Clinical trial results:
The effect of early administered cineole on the course of a common cold

Summary

EudraCT number	2020-000860-51
Trial protocol	DE
Global end of trial date	19 May 2021

Results information

Result version number	v1 (current)
This version publication date	30 November 2022
First version publication date	30 November 2022

Trial information

Trial identification

Sponsor protocol code	CASK0120

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	Gereonsmühlengasse 1, Cologne, Germany, 50670
Public contact	Global Scientific Development & Clinical Operations, Cassella-med GmbH & Co. KG, +49 2211652565, clinical.operations@klosterfrau.de
Scientific contact	Global Scientific Development & Clinical Operations, Cassella-med GmbH & Co. KG, +49 2211652565, 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	07 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2021
Global end of trial reached?	Yes
Global end of trial date	19 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this clinical trial is to investigate the relation between timing of treatment onset with cineole and course of a common cold with or without acute bronchitis.

Protection of trial subjects:

A SARS-CoV-2 test was performed at visit 2 to exclude Covid-19 positiv patients from participation at the study.
Despite this, in the event of fever and / or profound / protracted pain the patients were allowed to use rescue medication (paracetamol 500 mg).

Background therapy:

Not applicable.

Evidence for comparator:

As this trial aimed to investigate the relation between the timing of treatment onset with cineole and the course of a common cold with or without acute bronchitis, there was no treatment concurrent control or active comparator concurrent control.

Actual start date of recruitment	17 September 2020
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: 522
Worldwide total number of subjects	522
EEA total number of subjects	522

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)	505

From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited in 25 practices of general practitioners, otolaryngologists and specialists in internal medicine throughout Germany from 17th September 2020 until 19th May 2021.

Pre-assignment

Screening details:

Adult outpatients recollecting having at least 1 common cold in the last winter season were eligible for study participation if they meet all of the inclusion and exclusion criteria.

Period 1

Period 1 title	Screening phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Screening Phase
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Screening Phase
Started	522
Completed	522

Period 2

Period 2 title	Illness phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Onset of symptoms
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2[1]	Onset of symptoms
Started	329
Completed	329

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all patients fulfilled the criteria to enter the next period.

Period 3

Period 3 title	Treatment phase
Is this the baseline period?	Yes[2]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	≤12 h

Arm description:

Time to treatment stratum ≤12 h

Arm type	Experimental
Investigational medicinal product name	Soledum® forte capsules
Investigational medicinal product code	R05CA13
Other name	German original name: Soledum® Kapseln forte
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The IMP will be administered at home three times a day (morning, noon, evening, t.i.d.: 3x1 capsules). Treatment starts on the day of Visit 2 (Day 1) at the trial site and ends on the day of Visit 4 (Day 15±2) at home. Subjects, who recover from common cold before Visit 4, may terminate the administration of the IMP, once the first 10 WURSS-11 questions were rated by the subject "0" on two consecutive assessments in the eDiary.
On Day 1 (start of treatment), the IMP will be administered once (1x1 capsule), twice (2x1 capsule) or three times (3x1 capsule) by the subject depending on the time of Visit 2. On the day of Visit 4 (Day 15±2), the IMP will only be administered once in the morning (1x1 capsule, last dose).
IMP has to be swallowed unchewed with sufficient fluid (preferably one glass of water [200 mL]), but no hot beverage, approximately half an hour before a meal. Subjects with a sensitive stomach are recommended to take the IMP during their regular meals.

Arm title	>12 to 24 h

Arm description:

Time to treatment stratum >12 to 24 h

Arm type	Experimental
Investigational medicinal product name	Soledum® forte capsules
Investigational medicinal product code	R05CA13
Other name	German original name: Soledum® Kapseln forte
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The IMP will be administered at home three times a day (morning, noon, evening, t.i.d.: 3x1 capsules). Treatment starts on the day of Visit 2 (Day 1) at the trial site and ends on the day of Visit 4 (Day 15±2) at home. Subjects, who recover from common cold before Visit 4, may terminate the administration of the IMP, once the first 10 WURSS-11 questions were rated by the subject "0" on two consecutive assessments in the eDiary.
On Day 1 (start of treatment), the IMP will be administered once (1x1 capsule), twice (2x1 capsule) or three times (3x1 capsule) by the subject depending on the time of Visit 2. On the day of Visit 4 (Day 15±2), the IMP will only be administered once in the morning (1x1 capsule, last dose).
IMP has to be swallowed unchewed with sufficient fluid (preferably one glass of water [200 mL]), but no hot beverage, approximately half an hour before a meal. Subjects with a sensitive stomach are recommended to take the IMP during their regular meals.

Arm title	>24 h

Arm description:

Time to treatment stratum >24 h

Arm type	Experimental
Investigational medicinal product name	Soledum® forte capsules
Investigational medicinal product code	R05CA13
Other name	German original name: Soledum® Kapseln forte
Pharmaceutical forms	Gastro-resistant capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The IMP will be administered at home three times a day (morning, noon, evening, t.i.d.: 3x1 capsules). Treatment starts on the day of Visit 2 (Day 1) at the trial site and ends on the day of Visit 4 (Day 15±2) at home. Subjects, who recover from common cold before Visit 4, may terminate the administration of the IMP, once the first 10 WURSS-11 questions were rated by the subject "0" on two consecutive assessments in the eDiary.
On Day 1 (start of treatment), the IMP will be administered once (1x1 capsule), twice (2x1 capsule) or three times (3x1 capsule) by the subject depending on the time of Visit 2. On the day of Visit 4 (Day 15±2), the IMP will only be administered once in the morning (1x1 capsule, last dose).
IMP has to be swallowed unchewed with sufficient fluid (preferably one glass of water [200 mL]), but no hot beverage, approximately half an hour before a meal. Subjects with a sensitive stomach are recommended to take the IMP during their regular meals.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the screening phase and therefore not the baseline period.

Number of subjects in period 3[3][4]	≤12 h	>12 to 24 h	>24 h
Started	122	88	98
Completed	122	88	98

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The enrolled patients were first in the screening phase and only a part of them became ill and enterd the baseline period.
[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same

as the number completing the preceding period.
Justification: Not all patients fulfilled the criteria to enter the next period.

Baseline characteristics

Reporting groups	
Reporting group title	≤12 h
Reporting group description:	
Time to treatment stratum ≤12 h	
Reporting group title	>12 to 24 h
Reporting group description:	
Time to treatment stratum >12 to 24 h	
Reporting group title	>24 h
Reporting group description:	
Time to treatment stratum >24 h	

Reporting group values	≤12 h	>12 to 24 h	>24 h
Number of subjects	122	88	98
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 Units: years			
arithmetic mean	37.9	38.4	39.8
full range (min-max)	18 to 70	18 to 69	18 to 69
Gender categorical Units: Subjects			
Female	86	52	53
Male	36	36	45
Smoking status Units: Subjects			
Non-smoker	87	64	73
Ex-smoker	13	0	5
Smoker	22	24	20
Working status Units: Subjects			
(Self-) employed	94	66	79
Not employed	12	11	4
Student	16	11	15
Influenza vaccination for the coming/current winter season Units: Subjects			
No	98	72	87

Yes	24	16	11
Race Units: Subjects			
Caucasian (white)	120	85	98
Black	1	2	0
Other	1	1	0
Alcohol consumption Units: Subjects			
None	90	72	66
Low level consumption	15	6	7
Substantial consumption	17	10	25
Common cold episodes during previous winter			
September to March (number)			
Units: number			
median	2.0	2.0	2.0
full range (min-max)	1 to 7	1 to 10	1 to 5
Baseline WURSS score Units: number			
arithmetic mean	27.31	29.30	26.80
full range (min-max)	3.0 to 57.0	6.0 to 54.0	4.0 to 53.0

Reporting group values	Total		
Number of subjects	308		
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 Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	191		
Male	117		
Smoking status Units: Subjects			
Non-smoker	224		
Ex-smoker	18		
Smoker	66		
Working status Units: Subjects			

(Self-) employed	239		
Not employed	27		
Student	42		
Influenza vaccination for the coming/current winter season Units: Subjects			
No	257		
Yes	51		
Race Units: Subjects			
Caucasian (white)	303		
Black	3		
Other	2		
Alcohol consumption Units: Subjects			
None	228		
Low level consumption	28		
Substantial consumption	52		
Common cold episodes during previous winter			
September to March (number)			
Units: number			
median			
full range (min-max)	-		
Baseline WURSS score Units: number			
arithmetic mean			
full range (min-max)	-		

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified intention-to-treat set (mITT) comprised all subjects:
- who received at least 4 IMP doses within the first 4 days after Visit 2 with maximum one day without treatment;
- who provided at least 5 valid WURSS-11 assessments within the first 7 days after symptom onset with a maximum of 2 days without assessment;
- without intake of antibiotics after start of IMP treatment due to symptoms associated with upper respiratory tract infections.

The mITT was used for the identification of potential confounders and for the evaluation of primary and secondary endpoints in a more "real-life" setting.

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set (SAF) included all subjects, who received at least one dose of the IMP. The SAF was used for analysis of safety and tolerability.

Reporting group values	mITT	SAF	
Number of subjects	308	329	

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 Units: years			
arithmetic mean	38.7		
full range (min-max)	18 to 70		
Gender categorical Units: Subjects			
Female	191		
Male	117		
Smoking status Units: Subjects			
Non-smoker	224		
Ex-smoker	18		
Smoker	66		
Working status Units: Subjects			
(Self-) employed	239		
Not employed	27		
Student	42		
Influenza vaccination for the coming/current winter season Units: Subjects			
No	257		
Yes	51		
Race Units: Subjects			
Caucasian (white) Black Other			
Alcohol consumption Units: Subjects			
None Low level consumption Substantial consumption			
Common cold episodes during previous winter			
September to March (number)			
Units: number			
median	2.0		
full range (min-max)	1 to 10		
Baseline WURSS score			

Units: number			
arithmetic mean	27.71		
full range (min-max)	3.0 to 57.0		

End points

End points reporting groups

Reporting group title	Screening Phase
Reporting group description: -	
Reporting group title	Onset of symptoms
Reporting group description: -	
Reporting group title	≤12 h
Reporting group description: Time to treatment stratum ≤12 h	
Reporting group title	>12 to 24 h
Reporting group description: Time to treatment stratum >12 to 24 h	
Reporting group title	>24 h
Reporting group description: Time to treatment stratum >24 h	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified intention-to-treat set (mITT) comprised all subjects:
- who received at least 4 IMP doses within the first 4 days after Visit 2 with maximum one day without treatment;
- who provided at least 5 valid WURSS-11 assessments within the first 7 days after symptom onset with a maximum of 2 days without assessment;
- without intake of antibiotics after start of IMP treatment due to symptoms associated with upper respiratory tract infections.

The mITT was used for the identification of potential confounders and for the evaluation of primary and secondary endpoints in a more "real-life" setting.

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set (SAF) included all subjects, who received at least one dose of the IMP. The SAF was used for analysis of safety and tolerability.

Primary: Area under the curve global symptom severity curve (AUC-WURSS) - LS Means

End point title	Area under the curve global symptom severity curve (AUC-WURSS) - LS Means

End point description:

The primary efficacy endpoint was the Area under the curve global symptom severity (AUC-WURSS) using the primary efficacy variable subject-reported outcome WURSS-11.
The derivation of AUC-WURSS was based on mean daily total WURSS-11 scores, which were derived by averaging evening assessment of considered symptom day and morning assessment of the subsequent day separately for each item. If only one of both assessments was available, this assessment was used as mean item score for a symptom day.
The mean item scores for questions 2 to 10 (daily single item scores) were then summed up to the mean total score of a day. Imputation of missing data was performed up to (estimated) day of recovery.

End point type	Primary

End point timeframe:

The mean daily total scores (imputed) were summed up from Symptom Day 1 to Symptom Day 17 using trapezoidal approximation, which corresponds to a time frame of common cold onset to treatment day 15 (assuming treatment starts on Symptom Day 3

End point values	≤12 h	>12 to 24 h	>24 h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	122	88	98	
Units: AUC				
least squares mean (confidence interval 95%)	143.1 (117.7 to 168.5)	181.6 (152.5 to 210.8)	232.0 (203.4 to 260.5)	

Statistical analyses

Statistical analysis title	GLM model

Statistical analysis description:

Model contains time-to-treatment stratum, previous influenza vaccination, alcohol consumption, working status and categorized baseline WURSS-11 score.

Comparison groups	≤12 h v >12 to 24 h v >24 h
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA

Notes:

[1] - Effect time to treatment stratum.

Primary: Area under the curve global symptom severity curve (AUC-WURSS) LS means difference

End point title	Area under the curve global symptom severity curve (AUC-WURSS) LS means difference[2][3]

End point description:

Below the LS means difference were presented.

End point type	Primary

End point timeframe:

The mean daily total scores (imputed) were summed up from Symptom Day 1 to Symptom Day 17 using trapezoidal approximation, which corresponds to a time frame of common cold onset to treatment day 15 (assuming treatment starts on Symptom Day 3).

Notes:

[2] - 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: It is the same statistical analysis as for the other primary endpoint.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is due to the LS means difference. The results show the difference to the third arm.

End point values	≤12 h	>12 to 24 h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	88		
Units: AUC LS means differnence				
least squares mean (confidence interval 95%)	-88.9 (-118.0 to -59.8)	-50.3 (-82.0 to -18.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Course of mean daily total score:

End point title	Course of mean daily total score:

End point description:

Mean daily total scores were derived per Symptom Day as described for the primary efficacy endpoint and were analysed per symptom day.
Due to abundance of data for this secondary endpoint only the data of first symptom day is presented, data for all symptome days are presented in the enclosed graph in the attachment.

End point type	Secondary

End point timeframe:

Course of mean daily total scores from common cold onset to end-of-trial.

End point values	≤12 h	>12 to 24 h	>24 h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	122	88	98	
Units: WURSS-11 mean daily total score				
least squares mean (confidence interval 95%)	27.61 (25.73 to 29.49)	28.87 (26.67 to 31.07)	28.65 (26.55 to 30.76)	

Attachments (see zip file)	MMRM Model 2 for WURSS-11 mean daily total score/Figure

Statistical analyses

No statistical analyses for this end point

Secondary: Course of mean daily QoL score

End point title	Course of mean daily QoL score

End point description:

Mean daily group scores were derived analogously to mean daily total score by considering only WURSS-11 questions 2 to 8 for the symptom domain (i.e., aggregated for nasal, throat and item feeling tired) and WURSS-11 questions 9 and 10 for the QoL domain.
Due to the abundance of data only the data of first symptom day is presented, all symptomeday data is presented in the enclosed graph in the attachment.

End point type	Secondary

End point timeframe:

Course of mean daily QoL scores from common cold onset to end-of-trial.

End point values	≤12 h	>12 to 24 h	>24 h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	122	88	98	
Units: Scores				
least squares mean (confidence interval 95%)	6.07 (5.49 to 6.65)	6.03 (5.35 to 6.72)	6.23 (5.57 to 6.88)	

Attachments (see zip file)	MMRM Model 2 for WURSS-11 mean daily QoL Score/Figure

Statistical analyses

No statistical analyses for this end point

Secondary: Time to remission

End point title	Time to remission

End point description:

Remission was considered as present, if daily single item score of WURSS-11 question 1 was ≤1 together with only one symptom scored ≤3 and all other symptoms scored 0 of the considered day based on corresponding single item scores.
Time to remission was then defined as the symptom day of first documented remission. A subject was censored at the time of last measurement if no remission was observed before.

End point type	Secondary

End point timeframe:

From common cold onset to end-of-trial.

End point values	≤12 h	>12 to 24 h	>24 h	mITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	122	88	98	308
Units: Time to remission (days)				
median (full range (min-max))	9.0 (3 to 18)	10.0 (6 to 18)	11.0 (5 to 18)	10.0 (3 to 18)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of AEs - related, not related to IMP

End point title	Incidence of AEs - related, not related to IMP

End point description:

The number of AEs and the number and percentage of subjects with at least one AE were tabulated by MedDRA system organ class (SOC) and preferred term (PT).

End point type	Secondary

End point timeframe:

Start of IMP intake at visit 2, ends at last study visit per subject. If the investigator becomes aware of an AE up to one week after the administration of the last IMP / rescue medication intake this has also to be documented.

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	329			
Units: Numnber of AEs				
number (not applicable)				
Related	17			
Not related	8			
Total	25			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AE recording started after first IMP administration and ended at last trial visit per subject, related AEs 1 week after last intake. Not recovered AEs were to be followed up until resolved or stabilized so that no further improvement could be expected.

Adverse event reporting additional description:

At each visit, the investigator assessed by asking an open standard question (Have anything changed in your state of health since you last came to see me?) if any AEs (non-serious and serious) had occurred. Any AEs, spontaneously reported by the subject or by the subject's relatives/delegates or observed by the investigator were to be recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Safety Set

Reporting group description:

Safety set (SAF) included all subjects, who received at least one dose of the IMP. The SAF was used for analysis of safety and tolerability.

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 329 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 329 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The threshold to report non-serious adverse events is 5%. None of the non-serious AEs had a frequency of of 5% or more.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2020	Amendment 1 introduced the rapid antigen SARS-CoV-2 test as alternative to the PCR test. During the trial, new test methods for SARS-CoV-2 had been established, i.e., an antigen rapid test became commercially available on the market. To allow the sites also to use this antigen rapid test as an alternative to the already implemented PCR-test, this protocol amendment became necessary. The sites could use either the PCR test or the antigen rapid test. The advantage of the antigen rapid test was, that the result was available within a couple of minutes and a decision of exclusion of subject from further trial participation could be made immediately. Furthermore, the currently limited test capacities for PCR test were not blocked for trial purposes. This change was considered as a substantial change to the protocol. In parallel, some other minor protocol specifications were also changed (non-substantial).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported