



Clinical trial results:

A Randomised, Double-blind, Placebo-controlled, Multi-centre Clinical Study to Investigate the Efficacy and Safety of Three Doses of Cineole in Subjects with Severe Acute Bronchitis with or without Associated Common Cold

Summary

EudraCT number	2017-003044-20
Trial protocol	DE
Global end of trial date	11 May 2018

Results information

Result version number	v1 (current)
This version publication date	12 June 2022
First version publication date	12 June 2022

Trial information

Trial identification

Sponsor protocol code	CASK0117
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cassella-med GmbH & Co. KG
Sponsor organisation address	Gereonsmuehlengasse 1, Cologne, Germany,
Public contact	Clinical Operations, Cassella-med GmbH & Co. KG, 49 8001652200, dialog@cassella-med.eu
Scientific contact	Clinical Operations, Cassella-med GmbH & Co. KG, clinical.operations@klosterfrau.de

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	19 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2018
Global end of trial reached?	Yes
Global end of trial date	11 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is the dose-response behaviour of 600 mg, 900 mg and 1200 mg cineole in subjects with severe acute bronchitis with or without associated common cold.

Protection of trial subjects:

After participation in the trial, patients have been treated with the current standard therapy for acute bronchitis. Furthermore, the use of rescue medication was allowed during the study period if deemed to be needed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 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: 181
Worldwide total number of subjects	181
EEA total number of subjects	181

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)	171
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were recruited from the pool of subjects who spontaneously visited their GP because of acute severe bronchitis.

Pre-assignment

Screening details:

Subjects were eligible for inclusion if the main criteria were met:

- age between 18 and 65 years
- acute bronchitis since ≤ 48 hours, with or without associated common cold; BSS > 12 , indicating severe bronchitis
- women of childbearing potential with negative pregnancy test and effective contraception
- signed Informed Consent

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cineole 600mg/day

Arm description:

For the 200 mg cineole per dose group (total of 600 mg/day), 1 capsule of Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered.

Arm type	Experimental
Investigational medicinal product name	Soledum® Kapseln forte 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered for the 200 mg cineole per dose group. All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Investigational medicinal product name	Placebo capsules matching Soledum® Kapseln
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered for the 200 mg cineole per dose group. All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Arm title	Cineole 900mg/day
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Arm description:

For the 300 mg cineole per dose group (total of 900 mg/day), 1 capsule of Soledum® Kapseln forte, 1 capsule Soledum® Kapseln, and 1 placebo capsule matching Soledum® Kapseln were administered.

Arm type	Experimental
Investigational medicinal product name	Soledum® Kapseln
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Soledum® Kapseln forte, 1 capsule Soledum® Kapseln, and 1 placebo capsule matching Soledum® Kapseln were administered for the 300 mg cineole per dose group (total of 900 mg/day). All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Investigational medicinal product name	Soledum® Kapseln forte 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Soledum® Kapseln forte, 1 capsule Soledum® Kapseln, and 1 placebo capsule matching Soledum® Kapseln were administered for the 300 mg cineole per dose group (total of 900 mg/day). All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Investigational medicinal product name	placebo capsule matching Soledum® Kapseln
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Ocular use

Dosage and administration details:

1 capsule of Soledum® Kapseln forte, 1 capsule Soledum® Kapseln, and 1 placebo capsule matching Soledum® Kapseln were administered for the 300 mg cineole per dose group (total of 900 mg/day). All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Arm title	Cineole 1200mg/day
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Arm description:

For the 400 mg cineole per dose group (total of 1200 mg/day), 1 capsule of Soledum® Kapseln forte and 2 capsules of Soledum® Kapseln were administered.

Arm type	Experimental
Investigational medicinal product name	Soledum® Kapseln forte 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Soledum® Kapseln forte and 2 capsules of Soledum® Kapseln were administered for the 400 mg cineole per dose group (total of 1200 mg/day). All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Investigational medicinal product name	Soledum® Kapseln
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 capsule of Soledum® Kapseln forte and 2 capsules of Soledum® Kapseln were administered for the 400 mg cineole per dose group (total of 1200 mg/day). All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Arm title	Placebo
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Arm description:

For the placebo group, 1 placebo capsule matching Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered.

Arm type	Placebo
Investigational medicinal product name	placebo capsule matching Soledum® Kapseln
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 placebo capsule matching Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered for the placebo group. All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Investigational medicinal product name	placebo capsule matching Soledum® Kapseln forte
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 placebo capsule matching Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered for the placebo group. All 3 capsules were taken thrice daily (i.e., morning, noon, and evening - a total of 9 capsules per day) with plenty of liquid of moderate temperature (preferably 1 glass [200 mL] of drinking water), approximately 30 minutes before a regular meal.

Number of subjects in period 1	Cineole 600mg/day	Cineole 900mg/day	Cineole 1200mg/day
Started	43	46	45
Treated	43	45	43
Completed	41	41	40
Not completed	2	5	5
Consent withdrawn by subject	1	-	3
Lack of patient cooperation	-	1	-
Adverse event, non-fatal	1	2	1
Non-compliance with study medication	-	-	-
Patient does not want a final examination	-	1	-
Lost to follow-up	-	1	1
Protocol deviation	-	-	-

Number of subjects in period 1	Placebo
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Started	47
Treated	47
Completed	44
Not completed	3
Consent withdrawn by subject	-
Lack of patient cooperation	-
Adverse event, non-fatal	1
Non-compliance with study medication	1
Patient does not want a final examination	-
Lost to follow-up	-
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Cineole 600mg/day
Reporting group description: For the 200 mg cineole per dose group (total of 600 mg/day), 1 capsule of Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered.	
Reporting group title	Cineole 900mg/day
Reporting group description: For the 300 mg cineole per dose group (total of 900 mg/day), 1 capsule of Soledum® Kapseln forte, 1 capsule Soledum® Kapseln, and 1 placebo capsule matching Soledum® Kapseln were administered.	
Reporting group title	Cineole 1200mg/day
Reporting group description: For the 400 mg cineole per dose group (total of 1200 mg/day), 1 capsule of Soledum® Kapseln forte and 2 capsules of Soledum® Kapseln were administered.	
Reporting group title	Placebo
Reporting group description: For the placebo group, 1 placebo capsule matching Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered.	

Reporting group values	Cineole 600mg/day	Cineole 900mg/day	Cineole 1200mg/day
Number of subjects	43	46	45
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Summary on age as continuous variable in the 4 treatment groups.			
Units: years			
arithmetic mean	47.3	42.7	44.5
full range (min-max)	19 to 65	18 to 77	18 to 79
Gender categorical Units: Subjects			
Female	26	25	23
Male	17	21	22

Reporting group values	Placebo	Total	
Number of subjects	47	181	
Age categorical Units: Subjects			
In utero		0	

Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Summary on age as continuous variable in the 4 treatment groups.			
Units: years			
arithmetic mean	43.4		
full range (min-max)	18 to 69	-	
Gender categorical			
Units: Subjects			
Female	17	91	
Male	30	90	

Subject analysis sets

Subject analysis set title	FAS of the 600 mg/day dose group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the 600mg/day dose group.	
Subject analysis set title	FAS of the 900 mg/day dose group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the 900 mg/day dose group	
Subject analysis set title	FAS of the 1200 mg/day dose group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the 1200 mg/day dose group	
Subject analysis set title	FAS of the placebo group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the Placebo group	

Reporting group values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group
Number of subjects	43	45	43
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			

From 65-84 years			
85 years and over			

Age continuous			
Summary on age as continuous variable in the 4 treatment groups.			
Units: years			
arithmetic mean	47.3	42.7	44.5
full range (min-max)	19 to 65	18 to 77	18 to 79
Gender categorical			
Units: Subjects			
Female	26	24	22
Male	17	21	21

Reporting group values	FAS of the placebo group		
Number of subjects	47		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Summary on age as continuous variable in the 4 treatment groups.			
Units: years			
arithmetic mean	43.4		
full range (min-max)	18 to 69		
Gender categorical			
Units: Subjects			
Female	17		
Male	30		

End points

End points reporting groups

Reporting group title	Cineole 600mg/day
Reporting group description: For the 200 mg cineole per dose group (total of 600 mg/day), 1 capsule of Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered.	
Reporting group title	Cineole 900mg/day
Reporting group description: For the 300 mg cineole per dose group (total of 900 mg/day), 1 capsule of Soledum® Kapseln forte, 1 capsule Soledum® Kapseln, and 1 placebo capsule matching Soledum® Kapseln were administered.	
Reporting group title	Cineole 1200mg/day
Reporting group description: For the 400 mg cineole per dose group (total of 1200 mg/day), 1 capsule of Soledum® Kapseln forte and 2 capsules of Soledum® Kapseln were administered.	
Reporting group title	Placebo
Reporting group description: For the placebo group, 1 placebo capsule matching Soledum® Kapseln forte and 2 placebo capsules matching Soledum® Kapseln were administered.	
Subject analysis set title	FAS of the 600 mg/day dose group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the 600mg/day dose group.	
Subject analysis set title	FAS of the 900 mg/day dose group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the 900 mg/day dose group	
Subject analysis set title	FAS of the 1200 mg/day dose group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the 1200 mg/day dose group	
Subject analysis set title	FAS of the placebo group
Subject analysis set type	Full analysis
Subject analysis set description: Full analysis set of the Placebo group	

Primary: Change/course of the bronchitis symptoms from Study Day 1 (baseline) until Study Day 5 and Day 8

End point title	Change/course of the bronchitis symptoms from Study Day 1 (baseline) until Study Day 5 and Day 8 ^[1]
End point description: The primary efficacy variable was the change of the bronchitis Symptoms (reported by Principal Investigator) from the start of treatment (Study Day 1) until Study Day 5 and Study Day 8 represented by the sum score of the BBS. The primary analysis of the reported BBS scores was performed with the Full Analysis Set (FAS).	
End point type	Primary
End point timeframe: Assessment at the start of treatment (Study Day 1) on Study Day 5 and on Study Day 8	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary efficacy analysis used an adjusted MCPMod approach on the LSMeans from the longitudinal modelling step to test for the existence of dose-related effects. The MCPMod tests have been conducted at a one-sided significance

level of $\alpha=2.5\%$. All test procedures applied (exponential, EMax and SigEmax) resulted in non-significant p-values.

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	45	43	47
Units: BSS sum score				
least squares mean (standard error)				
Study Day 5	-6.21 (\pm 0.46)	-5.74 (\pm 0.46)	-6.19 (\pm 0.47)	-6.34 (\pm 0.45)
Study Day 8	-10.48 (\pm 0.47)	-9.26 (\pm 0.47)	-9.59 (\pm 0.47)	-10.43 (\pm 0.45)

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity, change from Study Day 1 (baseline) until Study Day 5 - on VAS

End point title	Cough Severity, change from Study Day 1 (baseline) until Study Day 5 - on VAS
End point description:	Severity of cough measured on a 100 mm Visual Analogue Scale (VAS) (ranging from 0 mm = no cough to 100 mm = worst cough ever) every day from inclusion - Study Day 1 and Study day 5.
End point type	Secondary
End point timeframe:	Every day from inclusion (Study Day 1) until Study Day 5

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	42	40	44
Units: mm				
arithmetic mean (standard deviation)				
Study Day 5	-22.9 (\pm 20.34)	-19.5 (\pm 20.61)	-19.8 (\pm 20.67)	-26.8 (\pm 20.04)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Efficacy Rating - 4 step rating scale on Study Day 5

End point title	Overall Efficacy Rating - 4 step rating scale on Study Day 5
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End point description:

The Overall efficacy rating was based on a verbal rating scale including 4 steps. The Investigator and the subject performed the assessment without knowing the other's rating. The efficacy rating was determined by the Investigator at Study Day 5, Study Day 8 and at Study Day 14 \pm 2 and was determined by the subject on Study Days 2 to 8 and on Study Day 14 \pm 2.

End point type	Secondary
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End point timeframe:

From Study Day 2 to Study Day 14 \pm 2

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	42	40	45
Units: number				
0 - bad	3	5	2	2
1 - satisfactory	13	17	14	9
2 - good	20	12	21	26
3 - very good	6	8	3	8

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Efficacy Rating - 4 step rating scale on Study Day 8

End point title	Overall Efficacy Rating - 4 step rating scale on Study Day 8
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End point description:

The Overall efficacy rating was based on a verbal rating scale including 4 steps. The Investigator and the subject performed the assessment without knowing the other's rating. The efficacy rating was determined by the Investigator at Study Day 5, Study Day 8 and at Study Day 14 \pm 2 and was determined by the subject on Study Days 2 to 8 and on Study Day 14 \pm 2.

End point type	Secondary
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End point timeframe:

From Study Day 2 to Study Day 14 \pm 2

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	41	40	45
Units: number				
0 - bad	1	4	3	3
1 - satisfactory	10	9	11	8
2 - good	20	18	21	22
3 - very good	10	10	5	12

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission - BBS sum score ≤ 2

End point title	Complete Remission - BBS sum score ≤ 2
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End point description:

Complete Remission was defined as BBS sum score ≤ 2 from the Investigator assessment on Study Days 5 and 8.

End point type	Secondary
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End point timeframe:

Study Day 5 and Study Day 8

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	42	41	45
Units: number				
Study Day 5	2	3	1	2
Study Day 8	18	13	18	22

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity, change from Study Day 1 (baseline) until Study Day 8 - on VAS

End point title	Cough Severity, change from Study Day 1 (baseline) until Study Day 8 - on VAS
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End point description:

Severity of cough measured on a 100 mm Visual Analogue Scale (VAS) (ranging from 0 mm = no cough to 100 mm = worst cough ever) every day from inclusion - Study Day 1 and Study Day 8.

End point type	Secondary
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End point timeframe:

Every day from inclusion (Study Day 1) until Study Day 8

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	28	25	26
Units: mm				
arithmetic mean (standard deviation)				
Study Day 8	-45.5 (± 21.68)	-34.5 (± 31.06)	-33.7 (± 23.75)	-47.0 (± 24.82)

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity, change from Study Day 1 (baseline) until Study Day 5 - PI reported

End point title	Cough Severity, change from Study Day 1 (baseline) until Study Day 5 - PI reported
End point description: Change from baseline in the per investigator reported BBS severity of cough, from inclusion - Study Day 1 and Study Day 5.	
End point type	Secondary
End point timeframe: Every day from inclusion (Study Day 1) until Study Day 5	

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	42	40	44
Units: mm				
arithmetic mean (standard deviation)				
Study Day 5	-1.4 (± 0.94)	-1.1 (± 0.78)	-1.2 (± 0.77)	-1.5 (± 0.98)

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity, change from Study Day 1 (baseline) until Study Day 8 - PI reported

End point title	Cough Severity, change from Study Day 1 (baseline) until Study Day 8 - PI reported
End point description: Change from baseline in the per investigator reported BBS severity of cough, from inclusion - Study Day 1 and Study Day 8.	
End point type	Secondary

End point timeframe:

Every day from inclusion (Study Day 1) until Study Day 8

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	41	40	44
Units: mm				
arithmetic mean (standard deviation)				
Study Day 8	-2.3 (± 0.95)	-1.9 (± 0.92)	-1.9 (± 1.02)	-2.4 (± 0.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Tolerability Rating - 4 step rating scale on Study Day 5

End point title	Overall Tolerability Rating - 4 step rating scale on Study Day 5
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End point description:

The Overall tolerability rating was based on a verbal rating scale including 4 steps. The Investigator and the subject performed the assessment without knowing the other's rating. The tolerability rating was determined by the Investigator at Study Day 5, Study Day 8 and at Study Day 14 ± 2 and was determined by the subject on Study Days 2 to 8 and on Study Day 14 ± 2.

End point type	Secondary
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End point timeframe:

From Study Day 2 to Study Day 14 ± 2

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	42	40	45
Units: numbers				
0 - bad	1	0	1	0
1 - satisfactory	1	1	4	1
2 - good	24	25	17	21
3 - very good	16	16	18	23

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Tolerability Rating - 4 step rating scale on Study Day 8

End point title	Overall Tolerability Rating - 4 step rating scale on Study Day 8
End point description:	
The overall tolerability rating was based on a verbal rating scale including 4 steps. The Investigator and the subject performed the assessment without knowing the other's rating. The tolerability rating was determined by the Investigator at Study Day 5, Study Day 8 and at Study Day 14 \pm 2 and was determined by the subject on Study Days 2 to 8 and on Study Day 14 \pm 2.	
End point type	Secondary
End point timeframe:	
From Study Day 2 to Study Day 14 \pm 2	

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	41	40	45
Units: numbers				
0 - bad	2	0	1	0
1 - satisfactory	3	2	4	1
2 - good	18	20	19	16
3 - very good	18	19	16	28

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Tolerability Rating - 4 step rating scale on Study Day 14 \pm 2

End point title	Overall Tolerability Rating - 4 step rating scale on Study Day 14 \pm 2
End point description:	
The overall tolerability rating was based on a verbal rating scale including 4 steps. The Investigator and the subject performed the assessment without knowing the other's rating. The tolerability rating was determined by the Investigator at Study Day 5, Study Day 8 and at Study Day 14 \pm 2 and was determined by the subject on Study Days 2 to 8 and on Study Day 14 \pm 2.	
End point type	Secondary
End point timeframe:	
From Study Day 2 to Study Day 14 \pm 2	

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	43	42	47
Units: numbers				
0 - bad	0	0	2	0
1 - satisfactory	3	0	5	1
2 - good	21	23	21	22
3 - very good	18	20	14	24

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Efficacy Rating - 4 step rating scale on Study Day 14 ± 2

End point title	Overall Efficacy Rating - 4 step rating scale on Study Day 14 ± 2
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End point description:

The Overall efficacy rating was based on a verbal rating scale including 4 steps. The Investigator and the subject performed the assessment without knowing the other's rating. The efficacy rating was determined by the Investigator at Study Day 5, Study Day 8 and at Study Day 14 ± 2 and was determined by the subject on Study Days 2 to 8 and on Study Day 14 ± 2.

End point type	Secondary
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End point timeframe:

From Study Day 2 to Study Day 14 ± 2

End point values	FAS of the 600 mg/day dose group	FAS of the 900 mg/day dose group	FAS of the 1200 mg/day dose group	FAS of the placebo group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	43	42	47
Units: numbers				
0 - bad	1	3	3	2
1 - satisfactory	11	9	12	7
2 - good	19	24	24	27
3 - very good	11	7	3	11

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

after signing ICF (Study Day 1) and up to completion of the follow-up period (Study Day 14 ± 2) or, in case of premature withdrawal, up to the last Study Visit in an individual subject

Adverse event reporting additional description:

ongoing AEs followed up for 15 days after the last study medication administration

ongoing study medication-related AEs followed up until resolution, unless in investigator's opinion, the AE is unlikely to resolve due to the subject's underlying disease

any new SAEs occurring up to 30 days after the last study medication administration

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Cineole 600 mg/day
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Cineole 1200 mg/day
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Reporting group description: -

Reporting group title	Cineole 900 mg/day
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Reporting group description: -

Serious adverse events	Cineole 600 mg/day	Placebo	Cineole 1200 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cineole 900 mg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Cineole 600 mg/day	Placebo	Cineole 1200 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 43 (20.93%)	2 / 47 (4.26%)	10 / 43 (23.26%)
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	2 / 43 (4.65%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences (all)	2	0	1
Pyrexia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Constipation			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			

subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	2
Eruption			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal hypermotility			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Acarodermatitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	2 / 43 (4.65%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Otitis externa			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0

Influenza subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 47 (2.13%) 1	1 / 43 (2.33%) 1
Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 47 (0.00%) 0	0 / 43 (0.00%) 0
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 47 (0.00%) 0	0 / 43 (0.00%) 0

Non-serious adverse events	Cineole 900 mg/day		
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 45 (17.78%)		
Injury, poisoning and procedural complications Chest injury subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 2		
General disorders and administration site conditions Condition aggravated subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0 1 / 45 (2.22%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		

Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Eructation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Infections and infestations			

Cystitis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Acarodermatitis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Otitis externa			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported