Clinical trial results:
A randomized, double-blind, placebo-controlled, 12-week treatment study to evaluate the effect of ACT-774312 in subjects with bilateral nasal polyposis

Summary

EudraCT number	2018-000851-42
Trial protocol	BE DE
Global end of trial date	01 December 2020

Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

Trial information

Trial identification

Sponsor protocol code	ID-084A201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03688555
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Idorsia Pharmaceuticals Ltd
Sponsor organisation address	Hegenheimermattweg 91, Allschwil, Switzerland, 4123
Public contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, +41 58 844 19 77, clinical-trials-disclosure@idorsia.com
Scientific contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, +41 58 844 19 77, clinical-trials-disclosure@idorsia.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	04 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2020
Global end of trial reached?	Yes
Global end of trial date	01 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of ACT-774312 on bilateral nasal polyposis (NP).

Protection of trial subjects:

Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC), i.e., a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation. The protocol and any material provided to the subject (such as a subject information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate IEC before the study was started. Sponsor personnel and the investigators were required to conduct the study in full compliance with ICH GCP Guidelines, the principles of the Declaration of Helsinki, and with the laws and regulations of the countries in which the study is conducted. Both the sponsor and the investigators had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests. The investigators were responsible for maintaining the subjects' identities in strictest confidence. Written informed consent was required to be obtained from each individual participating in the study prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It was made clear to each subject that he or she was completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

Background therapy:

Mandatory medications:
- Non-investigational medicinal product (standard background therapy): Mometasone furoate nasal spray 50 µg/actuation nasal spray, suspension. Dosing regimen: 2 actuations (50 µg/actuation) in each nostril twice daily (or once daily if twice daily was not tolerated).
- Mandatory therapy included any treatments required for contraception purposes in women of childbearing potential.

All subjects with asthma continued their prescribed treatment throughout the study. Additionally, 4 subjects took study-concomitant medications to treat other ongoing co-morbidities (hypercholesterolemia, gastritis, hypertension, and allergy). Other study-concomitant medications were administered to treat acute infections or infestations. These concomitant medications were not expected to interact with ACT-774312.

Evidence for comparator:

In this study, ACT-774312 was compared to placebo. Both study treatments were administered on top of standard background therapy: mometasone furoate nasal spray therapy.

Actual start date of recruitment	19 October 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	Belgium: 3
Country: Number of subjects enrolled	Germany: 7
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	9
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between the 19 Oct 2018 and 01 Dec 2020. The study was conducted at 2 sites in 2 countries (Belgium and Germany), both sites randomized subjects.

Pre-assignment

Screening details:

The screening period lasted for up to 21 days. This period started with the screening visit (Visit 1) and ended on Day 1 (Visit 2) just before the first ACT-774312 or placebo administration. At screening, subjects were on a stable regimen of intranasal corticosteroids for at least 8 weeks.

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ACT-774312

Arm description:

ACT-774312 was administered twice daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	ACT-774312
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received ACT-774312 400 mg twice daily in the morning and evening with or without food for 12 weeks.

Arm title	Placebo

Arm description:

Matching placebo capsules were administered twice daily for 12 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo capsules in the morning and evening with or without food for 12 weeks.

Number of subjects in period 1	ACT-774312	Placebo
Started	7	3
Completed	7	2
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ACT-774312
Reporting group description:	
ACT-774312 was administered twice daily for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Matching placebo capsules were administered twice daily for 12 weeks	

Reporting group values	ACT-774312	Placebo	Total
Number of subjects	7	3	10
Age categorical			
Units: Subjects			
Adults (18-64 years)	6	3	9
From 65-84 years	1	0	1
Age continuous			
Units: years			
arithmetic mean	50.3	54.7	
standard deviation	± 10.9	± 5.5	-
Gender categorical			
Units: Subjects			
Female	1	1	2
Male	6	2	8
Race			
Units: Subjects			
White	6	3	9
American Indian or Alaska Native	1	0	1
Body Mass Index (BMI)			
Units: kilogram(s)/square meter			
arithmetic mean	28.204	26.003	
standard deviation	± 5.254	± 2.807	-
Nasal Polyp Score			
The Nasal Polyp Score was scored by independent reviewers reviewing image recordings of nasal endoscopy. The sum of right and left nostril scores was used for a total score. The total score ranged from 0 to 8, where a score of 0 means there are no polyps in the nose. A score of 8 indicates the presence of large polyps causing complete obstruction/congestion of the inferior meatus in both nostrils. To be eligible for the study a participant had to have a minimum bilateral NPS of 5 out of a maximum of 8 for both nostrils (with at least a score of 2 for each nostril).			
Units: Score on a scale			
arithmetic mean	6.4	6.0	
standard deviation	± 0.5	± 1.0	-
Modified Lund-Mackay Score			
The modified Lund Mackay Score scores were given for the degree of opacification and their location in the sinus. The right & left sinuses are divided into 6 portions, i.e., maxillary sinus, anterior ethmoid sinuses, posterior ethmoid sinuses, sphenoid sinus, frontal sinus, and ostiomeatal complex (OMC). The OMC is given a score of 0 (no obstruction) or 1 (obstruction) for the frontal recess, middle meatus, infundibulum, and the sphenoethmoidal recess channels. The total score is the sum of the right and left nostril scores and range from 0 (normal sinuses) to a maximum of 48.			
Units: Score on scale			
arithmetic mean	30.7	34.7	
standard deviation	± 13.8	± 12.0	-

3D Volumetric computerized values - Volume of Air (Left maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	4.9	2.2	
standard deviation	± 6.0	± 1.5	-
3D Volumetric computerized values - Volume of Air (Right maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	7.1	2.3	
standard deviation	± 5.7	± 3.8	-
3D Volumetric computerized values - Volume of mucosa (Left maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	15.7	21.4	
standard deviation	± 7.9	± 4.3	-
3D Volumetric computerized values - Volume of mucosa (Right maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	13.7	22.1	
standard deviation	± 8.3	± 2.2	-
University of Pennsylvania Smell Identification Test			
The University of Pennsylvania Smell Identification Test measures an individual's ability to detect odors. The UPSI Test has 40 questions in total. The number of correct responses regarding the smells being experienced is summed to provide a total score that ranges from 0 (no correct response to all 40 questions) to 40 (correct response to all 40 questions), with a higher score indicating a better sense of smell.			
Units: Score on scale			
arithmetic mean	14.4	11.7	
standard deviation	± 8.9	± 3.8	-
Visual Analog Scale Symptoms Score			
The subject was asked to indicate on a Visual Analog Scale (VAS) the answer to the question: "How troublesome are your symptoms?" (for nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain) The sum total VAS (for all 5 symptoms) ranged from 0 (Not at all troublesome) to 500 (Extremely troublesome).			
Units: Score on scale			
arithmetic mean	328.6	355.7	
standard deviation	± 74.5	± 87.5	-
Physician Global Assessment Disease Severity Score			
The PGAC-DS questionnaire is a self-administered 1-item questionnaire designed to assess the physician's impression of change in disease severity since screening. The physician rated the change on the overall severity of the disease symptoms on a 7-point scales scored where: 'very much improved' (is scored 1), 'much improved' (is scored 2), 'minimally improved' (is scored 3), 'no change' (is scored 4), 'minimally worse' (is scored 5), 'much worse' (is scored 6), or 'very much worse' (is scored 7).			
Units: Score of scale			
arithmetic mean	3.3	3.3	
standard deviation	± 0.5	± 0.6	-
Sino-Nasal Outcome Test			
The SNOT-22 (Sino-Nasal Outcome Test) is a disease specific quality of life questionnaire measure that comprises a list of 22 symptoms and social or emotional consequences of the nasal disorder. Every subject was asked to rate how severe each problem had been for them over the past 2 weeks on a scale from 0 (no problem) to 5 (problem as bad as it can be). The total score is the sum of the scores for all 22 items, ranging from 0 to 110. Higher total scores on the SNOT-22 imply greater impact on Quality of Life.			
Units: Score on scale			
arithmetic mean	57.0	61.0	

standard deviation	± 13.0	± 13.7	-

Subject analysis sets	
Subject analysis set title	ACT-774312
Subject analysis set type	Per protocol

Subject analysis set description:

The ACT-774312 per protocol set included all randomized subjects that completed the ACT-774312 treatment up to Week 12 without protocol deviations that could affect the evaluation of the primary endpoint.

Subject analysis set title	Matching Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

The matching placebo per protocol set included all randomized subjects that completed the ACT-774312 treatment up to Week 12 without protocol deviations that could affect the evaluation of the primary endpoint.

Reporting group values	ACT-774312	Matching Placebo	
Number of subjects	5	2	
Age categorical Units: Subjects			
Adults (18-64 years)	2	5	
From 65-84 years	0	0	
Age continuous Units: years arithmetic mean standard deviation	 ±	 ±	
Gender categorical Units: Subjects			
Female	1	1	
Male	4	1	
Race Units: Subjects			
White	4	2	
American Indian or Alaska Native	1	0	
Body Mass Index (BMI) Units: kilogram(s)/square meter arithmetic mean standard deviation	 ±	 ±	
Nasal Polyp Score			
The Nasal Polyp Score was scored by independent reviewers reviewing image recordings of nasal endoscopy. The sum of right and left nostril scores was used for a total score. The total score ranged from 0 to 8, where a score of 0 means there are no polyps in the nose. A score of 8 indicates the presence of large polyps causing complete obstruction/congestion of the inferior meatus in both nostrils. To be eligible for the study a participant had to have a minimum bilateral NPS of 5 out of a maximum of 8 for both nostrils (with at least a score of 2 for each nostril).			
Units: Score on a scale arithmetic mean standard deviation	 6.4 ± 0.5	 6.5 ± 0.7	
Modified Lund-Mackay Score			
The modified Lund Mackay Score scores were given for the degree of opacification and their location in the sinus. The right & left sinuses are divided into 6 portions, i.e., maxillary sinus, anterior ethmoid			

sinuses, posterior ethmoid sinuses, sphenoid sinus, frontal sinus, and ostiomeatal complex (OMC). The OMC is given a score of 0 (no obstruction) or 1 (obstruction) for the frontal recess, middle meatus, infundibulum, and the sphenoethmoidal recess channels. The total score is the sum of the right and left nostril scores and range from 0 (normal sinuses) to a maximum of 48.			
Units: Score on scale			
arithmetic mean	26.6	28.5	
standard deviation	± 14.1	± 7.8	
3D Volumetric computerized values - Volume of Air (Left maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	6.4	3.1	
standard deviation	± 6.6	± 0.2	
3D Volumetric computerized values - Volume of Air (Right maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	9.0	3.5	
standard deviation	± 5.6	± 4.6	
3D Volumetric computerized values - Volume of mucosa (Left maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	15.4	20.6	
standard deviation	± 9.5	± 5.8	
3D Volumetric computerized values - Volume of mucosa (Right maxillary sinus)			
Units: millilitre(s)			
arithmetic mean	13.0	20.8	
standard deviation	± 9.8	± 0.06	
University of Pennsylvania Smell Identification Test			
The University of Pennsylvania Smell Identification Test measures an individual's ability to detect odors. The UPSI Test has 40 questions in total. The number of correct responses regarding the smells being experienced is summed to provide a total score that ranges from 0 (no correct response to all 40 questions) to 40 (correct response to all 40 questions), with a higher score indicating a better sense of smell.			
Units: Score on scale			
arithmetic mean	14.6	9.5	
standard deviation	± 10.9	± 0.7	
Visual Analog Scale Symptoms Score			
The subject was asked to indicate on a Visual Analog Scale (VAS) the answer to the question: "How troublesome are your symptoms?" (for nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain) The sum total VAS (for all 5 symptoms) ranged from 0 (Not at all troublesome) to 500 (Extremely troublesome).			
Units: Score on scale			
arithmetic mean	304.0	323.5	
standard deviation	± 75.0	± 95.5	
Physician Global Assessment Disease Severity Score			
The PGAC-DS questionnaire is a self-administered 1-item questionnaire designed to assess the physician's impression of change in disease severity since screening. The physician rated the change on the overall severity of the disease symptoms on a 7-point scales scored where: 'very much improved' (is scored 1), 'much improved' (is scored 2), 'minimally improved' (is scored 3), 'no change' (is scored 4), 'minimally worse' (is scored 5), 'much worse' (is scored 6), or 'very much worse' (is scored 7).			
Units: Score of scale			
arithmetic mean	3.0	3.0	
standard deviation	± 0.0	± 0.0	
Sino-Nasal Outcome Test			
The SNOT-22 (Sino-Nasal Outcome Test) is a disease specific quality of life questionnaire measure that			

comprises a list of 22 symptoms and social or emotional consequences of the nasal disorder. Every subject was asked to rate how severe each problem had been for them over the past 2 weeks on a scale from 0 (no problem) to 5 (problem as bad as it can be). The total score is the sum of the scores for all 22 items, ranging from 0 to 110. Higher total scores on the SNOT-22 imply greater impact on Quality of Life.			
Units: Score on scale			
arithmetic mean	61.4	59.5	
standard deviation	± 9.2	± 19.1	

End points

End points reporting groups

Reporting group title	ACT-774312
Reporting group description:	
ACT-774312 was administered twice daily for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Matching placebo capsules were administered twice daily for 12 weeks	
Subject analysis set title	ACT-774312
Subject analysis set type	Per protocol
Subject analysis set description:	
The ACT-774312 per protocol set included all randomized subjects that completed the ACT-774312 treatment up to Week 12 without protocol deviations that could affect the evaluation of the primary endpoint.	
Subject analysis set title	Matching Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
The matching placebo per protocol set included all randomized subjects that completed the ACT-774312 treatment up to Week 12 without protocol deviations that could affect the evaluation of the primary endpoint.	

Primary: Change from Baseline to Week 12 in the Nasal Polyps Score

End point title	Change from Baseline to Week 12 in the Nasal Polyps Score
End point description:	
Independent reviewers, blinded to treatment, reviewed image recordings of nasal endoscopies to determine total endoscopic nasal polyp score (NPS) based on nasal polyp (NP) size. The right and left nostrils were scored from 0 to 4 (0 = No polyps; 1 = Small polyps in the middle meatus not reaching below the inferior border of the middle concha; 2 = Polyps reaching below the lower border of the middle turbinate; 3 = Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha; and 4 = Large polyps causing complete obstruction/congestion of the inferior meatus). The total score is the sum of the right and left nostril scores and ranges from 0 to 8, higher scores indicate greater disease severity. Data up to Week 12 were included in the analyses. The main analysis was performed on the per-protocol set. Baseline was defined as Day 1 value. Change from Baseline = (Post-baseline visit value) minus (Baseline visit value).	
End point type	Primary
End point timeframe:	
Baseline (Day 1) and Week 12.	

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: score on scale				
least squares mean (standard error)	-0.23 (± 0.161)	-0.99 (± 0.253)		

Statistical analyses

Statistical analysis title	ACT-774312 vs placebo

Statistical analysis description:

All Nasal Polyp Score (NPS) values observed between baseline and Week 12 were included in the analysis. Changes from baseline to post-baseline visits in NPS were analyzed using a Mixed Model for Repeated Measurement (MMRM).

Comparison groups	ACT-774312 v Matching Placebo
Number of subjects included in analysis	7
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062
Method	Mixed model for repeated measurements
Parameter estimate	LS means difference
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	1.59
Variability estimate	Standard error of the mean
Dispersion value	0.301

Secondary: Change from Baseline to Week 12 in the sinus opacifications as assessed by Computer Tomography Scan using the modified Lund-Mackay Score

End point title	Change from Baseline to Week 12 in the sinus opacifications as assessed by Computer Tomography Scan using the modified Lund-Mackay Score

End point description:

Independent blinded reviewers reviewed image recordings of the computed tomography scan. The modified Lund Mackay Score scores were given for the degree of opacification and their location in the sinus. The right and left sinuses are divided into 6 portions, i.e., maxillary sinus, anterior ethmoid sinuses, posterior ethmoid sinuses, sphenoid sinus, frontal sinus, and ostiomeatal complex (OMC). The OMC is given a score of 0 (no obstruction) or 1 (obstruction) for the frontal recess, middle meatus, infundibulum, and the sphenoethmoidal recess channels. The total score is the sum of the right and left nostril scores and range from 0 to a maximum of 48. A positive change from baseline (Day 1) indicates a worsening.

Change in the modified Lund-Mackay score = (modified Lund-Mackay score at Week 12) minus (modified Lund-Mackay score at baseline).

A positive change from baseline indicated a worsening in the modified Lund-Mackay Score at Week 12 compared to baseline.

End point type	Secondary

End point timeframe:

Day 1 (Baseline) and Week 12.

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: Score on scale				
least squares mean (standard error)	0.86 (± 1.24)	4.84 (± 1.96)		

Statistical analyses

Statistical analysis title	Per-protocol analysis set: ACT-774312 vs placebo

Statistical analysis description:

The change from baseline to Week 12 in modified Lund-Mackay score was analyzed on the per protocol population using an ANCOVA model with a factor for treatment group and a covariate for the baseline score.

Comparison groups	ACT-774312 v Matching Placebo
Number of subjects included in analysis	7
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161
Method	ANCOVA
Parameter estimate	LS means difference
Point estimate	-3.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.41
upper limit	2.45
Variability estimate	Standard error of the mean
Dispersion value	2.316

Secondary: Change from Baseline to Week 12 in the Volume of Air in the Left Maxillary Sinus

End point title	Change from Baseline to Week 12 in the Volume of Air in the Left Maxillary Sinus

End point description:

Independent reviewers, blinded to treatment, reviewed image recordings of the computed tomography scan and performed 3D volumetric measurements of the left maxillary sinus. Absolute changes from baseline were calculated for volume of air (mL). Change in 3D volumetric measurement = (3D volumetric measurement at Week 12) minus (3D volumetric measurement at baseline). A positive change from baseline indicates that more volume for air is in the left maxillary sinus since the baseline visit. More volume of air indicates that the polyposis is improving in the left maxillary sinus.

End point type	Secondary

End point timeframe:

Day 1 (Baseline) and Week 12

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: millilitre(s)				
arithmetic mean (standard deviation)	1.17 (± 1.72)	-1.08 (± 2.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in the Volume of Air in the Right Maxillary Sinus

End point title	Change from Baseline to Week 12 in the Volume of Air in the Right Maxillary Sinus

End point description:

Independent reviewers, blinded to treatment, reviewed image recordings of the computed tomography scan and performed 3D volumetric measurements of the right maxillary sinus.
Absolute changes from baseline were calculated for the volume of air (mL) in the right maxillary sinus: Change in 3D volumetric measurement = (3D volumetric measurement at Week 12) minus (3D volumetric measurement at baseline). A positive change from baseline indicates that more volume for air is in the right maxillary sinus since the baseline visit. More volume of air indicates that the polyposis is improving in the right maxillary sinus.

End point type	Secondary

End point timeframe:

Day 1 (Baseline) and Week 12

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: millilitre(s)				
arithmetic mean (standard deviation)	-0.94 (± 4.36)	1.77 (± 1.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in the Left Maxillary Sinus Mucosal Volume

End point title	Change from Baseline to Week 12 in the Left Maxillary Sinus Mucosal Volume

End point description:

Independent reviewers, blinded to treatment, reviewed image recordings of the computed tomography scan and performed 3D volumetric measurements of the left maxillary sinus.
Absolute changes from baseline were calculated for the volume of air (mL) in the left maxillary sinus: Change in 3D volumetric measurement = (3D volumetric measurement at Week 12) minus (3D volumetric measurement at baseline). A negative change from baseline indicates that the left maxillary

sinus mucosal volume has decreased since the baseline visit. More mucosal volume, a positive change, indicates that the polyposis is worsening in the left maxillary sinus.

End point type	Secondary

End point timeframe:

Day 1 (baseline) and Week 12

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: millilitre(s)				
arithmetic mean (standard deviation)	-1.72 (± 1.72)	-1.08 (± 2.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in the Right Maxillary Sinus Mucosal Volume

End point title	Change from Baseline to Week 12 in the Right Maxillary Sinus Mucosal Volume

End point description:

Independent reviewers, blinded to treatment, reviewed image recordings of the computed tomography scan and performed 3D volumetric measurements of the right maxillary sinus.
Absolute changes from baseline were calculated for the volume of air (mL) in the right maxillary sinus: Change in 3D volumetric measurement = (3D volumetric measurement at Week 12) minus (3D volumetric measurement at baseline). A negative change from baseline indicates that the right maxillary sinus mucosal volume has decreased since the baseline visit. More mucosal volume, a positive change, indicates that the polyposis is worsening in the right maxillary sinus.

End point type	Secondary

End point timeframe:

Day 1 (Baseline) and Week 12

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: millilitre(s)				
arithmetic mean (standard deviation)	0.94 (± 4.36)	-1.78 (± 1.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in the University of Pennsylvania Smell Identification Test

End point title	Change from Baseline to Week 12 in the University of Pennsylvania Smell Identification Test

End point description:

The UPSIT (University of Pennsylvania Smell Identification Test) is a test that measures an individual's ability to detect odors. It consists of 4 workbooks of 10 pages each. On each page there is a different "scratch and sniff" strip which is embedded with a micro-encapsulated odorant and a question regarding the smell detected with a four-choice option for the response. The total number of questions in the UPSIT is 40. The number of correct responses regarding the smells being experienced is summed to provide a total score that ranges from 0 to 40, with a higher score indicating a better sense of smell. Absolute changes from baseline to Week 12 was calculated as follows: Change in UPSIT score = (UPSIT score at Week 12) minus (UPSIT score at baseline). A positive change from baseline in the UPSIT score is considered a favorable outcome.

End point type	Secondary

End point timeframe:

Day 1 (Baseline) and Week 12

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: Score on scale				
arithmetic mean (standard deviation)	1.0 (± 8.4)	-0.5 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Visual Analog Scale Symptoms Score

End point title	Change from Baseline in the Visual Analog Scale Symptoms Score

End point description:

The subject was asked to score on a Visual Analog Scale (VAS) the answer to the question: "How troublesome are your symptoms?" (for the 5 following symptoms: nasal obstruction, nasal discharge, - mucus in the throat, loss of smell, facial pain). The VAS ranges from 0 (Not at all troublesome) to 100 (Extremely troublesome). The sum of the score of all symptoms were added to a total VAS score which ranged from 0 to 500. The higher the VAS score the more troublesome the symptoms. Absolute changes from baseline to Weeks 2, 4, 8, 12, and EOS are calculated as follows: Change in total VAS score = (Total VAS score at visit) minus (Total VAS score at baseline). A negative change from baseline indicates an improvement.

End point type	Secondary

End point timeframe:

Day 1 (Baseline), Week 2, Week 4, Week 8, Week 12 and End of Study (Week 16)

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: Score on scale				
arithmetic mean (standard deviation)				
Week 2	-69.8 (± 68.4)	-77.5 (± 136.5)		
Week 4	-108 (± 106)	-58.0 (± 18.4)		
Week 8	-70.5 (± 121.3)	-88.50 (± 61.5)		
Week 12	-90.0 (± 55.9)	-156 (± 123.7)		
End of Study (Week 16)	-105.40 (± 78.88)	-57.00 (± 104.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Physician Global Assessment of Change in Disease Severity

End point title	Physician Global Assessment of Change in Disease Severity

End point description:

The Physician Global Assessment of Disease Severity questionnaire (PGAC-DS) was completed by the physician at Visit 2 and at each subsequent site visit until the End-of-Study (Week 16). The PGAC-DS questionnaire is a self-administered 1-item questionnaire designed to assess the physician's impression of change in disease severity since study treatment start. The physician rated the change since the participant study treatment start. The physician rated the change since the participant started study treatment on a 7-point scale. The rating for the overall score is: 'very much improved' (is scored 1), 'much improved' (is scored 2), 'minimally improved' (is scored 3), 'no change' (is scored 4), 'minimally worse' (is scored 5), 'much worse' (is scored 6), or 'very much worse' (is scored 7).

End point type	Secondary

End point timeframe:

Week 2, Week 4, Week 8, Week 12, and End of Study (Week 16)

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: Score on scale				
arithmetic mean (standard deviation)				
Week 2	3.4 (± 0.5)	3.0 (± 1.4)		
Week 4	3.0 (± 0.7)	3.0 (± 1.4)		
Week 8	3.6 (± 1.3)	2.5 (± 0.7)		
Week 12	3.4 (± 0.5)	4.0 (± 1.4)		
End of Study (Week 16)	3.6 (± 0.5)	4.0 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Sino-Nasal Outcome Test

End point title	Change from Baseline in the Sino-Nasal Outcome Test

End point description:

SNOT-22 (Sino-Nasal Outcome Test) is a disease specific quality of life questionnaire measure that comprises a list of 22 symptoms and social or emotional consequences of the nasal disorder. Every subject was asked to rate how severe each problem had been for them over the past 2 weeks on a scale from 0 (no problem) to 5 (problem as bad as it can be). The total score is the sum of the scores for all 22 items, ranging from 0 to 110. Higher total scores on the SNOT-22 imply greater impact on Quality of Life. Absolute changes from baseline to Weeks 2, 4, 8, 12, and 16 were calculated as follows: Change in SNOT-22 score = (SNOT-22 score at visit) minus (SNOT-22 score at baseline).
A negative change from baseline in SNOT-22 is considered a favorable outcome.

End point type	Secondary

End point timeframe:

Week 2, Week 4, Week 8, Week 12, End of Study (Week 16)

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: Score on scale				
arithmetic mean (standard deviation)				
Week 2	-7.2 (± 18.5)	-22.5 (± 27.6)		
Week 4	-21.4 (± 11.0)	-21.5 (± 16.3)		
Week 8	-14.4 (± 14.7)	-29.0 (± 18.4)		
Week 12	-15.2 (± 5.3)	-21.5 (± 16.3)		
End of Study (Week 16)	-16.4 (± 3.9)	-24.0 (± 22.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change in Disease Severity

End point title	Patient Global Impression of Change in Disease Severity

End point description:

A patient global impression of change in disease severity questionnaire (PGIC-DS) was completed by the subject at Week 2 and at each subsequent site visit until the End of study visit.
The PGIC-DS questionnaire was a self-administered 1-item questionnaire designed to assess subject's impression of change in disease severity since study treatment start.
Subjects rated their change since they started study treatment for the overall severity of the disease symptoms on a 7-point scale (1 to 7) scored as: "very much improved (1)," "much improved," (2) "minimally improved,"(3) "no change," (4) "minimally worse," (5) "much worse," (6) or "very much worse" (7).

End point type	Secondary

End point timeframe:

Week 2, Week 4, Week 8, Week 12, End of Study (Week 16)

End point values	ACT-774312	Matching Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2		
Units: Score on scale				
arithmetic mean (standard deviation)				
Week 2	3.2 (± 0.4)	2.5 (± 2.1)		
Week 4	3.0 (± 0.7)	2.5 (± 2.1)		
Week 8	3.4 (± 1.5)	2.0 (± 0.0)		
Week 12	3.4 (± 0.5)	2.0 (± 0.0)		
End of Study (Week 16)	3.4 (± 0.9)	2.5 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were all adverse events that occurred after first study treatment administration on Day 1 through to last study treatment administration on Day 84, and in the post-treatment period up to the end-of-study visit on Day 112.

Adverse event reporting additional description:

A treatment-emergent adverse event is any adverse event temporally associated with the use of a study treatment, whether or not considered related to the study treatment in all subjects that took at least one dose of treatment (placebo or ACT-774312).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	ACT-774312

Reporting group description:

ACT-774312 was administered twice daily for 12 weeks

Reporting group title	Placebo

Reporting group description:

Matching placebo capsules were administered twice daily for 12 weeks

Serious adverse events	ACT-774312	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (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: 0 %

Non-serious adverse events	ACT-774312	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	3 / 3 (100.00%)	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Premenstrual headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Nasal polyps	Additional description: Episodes of worsening of nasal polyps.		
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Chronic rhinosinusitis with nasal polyps			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Asthma	Additional description: Worsening of asthma bronchiale		
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nasal inflammation			

subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Myringitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Otosalpingitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 August 2019	The study was initially planned as a single-center study. Due to difficulties in recruiting subjects, it was decided to open up 1 additional site outside of Belgium, that is in Germany. The title as well as the overall study design and plan and the analysis method of the primary endpoint were updated accordingly for approvals in Germany. Eligibility criteria were changed: - A body mass index greater than or equal to 18 kg/m2 was added as an inclusion criterion. - Subject considered as vulnerable (e.g., sponsor or site employee, investigator subordinate, subject incapable of giving consent, subject committed to an institution by way of official or judicial order). - To be included the systolic blood pressure 90−160 mmHg, diastolic blood pressure 50−100 mmHg, and pulse rate 45−100 bpm (inclusive), measured on the dominant arm, after 5 minutes in the supine position at screening. - Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test pre-dose on Day 1. The assessment of the CT scans with the Lund-Mackay methodology was added. Study-specific criteria for interruption / premature discontinuation of study treatment was added: - The stopping criteria at the study level on thrombopenia was added. - A subject had to be immediately and permanently discontinued from study treatment if either of the following occurred: - severe thrombopenia (platelet count less than 50,000/µL) while on investigational treatment. - systolic blood pressure < 80 mmHg and diastolic blood pressure < 60 mmHg (confirmed by repeated BP measurement within 10 min) and associated with significant clinical symptoms while on investigational treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 March 2020	Recruitment was put on hold on during the COVID-19 pandemic from 30 March 2020 to 28 May 2020 in Germany and from 31 March 2020 to 11 June 2020 in Belgium. Recruitment was subsequently restarted.	28 May 2020

Notes:

Limitations and caveats

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

The p-values need to be cautiously interpreted due to the small study population size.

Notes: