Clinical trial results:
A randomised, multi-centre, parallel group, double-blind, placebo- and active-controlled clinical study to assess the efficacy and safety of Octenidine lozenges in the treatment of acute sore throat.

Summary

EudraCT number	2012-002876-15
Trial protocol	DE
Global end of trial date	09 November 2015

Results information

Result version number	v1 (current)
This version publication date	25 March 2022
First version publication date	25 March 2022

Trial information

Trial identification

Sponsor protocol code	MCMK0112

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, 50670
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	14 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives are to demonstrate superiority of Octenidine lozenges compared with placebo in terms of rate of responders, and to demonstrate non-inferiority of Octenidine lozenges compared with active comparator (neo angin®) in terms of the rate of responders.
Response is defined as a score of 4 or 5 on the Pain Relief Rating Scale (PRRS) (patient assessment) at visit 3 (study day 3 or 4, LOCF) and a total score of 0 or 1 on the Tonsillo-Pharyngitis Score (TPS) (investigator assessment) at visit 3 (study day 3 or 4, LOCF).
Both primary objectives are efficacy objectives

Protection of trial subjects:

Subjects were during the trial continuously under the supervision of an physician or an experienced nurse. If, in the opinion of the investigator, antibiotic treatment was indicated during the study, the patient was excluded and not allowed to continue the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 740
Worldwide total number of subjects	740
EEA total number of subjects	740

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)	87

Adults (18-64 years)	653
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Three winter periods (2012/2013; 2013/2014 and 2014/2015) were required to complete the recruitment of sufficient amount of patients. Study subjects were recruited from September 2012 through February 2015.

Pre-assignment

Screening details:

Prior to study enrolment, the investigator informed each patient in detail about the study and they were given the Patient Information. After the patients have voluntary singed the consent form, they were screened by confirming all inclusion and exclusion criteria.

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

Blinding implementation details:

Octenidine, placebo and active comparator were provided as indistinguishable lozenges.
Sealed individual random code envelopes were prepared for the purpose of individual unblinding of a patient's treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Octenidine

Arm description:

All patients randomized and treated with Octenidine

Arm type	Experimental
Investigational medicinal product name	Octenidine lozenges
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Lozenge
Routes of administration	Oral use

Dosage and administration details:

Octenidine lozenges were provided as lozenges containing 0.1% Octenidine.
One lozenge was to be taken every 2 to 3 hours, so that a total of 6 lozenges were taken within 24 hours. The lozenge was not to be swallowed immediately, but kept in the mouth until it was fully dissolved.

Arm title	Placebo

Arm description:

All patients treated with Placebo

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

Dosage and administration details:

Placebo contained the same ingredients as the Octenidine lozenges, except for Octenidine. One lozenge was to be taken every 2 to 3 hours, so that a total of 6 lozenges were taken within 24 hours. The lozenge was not to be swallowed immediately, but kept in the mouth until it was fully dissolved.

Arm title	Neo-Angin

Arm description:

All patients treated with Neo-Angin

Arm type	Active comparator
Investigational medicinal product name	Neo-Angin
Investigational medicinal product code	Neo-Angin
Other name	
Pharmaceutical forms	Lozenge
Routes of administration	Other use

Dosage and administration details:

Active comparator (Neo-Angin) was provided as the product that is marketed in Germany but without the ingrdient providing red colour (Batch No. 717052). This ingredient (Ponceau 4R) is pharmacologically irrelevant. One lozenge was to be taken every 2 to 3 hours so that a total of 6 lozenges were taken within 24 hours. The lozenge was not to be swallowed immediately but was to be kept in mouth until it is fully dissolved.

Number of subjects in period 1[1]	Octenidine	Placebo	Neo-Angin
Started	341	186	192
Completed	329	180	186
Not completed	12	6	6
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	9	3	2
Additional treatment required	-	1	2
Randomization failure	2	1	2

Notes:

[1] - 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 number of subjects reported as being in the baseline period are the same as the number of patients enrolled, but different from the number of patients randomized. Statistical analyses were carried out with the randomized patients of the three treatment arms, thus here the number of randomized patients was considered.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Efficacy results of the full Analysis set (FAS)	

Reporting group values	Overall trial	Total	
Number of subjects	719	719	
Age categorical			
All patients categorized by age			
Units: Subjects			
Adolescents (12-17 years)	83	83	
Adults (>= 18 years)	636	636	
Gender categorical			
All patients of the full analysis set categorized by gender			
Units: Subjects			
Male	0	0	
Female	0	0	
not recorded	719	719	

End points

End points reporting groups

Reporting group title	Octenidine
Reporting group description:	
All patients randomized and treated with Octenidine	
Reporting group title	Placebo
Reporting group description:	
All patients treated with Placebo	
Reporting group title	Neo-Angin
Reporting group description:	
All patients treated with Neo-Angin	

Primary: Superiority of Octenidine lozenges compared with placebo

End point title	Superiority of Octenidine lozenges compared with placebo[1]

End point description:

The primary objectives were to demonstrate superiority of Octenidine lozenges compared with placebo in terms of rate of responders.
Response was defined as a score of 4 or 5 on the Pain Relief Rating Scale (PRRS) (patient assessment) at visit 3 (Study Day 3 or 4, LOCF) and a total score of 0 or 1 on the Tonsillo-Pharyngitis Score (TPS) (investigator assessment) at visit 3 (Study Day 3 or 4, LOCF).

End point type	Primary

End point timeframe:

From visit 1 through visit 3 (study day 0 through study day 3 or 4)

Notes:

[1] - 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: Superiority of Octenidine lozenges refers only to placebo and not to comparator.

End point values	Octenidine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341	186		
Units: number of subjects				
Responder	194	81		
Non-responder	147	105		

Statistical analyses

Statistical analysis title	Full analysis set

Statistical analysis description:

Treatment response of the superiority group

Comparison groups	Octenidine v Placebo

Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0031 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.5
upper limit	22.2
Variability estimate	Standard deviation

Notes:

[2] - The study was planned using an adaptive 2-stage group sequential design with possible sample size adjustment after the planned Interim Analysis.
[3] - p-value for difference Octenidine vs. resp. group

Primary: Non-inferiority of Octenidine lozenges compared with active comparator

End point title	Non-inferiority of Octenidine lozenges compared with active comparator[4]

End point description:

Non-inferiority of Octenidine lozenges compared with active comparator (neo-angin) in terms of the rate of responders.
Response was defined as a score of 4 or 5 on the Pain Relief Rating Scale (PRRS) (patient assessment) at visit 3 (Study Day 3 or 4, LOCF) and a total score of 0 or 1 on the Tonsillo-Pharyngitis Score (TPS) (investigator assessment) at visit 3 (Study Day 3 or 4, LOCF).

End point type	Primary

End point timeframe:

From visit 1 through visit 3 (study day 0 through study day 3 or 4)

Notes:

[4] - 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: Non-inferiority of Octenidine lozenges refers only to comparator and not to placebo.

End point values	Octenidine	Neo-Angin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341	192		
Units: number of subjects				
Responder	194	104		
Non-Responder	147	88		

Statistical analyses

Statistical analysis title	Full analysis set

Statistical analysis description:

Treatment Response of the non-inferiority group.

Comparison groups	Octenidine v Neo-Angin

Number of subjects included in analysis	533
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	= 0.51 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	11.8
Variability estimate	Standard deviation

Notes:

[5] - The study was planned using an adaptive 2-stage group sequential design with possible sample size adjustment after the planned Interim Analysis.
[6] - p-value for difference Octenidine vs. resp. group

Secondary: Pain Relief Rating Scale (PRRS) - rate of patients with pain relief

End point title	Pain Relief Rating Scale (PRRS) - rate of patients with pain relief

End point description:

Rate of patients with pain relief at study day 1, 2, and 3/4. The patients were to be asked to assess the PRRS for sore throat using a 5 step rating scale. The results are representing the number of patients with any pain relief (PRRS score 1 to 5).

End point type	Secondary

End point timeframe:

Course of the study from visit 2 through visit 3 (study day 1 through study day 3 or 4).

End point values	Octenidine	Placebo	Neo-Angin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	341	186	192	
Units: number of subjects				
Study day 1	271	147	160	
Study day 2	312	173	179	
Study day 3/4	304	166	175	

Statistical analyses

No statistical analyses for this end point

Secondary: Tonsillo-Pharyngitis Score (TPS) - rate of patients with improvement

End point title	Tonsillo-Pharyngitis Score (TPS) - rate of patients with improvement

End point description:

The local findings in the pharynx using the TPS(10) by assessment of investigators. The results are representing rate of patients with improvement at study day 1 and study day 3/4.

End point type	Secondary

End point timeframe:

Course of the study from visit 2 through visit 3 (study day 1 through study day 3 or 4).

End point values	Octenidine	Placebo	Neo-Angin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	341	186	192	
Units: number of subjects				
Study day 1	219	131	132	
Study day 3/4	331	177	181	

Statistical analyses

No statistical analyses for this end point

Secondary: Tonsillo-Pharyngitis Score (TPS) - mean change at Visit 2

End point title	Tonsillo-Pharyngitis Score (TPS) - mean change at Visit 2

End point description:

The local findings in the pharynx using the TPS(10) by assessment of investigators. Results are representing the mean change from baseline at Visit 2 (study day 1).

End point type	Secondary

End point timeframe:

Course of the study from visit 1 through visit 2 (study day 0 to study day 1).

End point values	Octenidine	Placebo	Neo-Angin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	338	184	191	
Units: other				
arithmetic mean (standard deviation)	-1.0 (± 1.1)	-1.3 (± 1.2)	-1.0 (± 1.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tonsillo-Pharyngitis Score (TPS) - mean change at Visit 3

End point title	Tonsillo-Pharyngitis Score (TPS) - mean change at Visit 3

End point description:

The local findings in the pharynx using the TPS(10) by assessment of investigators. Results are representing the mean change from baseline at Visit 3 (study day 3/4).

End point type	Secondary

End point timeframe:

Course of the study from visit 1 through visit 3 (study day 0 through study day 3 or 4).

End point values	Octenidine	Placebo	Neo-Angin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	338	183	187	
Units: other				
arithmetic mean (standard deviation)	-3.3 (± 1.4)	-3.4 (± 1.7)	-3.0 (± 1.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scales (VAS) - mean change at Visit 2

End point title	Visual Analogue Scales (VAS) - mean change at Visit 2

End point description:

Mean change from baseline at visit 2 with regard to Sum of VAS at rest and VAS when swallowing [cm].

End point type	Secondary

End point timeframe:

Course of the study from visit 1 through visit 2 (study day 0 through study day 1).

End point values	Octenidine	Placebo	Neo-Angin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	338	184	191	
Units: other				
arithmetic mean (standard deviation)	-3.19 (± 2.90)	-3.04 (± 2.67)	-3.21 (± 3.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scales (VAS) - mean change at Visit 3

End point title	Visual Analogue Scales (VAS) - mean change at Visit 3

End point description:

Mean change from baseline at visit 3 with regard to Sum of VAS at rest and VAS when swallowing [cm].

End point type	Secondary

End point timeframe:

Course of the study from visit 1 through visit 3 (study day 0 through study day 3 or 4).

End point values	Octenidine	Placebo	Neo-Angin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	333	183	187	
Units: other				
arithmetic mean (standard deviation)	-10.53 (± 3.85)	-10.19 (± 4.41)	-10.16 (± 4.04)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events are to be reported during exposure to study medication from study day 0 through study day 3/4.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	Octenidine
Reporting group description: All patients received at least one treatment emergent Adverse Event in the Octenidine group	
Reporting group title	Neo-Angin
Reporting group description: All patients received at least one treatment emergent Adverse Event in the Neo-Angin group.	
Reporting group title	Placebo
Reporting group description: All patients received at least one treatment emergent Adverse Event in the placebo group.	

Serious adverse events	Octenidine	Neo-Angin	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain lower	Additional description: One patient in the neo-angin group reported an SAE of abdominal pain lower and was hospitalised with suspected appendicitis.		
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Octenidine	Neo-Angin	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 344 (8.72%)	15 / 191 (7.85%)	8 / 188 (4.26%)
Investigations			
Sputum abnormal			

subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	14 / 344 (4.07%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	14	2	1
Headache			
subjects affected / exposed	0 / 344 (0.00%)	2 / 191 (1.05%)	0 / 188 (0.00%)
occurrences (all)	14	2	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 344 (0.87%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	13	5	1
Diarrhoea			
subjects affected / exposed	3 / 344 (0.87%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Nausea			
subjects affected / exposed	3 / 344 (0.87%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Dry mouth			
subjects affected / exposed	2 / 344 (0.58%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Vomiting			
subjects affected / exposed	3 / 344 (0.87%)	0 / 191 (0.00%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Abdominal pain lower			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	13	5	1

Dyspepsia			
subjects affected / exposed	1 / 344 (0.29%)	0 / 191 (0.00%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Epigastric discomfort			
subjects affected / exposed	1 / 344 (0.29%)	0 / 191 (0.00%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Flatulence			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Glossodynia			
subjects affected / exposed	0 / 344 (0.00%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	13	5	1
Paraesthesia oral			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	13	5	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 344 (0.87%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	3	4	2
Oropharyngeal pain			
subjects affected / exposed	1 / 344 (0.29%)	1 / 191 (0.52%)	1 / 188 (0.53%)
occurrences (all)	3	4	2
Oropharyngeal discomfort			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	3	4	2
Productive cough			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	3	4	2
Musculoskeletal and connective tissue disorders			
Tendonitis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 344 (0.58%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	8	4	4

Nasopharyngitis			
subjects affected / exposed	3 / 344 (0.87%)	0 / 191 (0.00%)	0 / 188 (0.00%)
occurrences (all)	8	4	4
Rhinitis			
subjects affected / exposed	1 / 344 (0.29%)	1 / 191 (0.52%)	1 / 188 (0.53%)
occurrences (all)	8	4	4
Sinusitis			
subjects affected / exposed	1 / 344 (0.29%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	8	4	4
Tonsillitis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	8	4	4
Herpes zoster			
subjects affected / exposed	0 / 344 (0.00%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	8	4	4
Laryngitis			
subjects affected / exposed	0 / 344 (0.00%)	1 / 191 (0.52%)	0 / 188 (0.00%)
occurrences (all)	8	4	4
Pharyngitis			
subjects affected / exposed	0 / 344 (0.00%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	8	4	4
Tonsillitis streptococcal			
subjects affected / exposed	1 / 344 (0.29%)	0 / 191 (0.00%)	0 / 188 (0.00%)
occurrences (all)	8	4	4
Pharyngeal hypoaesthesia			
subjects affected / exposed	0 / 344 (0.00%)	0 / 191 (0.00%)	1 / 188 (0.53%)
occurrences (all)	3	4	2

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