, 21, and 49.

Serious adverse events	25 mg AX001	250 mg AX001	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	25 mg AX001	250 mg AX001	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 15 (73.33%)	10 / 14 (71.43%)	7 / 10 (70.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0

General disorders and administration site conditions			
Facial pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Nasal congestion			
subjects affected / exposed	2 / 15 (13.33%)	2 / 14 (14.29%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Nasal discharge discolouration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nasal obstruction			

subjects affected / exposed	3 / 15 (20.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Throat irritation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Heart rate increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Weight increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Upper limb fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Ventricular extrasystoles			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	2 / 15 (13.33%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Memory impairment			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Syncope			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Toothache			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	1 / 10 (10.00%)
occurrences (all)	1	1	1

Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Angioedema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Erythema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Generalised erythema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Pruritus generalised			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Muscle fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			

subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Impetigo			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	4 / 15 (26.67%)	2 / 14 (14.29%)	1 / 10 (10.00%)
occurrences (all)	4	3	2
Otitis media acute			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3	0 / 14 (0.00%) 0	0 / 10 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 14 (7.14%) 1	0 / 10 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2016	Amendment 2: - specified that 2 doses of AK001 were being evaluated - clarified the handling of biomarker samples - corrected typographical errors - specified that dose preparation and administration were provided in a Study Manual - clarified labelling information and methods of unblinding - removed the recording of patient's initials in the eCRF.
05 September 2016	Amendment 1: - following a health authority request, inclusion criteria were changed - changed visit window of last study visit - extended the Run-In Period into the Screening period - added the assessment of clinical symptoms for rhinosinusitis by using a validated scale - removed unnecessary requirements (i.e. 2-hour fasting, assessment of vital signs before blood draw, post-dose blood draw for pharmacokinetics) - clarifications

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.

After 40 of the 70 patients planned were randomized in the study, enrollment was stopped as the Sponsor decided not to pursue further development of AK001. The study was not stopped for any safety concern.

Notes: