Clinical trial results:
Phase IV study comparing the efficacy and safety of Benzydamine hydrochloride 0,3% oromucosal spray and Benzydamine hydrochloride 3 mg lozenges in patients with acute sore throat.

Summary

EudraCT number	2019-003257-29
Trial protocol	HU PL
Global end of trial date	30 June 2021

Results information

Result version number	v1 (current)
This version publication date	13 July 2022
First version publication date	13 July 2022

Trial information

Trial identification

Sponsor protocol code	030(Z)WO19176

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04941976
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Angelini Pharma S.p.A
Sponsor organisation address	Via Amelia 70, Roma, Italy, 00181
Public contact	Study Manager, Angelini S.p.A., 39 0691045567, carmelina.valerio@angelinipharma.com
Scientific contact	Study Manager, Angelini S.p.A., 39 0691045567, carmelina.valerio@angelinipharma.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	30 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2021
Global end of trial reached?	Yes
Global end of trial date	30 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess the pain relief in patients with acute sore throat, at 2 minutes (T2 min), after a single dose administration of benzydamine hydrochloride 0,3% oromucosal spray or benzydamine hydrochloride 3 mg lozenges. Moreover, safety and efficacy evaluations up to a 7-days treatment period, were performed.

The study was initiated at 16 sites and enrolment was performed at 12 sites located among Poland (4 sites), Hungary (1 site) and Russia (7 sites).

Protection of trial subjects:

This trial was conducted in accordance with the study protocol, GCPs, Declaration of Helsinki (including up-to-date versions) and applicable regulatory requirements and started after the Institutional Review Board/Ethics Committee written approval and in absence of any non-acceptance grounds by the Competent Authority.
Before entering the study, patients were fully informed about the purposes of the research, possible benefits, any potential personal reasonable risk or discomfort, the expected duration of their participation in the trial. The patient was also informed by the Investigator of all aspects related to his/her personal data processing, as well as his/her rights on this matter.
Before recruitment, a copy of the ICF (including the information sheet) and DCPPD (including the Information on Processing of Personal Data) was given to the patient. The patient entered the study by signing the ICF and DCPPD
A temporary suspension of the study was performed on April 3rd, 2020 in Hungary according to the EMA Guidance for the management of COVID-19 and Hungarian RA recommendations. Sponsor and its delegate have promptly informed all Investigators conducting the trial about the suspension of clinical phase, which was re-started on June 24th, 2020 after official communication to the RA.

Background therapy:

Not applicable

Evidence for comparator:

The benzydamine lozenges formulations was used as a comparator drug with the aim to better understand if a difference exists in terms of onset of pain relief between spray and lozenges, with the final goal to provide patients with two different treatment formats to choose from, according to their own preferences: some patients, for example, could prefer the demulcent effect of a lozenge and other the convenience of a spray.

Actual start date of recruitment	13 August 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	Russian Federation: 256
Country: Number of subjects enrolled	Poland: 78

Country: Number of subjects enrolled	Hungary: 29
Worldwide total number of subjects	363
EEA total number of subjects	107

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)	342
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 363 male and female patients (aged 18 – 75 years, limits included) were randomized to benzydamine hydrochloride 0.3% spray or lozenges 3 mg mint flavour. Patients enrolment was competitive among clinical sites.

Pre-assignment

Screening details:

At Visit 0 (Screening/Baseline), the Investigator assigned the Screening number to each potentially eligible patient, following a sequential order, after the relevant ICF was signed and dated.

Period 1

Period 1 title	PERIOD 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The two different pharmaceutical forms of the investigated drugs did not permit to mask the two treatments, for this reason an open label design has been selected.
After randomization, both the Investigator and patient were aware of the assigned medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	BNZ hydrochloride 0,3% spray

Arm description:

One administration (2-4 nebulizations) up to 6 times a day. Each nebulization contains 0.17 ml of the solution; a total of 4 nebulizations corresponds to 2.04 mg of benzydamine

Arm type	Experimental
Investigational medicinal product name	Benzydamine hydrochloride spray oromucosal solution
Investigational medicinal product code	030
Other name	
Pharmaceutical forms	Oromucosal solution
Routes of administration	Oromucosal use

Dosage and administration details:

Single application of 0.3% benzydamine hydrochloride spray oromucosal solution, corresponding to 2.04 mg of benzydamine, for a total of 4 nebulizations;

Arm title	BNZ hydrochloride 3 mg LOZENGE (mint flavour)

Arm description:

One lozenge corresponding to 2.68 mg of benzydamine 3 times a day (Poland and Russia);
One lozenge corresponding to 2.68 mg of benzydamine 3-4 times a day (Hungary);

Arm type	Active comparator
Investigational medicinal product name	Benzydamine hydrochloride lozenge (mint flavour)
Investigational medicinal product code	030
Other name	
Pharmaceutical forms	Lozenge
Routes of administration	Oral use

Dosage and administration details:

Single 3 mg lozenge of benzydamine hydrochloride (mint flavour), corresponding to 2.68 mg of benzydamine.

Number of subjects in period 1	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)
Started	181	182
Completed	181	182

Baseline characteristics

Reporting groups

Reporting group title	PERIOD 1 (overall period)

Reporting group description: -

Reporting group values	PERIOD 1 (overall period)	Total	
Number of subjects	363	363	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	342	342	
From 65-84 years	21	21	
85 years and over	0	0	
Subjects	0	0	
Adults	0	0	
Age continuous Units: years			
arithmetic mean	39.9		
standard deviation	± 13.27	-	
Gender categorical Units: Subjects			
Female	231	231	
Male	132	132	

Subject analysis sets

Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized patients who took at least the first dose of the study medication and having all Day 0 (up to 120 minutes) STRRS evaluations, with no major protocol violations.

Subject analysis set title	Modified Intention-to Treat (m-IIT) population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized patients who took at least one dose of the study medication and performed the 2 minutes post-treatment efficacy assessment with STRRS.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who took at least one dose of the study medication

Reporting group values	Per Protocol (PP) population	Modified Intention-to Treat (m-IIT) population	Safety population
Number of subjects	355	363	363
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	335	342	342
From 65-84 years	20	21	21
85 years and over	0	0	0
Subjects	0	0	0
Adults	0	0	0
Age continuous			
Units: years			
arithmetic mean	39.9	39.9	39.9
standard deviation	± 13.20	± 13.27	± 13.27
Gender categorical			
Units: Subjects			
Female	127	132	132
Male	228	131	131

End points

End points reporting groups

Reporting group title	BNZ hydrochloride 0,3% spray

Reporting group description:

One administration (2-4 nebulizations) up to 6 times a day. Each nebulization contains 0.17 ml of the solution; a total of 4 nebulizations corresponds to 2.04 mg of benzydamine

Reporting group title	BNZ hydrochloride 3 mg LOZENGE (mint flavour)

Reporting group description:

One lozenge corresponding to 2.68 mg of benzydamine 3 times a day (Poland and Russia);
One lozenge corresponding to 2.68 mg of benzydamine 3-4 times a day (Hungary);

Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized patients who took at least the first dose of the study medication and having all Day 0 (up to 120 minutes) STRRS evaluations, with no major protocol violations.

Subject analysis set title	Modified Intention-to Treat (m-IIT) population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized patients who took at least one dose of the study medication and performed the 2 minutes post-treatment efficacy assessment with STRRS.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who took at least one dose of the study medication

Primary: STRRS at 2 minutes

End point title	STRRS at 2 minutes

End point description:

Percentage of responders defined as patients who reported at least a “slight relief” (STRRS score ≥1) at 2 minutes after the first application of benzydamine hydrochloride 0.3% spray or benzydamine hydrochloride 3mg lozenges

End point type	Primary

End point timeframe:

2 minutes after post study drug application

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181[1]	182[2]		
Units: percent				
number (not applicable)	91.7	90.7		

Notes:

[1] - Percentage of responders

[2] - Percentage of responders

Statistical analyses

Statistical analysis title	95% Confidence Interval

Statistical analysis description:

Lower limit of the two-sided 95% Confidence Interval (95% CI) of the difference between the study drugs in the responder rates

Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	95% CI
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.78
upper limit	6.88

Secondary: STRRS at 1 minute

End point title	STRRS at 1 minute

End point description:

A "slight relief" in STRRS (score ≥ 1) will be considered as the first perceived pain relief;

End point type	Secondary

End point timeframe:

At 1 minute after a single dose administration.

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: percent				
number (not applicable)	77.9	87.4		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)

Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0041
Method	Cochran-Mantel-Haenszel

Secondary: STRRS at 5 minutes

End point title	STRRS at 5 minutes

End point description:

Percentage of patients recording a meaningful sore throat relief assessed at T5 min after a single dose administration. A "meaningful sore throat relief" was considered as a score ≥ 3 (moderate relief) in the STRRS;

End point type	Secondary

End point timeframe:

At 5 minutes

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: percent				
number (not applicable)	48.6	59.9		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0058
Method	Cochran-Mantel-Haenszel

Secondary: STRRS at 10 minutes

End point title	STRRS at 10 minutes

End point description:

Percentage of patients recording a meaningful sore throat relief assessed at T10 min after a single dose administration. A "meaningful sore throat relief" was considered as a score ≥ 3 (moderate relief) in the STRRS.

End point type	Secondary

End point timeframe:
At 10 minutes

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: percent				
number (not applicable)	66.9	74.2		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0866
Method	Cochran-Mantel-Haenszel

Secondary: STRRS at 15 minutes

End point title	STRRS at 15 minutes
End point description:	
Percentage of patients recording a meaningful sore throat relief assessed at T15 min after a single dose administration. A "meaningful sore throat relief" was considered as a score ≥ 3 (moderate relief) in the STRRS.	
End point type	Secondary
End point timeframe:	
At 15 minutes	

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: percent				
number (not applicable)	75.7	83.0		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0634
Method	Cochran-Mantel-Haenszel

Secondary: STRRS at 30 minutes

End point title	STRRS at 30 minutes

End point description:

Percentage of patients recording a meaningful sore throat relief assessed at T30 minutes after a single dose administration. A "meaningful sore throat relief" was considered as a score ≥ 3 (moderate relief) in the STRRS.

End point type	Secondary

End point timeframe:

At 30 minutes

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: percent				
number (not applicable)	71.8	83.5		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)

Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0035
Method	Cochran-Mantel-Haenszel

Secondary: STRRS at 60 minutes

End point title	STRRS at 60 minutes

End point description:

Percentage of patients recording a meaningful sore throat relief assessed at T60 minutes after a single dose administration. A "meaningful sore throat relief" was considered as a score ≥ 3 (moderate relief) in the STRRS.

End point type	Secondary

End point timeframe:

At 60 minutes

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: percent				
number (not applicable)	55.2	63.7		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0327
Method	Cochran-Mantel-Haenszel

Secondary: STRRS at 120 minutes

End point title	STRRS at 120 minutes

End point description:

Percentage of patients recording a meaningful sore throat relief assessed at T120 minutes after a single dose administration. A "meaningful sore throat relief" was considered as a score ≥ 3 (moderate relief) in the STRRS.

End point type	Secondary

End point timeframe:
At 120 minutes

End point values	BNZ hydrochloride 0,3% spray	BNZ hydrochloride 3 mg LOZENGE (mint flavour)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	182		
Units: percent				
number (not applicable)	47.5	51.6		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	BNZ hydrochloride 0,3% spray v BNZ hydrochloride 3 mg LOZENGE (mint flavour)
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.216
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time frame for reporting adverse events is from Informed consent signature up to the last visit (visit 2 or ETV).

Adverse event reporting additional description:

Treatment Emergent Adverse Events (TEAEs):any event started on or after the first study medication administration and was not a pre-existing medical condition.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	BNZ hydrocloride 0.3% spray

Reporting group description:

Patients randomized to the spray applied 4 nebulizations (1 dose) of benzydamine hydrochloride spray oromucosal solution, corresponding to 2.04 mg of benzydamine on the inflamed area.

Reporting group title	BNZ hydrocloride 3 mg LOZENGE (mint flavour)

Reporting group description:

Patients who took one 3 mg lozenge of benzydamine hydrochloride mint flavour, corresponding to 2.68 mg of benzydamine

Serious adverse events	BNZ hydrocloride 0.3% spray	BNZ hydrocloride 3 mg LOZENGE (mint flavour)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 181 (0.00%)	0 / 182 (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: 1 %

Non-serious adverse events	BNZ hydrocloride 0.3% spray	BNZ hydrocloride 3 mg LOZENGE (mint flavour)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 181 (0.55%)	21 / 182 (11.54%)	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 181 (0.00%)	17 / 182 (9.34%)	
occurrences (all)	0	19	

Intentional product misuse			
subjects affected / exposed	0 / 181 (0.00%)	3 / 182 (1.65%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Administration site dysaesthesia			
subjects affected / exposed	1 / 181 (0.55%)	3 / 182 (1.65%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Tongue discomfort			
subjects affected / exposed	0 / 181 (0.00%)	1 / 182 (0.55%)	
occurrences (all)	0	1	
Paraesthesia oral			
subjects affected / exposed	0 / 181 (0.00%)	1 / 182 (0.55%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 181 (0.00%)	1 / 182 (0.55%)	
occurrences (all)	0	1	
Hypoaesthesia oral			
subjects affected / exposed	0 / 181 (0.00%)	1 / 182 (0.55%)	
occurrences (all)	0	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? Yes

Date	Interruption	Restart date
03 April 2020	A temporary suspension of the study was performed on April 3rd, 2020 in Hungary according to the EMA Guidance for the management of COVID-19 and Hungarian RA recommendations. Sponsor and its delegate have promptly informed all Investigators conducting the trial about the suspension of clinical phase, which was re-started on June 24th, 2020 after official communication to the RA.	24 June 2020

Notes:

Limitations and caveats

None reported