



Clinical trial results:

Investigation of the efficacy and safety of ANGOCIN® Anti-Infekt N versus placebo in adult patients with acute, uncomplicated rhinosinusitis. A multi-center, randomized, double-blind, placebo-controlled, parallel-group phase IV clinical trial.

Summary

EudraCT number	2017-002081-40
Trial protocol	DE
Global end of trial date	28 March 2018

Results information

Result version number	v1 (current)
This version publication date	06 July 2022
First version publication date	06 July 2022

Trial information

Trial identification

Sponsor protocol code	Repha_1431
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Repha GmbH
Sponsor organisation address	Alt-Godshorn 87, Langenhagen, Germany, 30855
Public contact	Mediconomics GmbH, CRO, Mediconomics GmbH, 049 0511 5609980, info@mediconomics.com
Scientific contact	Mediconomics GmbH, CRO, Mediconomics GmbH, 049 0511 5609980, info@mediconomics.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	28 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2018
Global end of trial reached?	Yes
Global end of trial date	28 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this parallel-group phase IV study, the aim was to investigate the use of Angocin® Anti-Infect N under routine conditions in the treatment of acute uncomplicated rhinosinusitis in adults between 18 and 75 years of age with a focus on efficacy, safety and tolerability.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), which has its origins in the Declaration of Helsinki, and in strict compliance with the German Drug Law (AMG) and the German Federal Data Protection Act (BDSG), in order to protect the rights, safety and well-being of patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 2017
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	Germany: 380
Worldwide total number of subjects	380
EEA total number of subjects	380

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)	362
From 65 to 84 years	18

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

A 14-day treatment with a total of 5 visits was planned for each patient of which 3 were face-to-face visits at the study centre and 2 visits were conducted by telephone. The study began on day 0 (visit 1) with randomisation and in the presence of acute, uncomplicated rhinosinusitis.

Pre-assignment

Screening details:

All patients who appeared suitable for the clinical trial, taking into account the inclusion and exclusion criteria, and who had given their written consent to participate in the clinical trial were entered into the Patient Identification Log and the Patient Identification List at visit 1.

Period 1

Period 1 title	Therapy Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Blinding of investigator and patient was achieved by the following measures:

Verum and placebo did not differ visually.

The blisters and secondary packaging did not contain any information on the name and strength of the study medication.

The study medication of the two study arms was labelled with the same batch name and expiry date, traceability was ensured via the randomisation number and the manufacturing documentation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Investigational product

Arm description:

Angocin Anti-Infekt N 3x4 tablets daily

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

Dosage and administration details:

3x4 tablets daily for a total of 14 days

Arm title	Placebo
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Arm description:

3x4 tablets per day for a total of 14 days

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:

3x4 tablets daily for a total of 14 days

Number of subjects in period 1	Investigational product	Placebo
Started	192	188
Completed	179	177
Not completed	13	11
violation of selection criteria	-	1
Consent withdrawn by subject	4	1
administration of antibiotics	-	5
Adverse event, non-fatal	3	3
antibiotics were prescribed	5	-
Occurrence of exclusion criterium	-	1
personal reasons	1	-

Baseline characteristics

Reporting groups

Reporting group title	Investigational product
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Reporting group description:

Angocin Anti-Infekt N 3x4 tablets daily

Reporting group title	Placebo
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Reporting group description:

3x4 tablets per day for a total of 14 days

Reporting group values	Investigational product	Placebo	Total
Number of subjects	192	188	380
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)	185	177	362
From 65-84 years	7	11	18
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	133	119	252
Male	59	69	128

End points

End points reporting groups

Reporting group title	Investigational product
Reporting group description: Angocin Anti-Infekt N 3x4 tablets daily	
Reporting group title	Placebo
Reporting group description: 3x4 tablets per day for a total of 14 days	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population included all patients treated in the study, i.e. who took at least one tablet. The safety population was the primary analysis population for the safety evaluation. Patients were evaluated according to their actual treatment.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The FAS excludes patients with a presumed seasonal rhinosinusitis. The FAS was used for the assessment of the efficacy.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol population (PP population) comprised all patients of the FAS population for whom no serious protocol violations were present. Protocol violations were assessed before unblinding.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat population (ITT population) comprised all randomised patients in the safety population for whom at least one co-primary post-baseline value was collected. According to data review, 10 patients did not have a co-primary endpoint.	

Primary: Difference in the mean symptom scores MRSSInv/MRSSpat between both treatment Groups in the course of the treatment Phase

End point title	Difference in the mean symptom scores MRSSInv/MRSSpat between both treatment Groups in the course of the treatment Phase
End point description: The change of the area under the curve (AUC) with Last Observation Carried Forward (LOCF) under the mean curve Major Rhinosinusitis symptom score as assessed by the investigator (MRSSInv)/ Major Rhinosinusitis symptom score as assessed by the patient (MRSSpat) from day 6 to day 10, Calculated according to the trapezoidal method and completion of missing data according to Next Observation Carried Backward (NOCB)/LOCF was used as primary objective. AUC(SENS) denotes the respective area, if missing data was completed using NOCB, interpolation and linear regression. AUC(LOCF) and AUC(SENS) were tested in hierarchical order.	
End point type	Primary
End point timeframe: Day 6 to Day 10	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: number				
least squares mean (standard error)	15.97 ($\pm$ 1.20)	18.58 ($\pm$ 1.20)		

Statistical analyses

Statistical analysis title	Primary endpoint - day 3
Statistical analysis description: Primary endpoint was MRSS inv/MRSS pat documented between day 6 and day 10, computed as AUC, assessed by ANCOVA with day 3 as covariate.	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	ANCOVA

Statistical analysis title	Primary endpoint - day 0
Statistical analysis description: Primary endpoint was MRSS inv/MRSS pat documented between day 6 and day 10, computed as AUC, assessed by ANCOVA with day 0 as covariate.	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0306
Method	ANCOVA

Secondary: Change of MRSSinv anterior secretion

End point title	Change of MRSSinv anterior secretion
End point description: Change of anterior secretion score as assessed by the investigator between baseline (visit 1) and the visits 2,3,4 and 5 as well as in the course of the study. FAS	
End point type	Secondary
End point timeframe: Visit 1 - Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Symptom Score mean				
arithmetic mean (standard deviation)	1.94 ($\pm$ 0.54)	1.98 ($\pm$ 0.57)		

Statistical analyses

Statistical analysis title	Wilcoxon-Mann-Whitney U-Test Anterior Secretion
Comparison groups	Placebo v Investigational product
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9005
Method	Wilcoxon (Mann-Whitney)

Secondary: Change of MRSSInv posterior secretion

End point title	Change of MRSSInv posterior secretion
End point description:	
Change of posterior secretion score as assessed by the investigator between baseline (visit 1) and the visits 2,3,4 and 5 as well as in the course of the study. FAS	
End point type	Secondary
End point timeframe:	
Visit 1 to Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Symptom score mean				
arithmetic mean (standard deviation)	1.74 ($\pm$ 0.70)	1.78 ($\pm$ 0.70)		

Statistical analyses

Statistical analysis title	Wilcoxon-Mann-Whitney U-Test Posterior Secretion
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6567
Method	Wilcoxon (Mann-Whitney)

Secondary: Change of MRSSInv nasal breathing obstruction

End point title	Change of MRSSInv nasal breathing obstruction
End point description: Change of nasal breathing obstruction score as assessed by the investigator between baseline (visit 1) and the visits 2,3,4 and 5 as well as in the course of the study. FAS	
End point type	Secondary
End point timeframe: Visit 1 to Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Symptom score mean				
arithmetic mean (standard deviation)	2.26 (± 0.55)	2.00 (± 0.57)		

Statistical analyses

Statistical analysis title	Wilcoxon-Mann-Whitney U-Test Nasal Obstruction
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9374
Method	Wilcoxon (Mann-Whitney)

Secondary: Change of MRSSInv headache

End point title	Change of MRSSInv headache
End point description: Change of headache score as assessed by the investigator between baseline (visit 1) and the visits 2,3,4 and 5 as well as in the course of the study. FAS	
End point type	Secondary
End point timeframe: Visit 1- Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Symptom score mean				
arithmetic mean (standard deviation)	1.64 (± 0.73)	1.52 (± 0.71)		

Statistical analyses

Statistical analysis title	Wilcoxon-Mann-Whitney U-Test Headache
Comparison groups	Placebo v Investigational product
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9556
Method	Wilcoxon (Mann-Whitney)

Secondary: Change of MRSSInv facial pain

End point title	Change of MRSSInv facial pain
End point description:	Change of anterior secretion score as assessed by the investigator between baseline (visit 1) and the visits 2,3,4 and 5 as well as in the course of the study. FAS
End point type	Secondary
End point timeframe:	
Visit 1 - Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Symptom score mean				
arithmetic mean (standard deviation)	1.74 (± 0.44)	1.68 (± 0.47)		

Statistical analyses

Statistical analysis title	Wilcoxon-Mann-Whitney U-Test facial swelling
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8418
Method	Wilcoxon (Mann-Whitney)

Secondary: Healingscore

End point title	Healingscore
End point description: The healing as a quantitative objective was defined as Major Rinosinusitis Score as defined by the patient (MRSSpat) $\leq$ 2. Three patients were not enclosed due to MRSSpat $\leq$ 2 at baseline. FAS.	
End point type	Secondary
End point timeframe: Visit 3	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[1]	119 ^[2]		
Units: number of patients	89	95		

Notes:

[1] - 2 patients were disregarded from the FAS due to MRSSpat $\leq$ 2 at baseline

[2] - 1 patient was disregarded from the FAS due to MRSSpat $\leq$ 2 at baseline

Statistical analyses

Statistical analysis title	Healing
Statistical analysis description: Chi squared tests of responder rates	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5634
Method	Chi-squared

Secondary: Time to healing

End point title	Time to healing
End point description: FAS	
End point type	Secondary
End point timeframe: Visit 1 to Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: days	9	10		

Statistical analyses

Statistical analysis title	PP set
Statistical analysis description: Healing rates (MRRpat>2), PP set Angocin: 89/110 Placebo: 92/113	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8978 ^[3]
Method	Chi-squared

Notes:

[3] - including three patients in the investigational arm with MRRSpat ≤ 2 at baseline

Secondary: Recurrence rate

End point title	Recurrence rate
End point description: In the FAS, 91 patients from the investigational arm were classified as responders vs. 96 patients of the placebo arm. Recurrence is defined as values of Major Rhinosinusitis score as assessed by the patient above or equal 8.	
End point type	Secondary
End point timeframe: Visit 1 - visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	96		
Units: number of patients	3	5		

Statistical analyses

Statistical analysis title	Recurrence rates
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5185
Method	Chi-squared

Secondary: General efficacy as assessed by the investigator

End point title	General efficacy as assessed by the investigator
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118 ^[4]	120		
Units: number of patients				
Symptoms healed	0	0		
Symptoms improved	78	84		
Symptoms unchanged	33	33		
Symptoms worsened	7	3		

Notes:

[4] - Visit 2

Statistical analyses

Statistical analysis title	General efficacy Visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4298
Method	Wilcoxon (Mann-Whitney)

Secondary: General efficacy as assessed by the investigator

End point title	General efficacy as assessed by the investigator
End point description:	
End point type	Secondary

End point timeframe:

Visit 3

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	120		
Units: number of patients				
Symptoms healed	3	6		
Symptoms improved	102	94		
Symptoms unchanged	7	13		
Symptoms worsened	2	7		

Statistical analyses

Statistical analysis title	General efficacy Visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1792
Method	Wilcoxon (Mann-Whitney)

Secondary: General efficacy as assessed by the investigator

End point title	General efficacy as assessed by the investigator
End point description:	
End point type	Secondary
End point timeframe:	
Visit 4	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113 ^[5]	115		
Units: number of patients				
Symptoms healed	22	17		
Syptoms improved	86	94		
Symptoms unchanged	4	2		
Symptoms worsened	1	2		

Notes:

[5] - Visit 4

Statistical analyses

Statistical analysis title	General efficacy Visit 4
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4896
Method	Wilcoxon (Mann-Whitney)

Secondary: General efficacy as assessed by the investigator

End point title	General efficacy as assessed by the investigator
End point description:	
End point type	Secondary
End point timeframe:	
Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113 ^[6]	120		
Units: number of patients				
Symptoms healed	53	61		
Symptoms improved	55	50		
Symptoms unchanged	4	1		
Symptoms worsened	1	3		

Notes:

[6] - Visit 5

Statistical analyses

Statistical analysis title	General efficacy Visit 5
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3527
Method	Wilcoxon (Mann-Whitney)

Secondary: SNOT-20 GAV total

End point title	SNOT-20 GAV total
End point description: 6 point scala of 20 main criteria of a rhinosinusitis (SNOT-20 GAV). Change of total score between baseline, visit 3 and visit 5 was assessed. FAS.	
End point type	Secondary
End point timeframe: Visit 1, Visit 3 and Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[7]	120 ^[8]		
Units: Symptom score				
arithmetic mean (standard deviation)				
Baseline	43.04 (± 12.26)	43.58 (± 13.95)		
Visit 3	22.47 (± 13.54)	26.00 (± 15.59)		
Visit 5	10.00 (± 13.26)	9.31 (± 13.74)		

Notes:

[7] - 116 patients at baseline and visit 3, 113 at visit 5

[8] - 120 subjects at baseline and visit 3, 115 subjects at visit 5

Statistical analyses

Statistical analysis title	MMRM V3
Statistical analysis description: Difference of Least square means of Angocin and Placebo	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0542
Method	Mixed models analysis

Statistical analysis title	MMRM V5
Statistical analysis description: Difference of Least square means of Angocin and Placebo	

Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8237
Method	Mixed models analysis

Secondary: SNOT-20 GAV Nasal Symptoms

End point title	SNOT-20 GAV Nasal Symptoms
End point description: 6 point scala of nasal main criteria of a rhinosinusitis (SNOT-20 GAV). Change of total score between baseline, visit 3 and visit 5 was assessed. FAS	
End point type	Secondary
End point timeframe: Visit 1, Visit 3 and Visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[9]	120 ^[10]		
Units: Symptom Score				
arithmetic mean (standard deviation)				
Baseline	52.62 (± 14.67)	53.80 (± 15.01)		
Visit 3	29.93 (± 16.67)	34.63 (± 18.42)		
Visit 5	12.46 (± 15.89)	12.56 (± 16.72)		

Notes:

[9] - 116 subjects at baseline and visit 3, 113 subjects at visit 5

[10] - 120 subjects at baseline and visit 3, 115 subjects at visit 5

Statistical analyses

Statistical analysis title	MMRM V3
Statistical analysis description: Difference of Least square means of Angocin and Placebo	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0427
Method	Mixed models analysis

Statistical analysis title	MMRM V5
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Statistical analysis description:

Difference of Least square means of Angocin and Placebo

Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8364
Method	Mixed models analysis

Secondary: SNOT-20 GAV Rhino-associated Symptoms

End point title	SNOT-20 GAV Rhino-associated Symptoms
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End point description:

6 point scala of rhino-associated main criteria of a rhinosinusitis (SNOT-20 GAV). Change of total score between baseline, visit 3 and visit 5 was assessed. FAS.

End point type	Secondary
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End point timeframe:

Baseline, Visit 3 and visit 5

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[11]	120 ^[12]		
Units: Symptom score				
arithmetic mean (standard deviation)				
Baseline	44.19 (± 13.74)	46.87 (± 15.85)		
Visit 3	22.14 (± 14.25)	27.73 (± 17.73)		
Visit 5	9.48 (± 13.68)	9.10 (± 14.87)		

Notes:

[11] - 116 subjects at baseline, visit 3 and 113 at visit 5

[12] - 120 subjects at baseline, visit 3 and 115 at visit 5

Statistical analyses

Statistical analysis title	MMRM V3
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Statistical analysis description:

Difference of Least square means of Angocin and Placebo

Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0128
Method	Mixed models analysis

Statistical analysis title	MMRM V5
Statistical analysis description: Difference of Least square means of Angocin and Placebo	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6194
Method	Mixed models analysis

Secondary: SNOT-20 GAV general quality of life

End point title	SNOT-20 GAV general quality of life
End point description: 6 point scala of quality of life criteria of a rhinosinusitis (SNOT-20 GAV). Change of total score between baseline, visit 3 and visit 5 was assessed. FAS.	
End point type	Secondary
End point timeframe: Baseline, visit 3 and visit 5	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116 ^[13]	120 ^[14]		
Units: Symptom score				
arithmetic mean (standard deviation)				
Baseline	36.96 (± 17.60)	35.69 (± 18.24)		
Visit 3	18.49 (± 17.03)	20.06 (± 17.60)		
Visit 5	8.91 (± 13.73)	7.62 (± 13.88)		

Notes:

[13] - 116 subjects at baseline and visit 3, 113 subjects at visit 5

[14] - 120 subjects at baseline and visit 3, 115 subjects at visit 5

Statistical analyses

Statistical analysis title	MMRM V3
Statistical analysis description: Difference of Least square means of Angocin and Placebo	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2534
Method	Mixed models analysis

Statistical analysis title	MMRM V5
Statistical analysis description:	
Difference of Least square means of Angocin and Placebo	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	other ^[15]
P-value	= 0.8281
Method	Mixed models analysis

Notes:

[15] - Visit 5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator had to report all serious adverse events (SAEs) immediately, but no later than within 24 hours of becoming aware of them and submit a detailed written report (SAE report form)

Adverse event reporting additional description:

Serious AEs that occurred after completion of the trial and could be linked to the study were also reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Investigational product
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Reporting group description:

All patients from the safety-set having been allocated investigational product. The safety set consisted of all patients, who had taken at least on tablet of study medication.

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Investigational product	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 192 (0.00%)	1 / 188 (0.53%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Visual field defect			
subjects affected / exposed	0 / 192 (0.00%)	1 / 188 (0.53%)	
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	Investigational product	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 192 (21.88%)	34 / 188 (18.09%)	
Vascular disorders			
Hot flush			

subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Hypertonia subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2	0 / 188 (0.00%) 0	
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Fatigue subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	4 / 188 (2.13%) 5	
Facial pain subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Discomfort subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Malaise subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Paranasal sinus discomfort subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Dysphonia subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	1 / 188 (0.53%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	1 / 188 (0.53%) 1	
Epistaxis			

subjects affected / exposed	0 / 192 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Cough			
subjects affected / exposed	3 / 192 (1.56%)	3 / 188 (1.60%)	
occurrences (all)	3	3	
productive cough			
subjects affected / exposed	1 / 192 (0.52%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Nasal congestion			
subjects affected / exposed	1 / 192 (0.52%)	1 / 188 (0.53%)	
occurrences (all)	1	1	
Sneezing			
subjects affected / exposed	1 / 192 (0.52%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 192 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 192 (0.52%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Sinus pain			
subjects affected / exposed	1 / 192 (0.52%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 192 (0.52%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 192 (0.52%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Body temperature increased			
subjects affected / exposed	1 / 192 (0.52%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Ligament sprain subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	15 / 192 (7.81%) 16	14 / 188 (7.45%) 16	
Migraine subjects affected / exposed occurrences (all)	3 / 192 (1.56%) 3	1 / 188 (0.53%) 1	
Dizziness subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2	2 / 188 (1.06%) 2	
Blood and lymphatic system disorders			
Leukocytosis subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Ear and labyrinth disorders			
Hypoacusis subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Ear discomfort subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	1 / 188 (0.53%) 1	
Ear pain subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Tinnitus subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	1 / 188 (0.53%) 1	
Eye disorders			
Eye pain subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Dark circles under eyes subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	

Lacrimation increased subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	1 / 188 (0.53%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2	1 / 188 (0.53%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 192 (1.56%) 3	1 / 188 (0.53%) 1	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Vomiting subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2	0 / 188 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2	1 / 188 (0.53%) 1	
Oral pain subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 192 (1.04%) 2	0 / 188 (0.00%) 0	
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Defaecation urgency			

subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	4 / 192 (2.08%) 4	0 / 188 (0.00%) 0	
toothache subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Erythema subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Neurodermatitis subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	1 / 192 (0.52%) 1	0 / 188 (0.00%) 0	
Swelling face subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Dry skin subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	2 / 188 (1.06%) 2	
Renal and urinary disorders			
Renal pain subjects affected / exposed occurrences (all)	0 / 192 (0.00%) 0	1 / 188 (0.53%) 1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 192 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 192 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 192 (0.52%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 192 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	2 / 192 (1.04%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Angular cheilitis			
subjects affected / exposed	0 / 192 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	2 / 192 (1.04%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Gastrointestinal infection			
subjects affected / exposed	1 / 192 (0.52%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 192 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	2 / 192 (1.04%)	0 / 188 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2017	Addition of study centers, changes in study related documents
27 November 2017	Addition of study centers
28 February 2018	Inter alia change of QPPV, editorial changes, addition of certificates of analyses in the IMPD. The date of the submission of the amendment is provided, here.
07 March 2018	Addition of study centers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported