



Clinical trial results:

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

Summary

EudraCT number	2018-001395-37
Trial protocol	DE
Global end of trial date	10 December 2020

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_1430
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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	Clinical Research, Mediconomics GmbH, 0049 05115609980, info@mediconomics.com
Scientific contact	Clinical Research, Mediconomics GmbH, 0049 05115609980, 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	10 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2020
Global end of trial reached?	Yes
Global end of trial date	10 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy, safety and tolerability of ANGOCIN® Anti-Infekt N versus placebo in the treatment of acute bronchitis.

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 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	12 September 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	Germany: 384
Worldwide total number of subjects	384
EEA total number of subjects	384

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)	372
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A 10-day treatment with a total of 4 visits was planned for each patient. On day 0, visit 1, at which the baseline BSSinv was determined and randomisation took place, the patients were given the study medication. The course of the disease was assessed by the investigator during each visit.

Pre-assignment

Screening details:

All patients who appeared suitable for the clinical trial according to the inclusion and exclusion criteria and who had given their written consent to participate in the clinical trial were entered in the patient identification log on visit 1 (day 0). Subjects were assigned a consecutive patient identification number.

Period 1

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

Blinding implementation details:

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

Verum and placebo did not differ visually,

There was no information on the name and strength of the study medication on the blisters and secondary packaging,

The study medication of the two study arms was labelled with the same batch designation 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:

3x4 film coated tablets daily, 10 days

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 film coated tablets daily, 10 days

Arm title	Placebo
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Arm description:

3x4 film coated tablets daily, 10 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 film coated tablets daily, 10 days

Number of subjects in period 1	Investigational product	Placebo
Started	195	189
Completed	191	188
Not completed	4	1
Consent withdrawn by subject	1	1
Adverse event, non-fatal	2	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment phase
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Reporting group description: -

Reporting group values	Treatment phase	Total	
Number of subjects	384	384	
Age categorical Units: Subjects			
Adults (18-64 years)	372	372	
From 65-84 years	12	12	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	250	250	
Male	134	134	

End points

End points reporting groups

Reporting group title	Investigational product
Reporting group description:	
3x4 film coated tablets daily, 10 days	
Reporting group title	Placebo
Reporting group description:	
3x4 film coated tablets daily, 10 days	

Primary: Change of BSSinv Visit 1-Visit 3

End point title	Change of BSSinv Visit 1-Visit 3
End point description:	
Symptomscore of bronchitis (BSS) as assessed by the investigator as summary score of cough, mucous production, chest pain, rales and dyspnea as a difference between visit 3 (day 7) as opposed to baseline, ITT	
End point type	Primary
End point timeframe:	
Comparison of the Change within the mean BSSinv (Baseline to Day 7) between both Treatment groups	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS				
arithmetic mean (standard deviation)				
Visit 1	7.4 (± 1.9)	7.3 (± 1.9)		
Visit 2	6.2 (± 2.1)	6.6 (± 2.3)		
Visit 3	3.5 (± 2.0)	4.3 (± 2.4)		

Statistical analyses

Statistical analysis title	BSSinv total Visit 3
Comparison groups	Placebo v Investigational product
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ANCOVA primary endpoint ITT
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Statistical analysis description:

The co-variate analysis of the difference in bronchitis symptom score with baseline as covariate in the ITT set showed a p-value of p=0.000243 (the treatment effect is 0.81 score-units with a standard error of 0.22 units), meaning a superiority of Angocin vs. placebo in the decrease of the bronchitis symptom score. The results of the primary endpoint show superiority of Angocin also in the per protocol set, with p=0.000119 (treatment effect 0.76 score-units with a standard error of 0.20 units)

Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000243 [1]
Method	ANCOVA

Notes:

[1] - mixed model, ITT

Statistical analysis title	ANCOVA primary endpoint PP
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Statistical analysis description:

The co-variate analysis of the difference in bronchitis symptom score with baseline as covariate in the eITT set showed a p-value of p=0.000243 (the treatment effect is 0.81 score-units with a standard error of 0.22 units), meaning a superiority of Angocin vs. placebo in the decrease of the bronchitis symptom score. The results of the primary endpoint show superiority of Angocin also in the per protocol set, with p=0.000119 (treatment effect 0.76 score-units with a standard error of 0.20 units)

Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000119 [2]
Method	ANCOVA

Notes:

[2] - mixed model, PP

Secondary: Difference of mean BSS total symptomscore between V1 (Baseline) and V2

End point title	Difference of mean BSS total symptomscore between V1 (Baseline) and V2
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End point description:

Symptomscore of bronchitis (BSS) as assessed by the investigator as summary score of cough, mucous production, chest pain, rales and dyspnea as a difference between visit 2 (day 7) as opposed to baseline

End point type	Secondary
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End point timeframe:

Between Baseline (Visit 1) and Visit 2

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS				
arithmetic mean (standard deviation)	-1.2 (± 1.6)	-0.7 (± 2.0)		

Statistical analyses

Statistical analysis title	BSS total V1-V2
Statistical analysis description: Mean of difference values (Visit 2 -minus- baseline)	
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference of mean BSS total symptomscore between V1 (Baseline) and V4

End point title	Difference of mean BSS total symptomscore between V1 (Baseline) and V4
End point description: Symptomscore of bronchitis (BSS) as assessed by the investigator as summary score of cough, mucous production, chest pain, rales and dyspnea as a difference between visit 4 (day 7) as opposed to baseline	
End point type	Secondary
End point timeframe: Between baseline (Visit 1) and Visit 4	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS				
arithmetic mean (standard deviation)	-5.7 (± 2.4)	-4.9 (± 3.1)		

Statistical analyses

Statistical analysis title	BSS total V1-V4
Statistical analysis description: Mean of difference values (Visit 4 -minus- baseline)	
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS cough Visit 1 and Visit 2

End point title	Difference mean BSS cough Visit 1 and Visit 2
End point description:	Symptomscore of bronchitis (BSS), symptom cough as assessed by the investigator as a difference between visit 2 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Visit 1 and Visit 2

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS cough arithmetic mean (standard deviation)	-0.3 (± 0.6)	-0.2 (± 0.6)		

Statistical analyses

Statistical analysis title	BSS cough Visit 1-Visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.037
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS cough Visit 1 and Visit 3

End point title	Difference mean BSS cough Visit 1 and Visit 3
End point description:	Symptomscore of bronchitis (BSS), symptom cough as assessed by the investigator as a difference between visit 3 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Basleine (Visit 1) and Visit 3

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS cough				
arithmetic mean (standard deviation)	-0.9 (± 0.8)	-0.7 (± 0.8)		

Statistical analyses

Statistical analysis title	BSS cough Visit 1-Visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS cough Visit 1 and Visit 4

End point title	Difference mean BSS cough Visit 1 and Visit 4
End point description:	Symptomscore of bronchitis (BSS), symptom cough as assessed by the investigator as a difference between visit 4 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 4

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS				
arithmetic mean (standard deviation)	-1.5 (± 0.8)	-1.3 (± 1.0)		

Statistical analyses

Statistical analysis title	BSScough Visit 1-Visit 4
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS mucous Visit 1 and Visit 2

End point title	Difference mean BSS mucous Visit 1 and Visit 2
End point description:	Symptomscore of bronchitis (BSS), symptom mucous as assessed by the investigator as a difference between visit 2 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 2

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS mucous arithmetic mean (standard deviation)	-0.1 (\pm 0.6)	0.0 (\pm 0.6)		

Statistical analyses

Statistical analysis title	BSSmucous Visit 1-Visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.074
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS mucous Visit 1 and Visit 3

End point title	Difference mean BSS mucous Visit 1 and Visit 3
End point description:	Symptomscore of bronchitis (BSS), symptom mucous as assessed by the investigator as a difference between visit 3 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 3

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolut values of BSSmucous				
arithmetic mean (standard deviation)	-0.8 (± 0.8)	-0.5 (± 0.9)		

Statistical analyses

Statistical analysis title	BSSmucous Visit 1-Visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS mucous Visit 1 and Visit 4

End point title	Difference mean BSS mucous Visit 1 and Visit 4
End point description:	Symptomscore of bronchitis (BSS), symptom mucous as assessed by the investigator as a difference between visit 4 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 4

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values BSSmucous				
arithmetic mean (standard deviation)	-1.5 (± 0.8)	-1.1 (± 1.0)		

Statistical analyses

Statistical analysis title	BSSmucous Visit 1-Visit 4
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS chest pain Visit 1 and Visit 2

End point title	Difference mean BSS chest pain Visit 1 and Visit 2
End point description:	Symptomscore of bronchitis (BSS), symptom chest pain as assessed by the investigator as a difference between visit 2 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 2

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS chestpain arithmetic mean (standard deviation)	-0.4 (± 0.6)	-0.2 (± 0.7)		

Statistical analyses

Statistical analysis title	BSSchestpain Visit 1-Visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS chest pain Visit 1 and Visit 3

End point title	Difference mean BSS chest pain Visit 1 and Visit 3
End point description:	Symptomscore of bronchitis (BSS), symptom chest pain as assessed by the investigator as a difference between visit 3 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 3

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS chestpain				
arithmetic mean (standard deviation)	-0.9 (± 0.9)	-0.7 (± 0.9)		

Statistical analyses

Statistical analysis title	BSSchestpain Visit 1-Visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS chest pain Visit 1 and Visit 4

End point title	Difference mean BSS chest pain Visit 1 and Visit 4
End point description:	Symptomscore of bronchitis (BSS), symptom chest pain as assessed by the investigator as a difference between visit 4 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 4

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute value of BSS chest pain				
arithmetic mean (standard deviation)	-1.2 (± 0.8)	-1.1 (± 0.9)		

Statistical analyses

Statistical analysis title	BSSchestpain Visit 1-Visit 4
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.024
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS rales Visit 1 and Visit 2

End point title	Difference mean BSS rales Visit 1 and Visit 2
End point description:	Symptomscore of bronchitis (BSS), symptom rales as assessed by the investigator as a difference between visit 2 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 2

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values of BSS rales				
arithmetic mean (standard deviation)	-0.1 (± 0.4)	-0.1 (± 0.6)		

Statistical analyses

Statistical analysis title	BSSrales Visit 1-Visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.415
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS rales Visit 1 and Visit 3

End point title	Difference mean BSS rales Visit 1 and Visit 3
End point description:	Symptomscore of bronchitis (BSS), symptom rales as assessed by the investigator as a difference between visit 3 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 3

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values BSS rates				
arithmetic mean (standard deviation)	-0.6 (± 0.6)	-0.5 (± 0.8)		

Statistical analyses

Statistical analysis title	BSSrates Visit 1-Visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.229
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS rates Visit 1 and Visit 4

End point title	Difference mean BSS rates Visit 1 and Visit 4
End point description:	Symptomscore of bronchitis (BSS), symptom rates as assessed by the investigator as a difference between visit 4 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 4

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute value BSS rates				
arithmetic mean (standard deviation)	-0.7 (± 0.7)	-0.6 (± 0.8)		

Statistical analyses

Statistical analysis title	BSSrates Visit 1-Visit 4
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.521
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS dyspnoea Visit 1 and Visit 2

End point title	Difference mean BSS dyspnoea Visit 1 and Visit 2
End point description:	Symptomscore of bronchitis (BSS), symptom dyspnea as assessed by the investigator as a difference between visit 2 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 2

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute values BSS dyspnoea				
arithmetic mean (standard deviation)	-0.3 (± 0.6)	-0.2 (± 0.6)		

Statistical analyses

Statistical analysis title	BSSdyspnoea Visit 1-Visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.241
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS dyspnoea Visit 1 and Visit 3

End point title	Difference mean BSS dyspnoea Visit 1 and Visit 3
End point description:	Symptomscore of bronchitis (BSS), symptom dyspnoea as assessed by the investigator as a difference between visit 3 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 3

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute value BSS dyspnoea				
arithmetic mean (standard deviation)	-0.6 (± 0.7)	-0.6 (± 0.8)		

Statistical analyses

Statistical analysis title	BSSdyspnoea Visit 1-Visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.587
Method	Wilcoxon (Mann-Whitney)

Secondary: Difference mean BSS dyspnoea Visit 1 and Visit 4

End point title	Difference mean BSS dyspnoea Visit 1 and Visit 4
End point description:	Symptomscore of bronchitis (BSS), symptom dyspnoea as assessed by the investigator as a difference between visit 4 as opposed to baseline
End point type	Secondary
End point timeframe:	Between Baseline (Visit 1) and Visit 4

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Absolute value BSS dyspnoea				
arithmetic mean (standard deviation)	-0.8 (± 0.7)	-0.8 (± 0.8)		

Statistical analyses

Statistical analysis title	BSSdyspnoea Visit 1-Visit 4
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.495
Method	Wilcoxon (Mann-Whitney)

Secondary: Rate of patients who underwent antibiotic therapy for the treatment of acute bronchitis between V1 and V4 (Antibiotic rate).

End point title	Rate of patients who underwent antibiotic therapy for the treatment of acute bronchitis between V1 and V4 (Antibiotic rate).
End point description:	Patients with antibiotic or analgesic medication were counted and compared between arms. Overall numbers were too low to evaluate significance levels.
End point type	Secondary
End point timeframe:	
Therapy phase	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: number of patients				
Antibiotics	0	2		
Analgetics	16	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Responder rate Visit 1 - Visit 4

End point title	Responder rate Visit 1 - Visit 4
End point description:	Patients whose symptoms had improved in the BSS or who were cured were classified as "responders".
End point type	Secondary
End point timeframe:	
Visit 1 to Visit 4	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: number of patients				
Visit 2	120	82		
Visit 3	181	164		
Visit 4	188	178		

Statistical analyses

Statistical analysis title	Responder rate Visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Chi-squared

Statistical analysis title	Responder rate Visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	Chi-squared

Statistical analysis title	Responder rate Visit 4
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.301
Method	Chi-squared

Secondary: Non-Responder rate

End point title	Non-Responder rate
End point description:	Patients whose symptoms were unchanged or had worsened were classified as "non-responders".
End point type	Secondary
End point timeframe:	Visit 1 - Visit 4

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: number of patients				
Visit 2	78	113		
Visit 3	12	26		
Visit 4	4	11		

Statistical analyses

Statistical analysis title	Non-responder rate visit 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Chi-squared

Statistical analysis title	Non-responder rate visit 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.015
Method	Chi-squared

Statistical analysis title	Non-responder rate visit 4
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.061
Method	Chi-squared

Secondary: Change in CAT (COPD Assessment Test) during the course of treatment.

End point title	Change in CAT (COPD Assessment Test) during the course of treatment.
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End point description:

Improvement of CAT (COPD assessment, sum of bronchial symptoms from 8 criteria).

End point type Secondary

End point timeframe:

Day 1 - Day 11

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: CAT sum score				
arithmetic mean (standard deviation)				
Day 1	23.6 (± 5.0)	22.7 (± 5.4)		
Day 2	22.0 (± 4.8)	21.8 (± 5.5)		
Day 3	20.4 (± 4.7)	20.6 (± 5.5)		
Day 4	18.9 (± 4.6)	19.5 (± 5.4)		
Day 5	17.4 (± 4.8)	18.2 (± 5.0)		
Day 6	16.3 (± 4.4)	17.2 (± 4.9)		
Day 7	15.3 (± 4.3)	16.1 (± 4.7)		
Day 8	14.0 (± 4.3)	14.9 (± 4.8)		
Day 9	13.2 (± 4.7)	13.6 (± 4.6)		
Day 10	12.0 (± 4.4)	13.5 (± 5.0)		
Day 11	13.1 (± 6.6)	12.3 (± 4.9)		

Statistical analyses

Statistical analysis title	CAT Day 1
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.075
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 2
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.835
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 3
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.711
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 4
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.154
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 5
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.061
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 6
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.06
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 7
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.087
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 8
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 9
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.217
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 10
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CAT Day 11
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.896
Method	Wilcoxon (Mann-Whitney)

Secondary: SF-12 - Physical health

End point title	SF-12 - Physical health
End point description:	
End point type	Secondary

End point timeframe:

Visit 1 - Visit 4

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Sum score				
arithmetic mean (standard deviation)				
Day 0	41.2 (± 7.3)	40.4 (± 8.2)		
Day 7	44.2 (± 7.5)	43.1 (± 8.0)		
Day 10	48.0 (± 6.8)	47.1 (± 7.3)		
Difference between day 0 and day 7	2.1 (± 10.1)	2.5 (± 9.1)		
Difference between day 0 and day 10	5.9 (± 10.5)	6.4 (± 9.7)		

Statistical analyses

Statistical analysis title	SF12 Physical Day 0
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.29
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SF12 Physical Day 7
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.19
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SF12 Physical Day 10
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.272
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SF12 Physical Day 0-Day7
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.778
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SF12 Physical Day 0-Day10
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.934
Method	Wilcoxon (Mann-Whitney)

Secondary: SF12 - Mental health

End point title	SF12 - Mental health
End point description: The SF-12 questionnaire was designed to detect group differences in the physical and mental health of the patients. These were not found.	
End point type	Secondary
End point timeframe: Visit 1 - Visit 4	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	189		
Units: Sum score				
arithmetic mean (standard deviation)				
Day 0	46.3 (± 10)	47.7 (± 9.3)		
Day 7	46.5 (± 8.5)	45.8 (± 8.2)		
Day 10	48.1 (± 8.2)	47.3 (± 8.6)		
Difference between day 0 and day 7	-0.8 (± 11.7)	-2.2 (± 10.6)		
Difference between day 0 and day 10	0.8 (± 12.2)	-0.7 (± 11.1)		

Statistical analyses

Statistical analysis title	SF12- Mental health day
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.122
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SF12- Mental health day 7
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.404
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SF12- Mental health day 10
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.419
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SF12- Mental health day 0-day7
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.182
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Copy of SF12- Mental health day 0-day10
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.215
Method	Wilcoxon (Mann-Whitney)

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)

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: -

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 / 195 (0.00%)	0 / 189 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Investigational product	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 195 (14.36%)	17 / 189 (8.99%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 195 (1.03%)	0 / 189 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 195 (0.00%)	1 / 189 (0.53%)	
occurrences (all)	0	2	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	10 / 195 (5.13%) 10	7 / 189 (3.70%) 7	
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1	0 / 189 (0.00%) 0	
Hypochromic anaemia subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	1 / 189 (0.53%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 195 (1.03%) 2	1 / 189 (0.53%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 195 (2.05%) 4	0 / 189 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1	0 / 189 (0.00%) 0	
Abdominal distension subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1	0 / 189 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1	0 / 189 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	2 / 195 (1.03%) 2	0 / 189 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1	0 / 189 (0.00%) 0	
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	1 / 189 (0.53%) 1	
Reproductive system and breast disorders			

Menstrual discomfort subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	1 / 189 (0.53%) 1	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1 0 / 195 (0.00%) 0	0 / 189 (0.00%) 0 1 / 189 (0.53%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	1 / 189 (0.53%) 1	
Infections and infestations Sinusitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Urinary infection subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1 0 / 195 (0.00%) 0 0 / 195 (0.00%) 0	0 / 189 (0.00%) 0 2 / 189 (1.06%) 2 1 / 189 (0.53%) 1	
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 195 (0.51%) 1	0 / 189 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2018	Editorial changes, specification of exclusion criteria, specification of documentation of immune-modulating and immune-suppressing medication
10 May 2019	Prolongation of study duration, change of deputy QPPV of CRO
17 October 2019	Prolongation of study duration
24 February 2020	Prolongation of study duration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported