Clinical trial results:
Efficacy and safety of an alcohol-free formulation of 0.15% benzydamine spray in children with sore throat. Randomized, double blind, placebo-controlled study

Summary

EudraCT number	2009-014401-13
Trial protocol	IT AT SK RO ES
Global end of trial date	21 October 2011

Results information

Result version number	v2 (current)
This version publication date	18 August 2018
First version publication date	02 August 2015
Version creation reason	• Changes to summary attachments A summary of results is uploaded replacing the CSR
Summary attachment (see zip file)	Synopsis (2009_014401-13.pdf)

Trial information

Trial identification

Sponsor protocol code	030(B)SC09047

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ACRAF SpA
Sponsor organisation address	Piazzale della stazione, s.n.c., S.Palomba- Pomezia (Rome), Italy, 00071
Public contact	Clinical Trial application Unit, ACRAF SpA, +39 0691045335, ctaunit@angelini.it
Scientific contact	Clinical Trial application Unit, ACRAF SpA, +39 0691045432, ctaunit@angelini.it

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 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the analgesic activity of 0.15% benzydamine spray in single administration compared to placebo.

Protection of trial subjects:

The study was performed in accordance with the protocol (unless otherwise indicated), Good Clinical Practice (GCP) requirements, the Declaration of Helsinki (updated version), and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2010
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	Romania: 89
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Austria: 40
Country: Number of subjects enrolled	Italy: 59
Worldwide total number of subjects	201
EEA total number of subjects	201

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)	194
Adolescents (12-17 years)	7
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were male and female outpatients 6-12 years old with objective findings that confirm the sore throat diagnosis with Tonsillo-Pharyngitis Scale > 6 points; onset of sore throat symptoms within 7 days; moderate-to-severe sore throat (Children's Sore Throat Pain Thermometer > 120mm).

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	Benzydamine

Arm description:

Benzydamnine 0,15 % spray, a single application (4 nebulizations).

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

Dosage and administration details:

A single application constituted of 4 nebulizations; each nebulization corresponds to 1.17 ml and contains about 0.25 mg of benzydamine.

Arm title	Placebo

Arm description:

Placebo spray, a single application (4 nebulizations).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal spray
Routes of administration	Oromucosal use

Dosage and administration details:

A single application, constituted of 4 nebulizations.

Number of subjects in period 1	Benzydamine	Placebo
Started	99	102
Completed	99	102

Baseline characteristics

Reporting groups	
Reporting group title	Benzydamine
Reporting group description:	
Benzydamnine 0,15 % spray, a single application (4 nebulizations).	
Reporting group title	Placebo
Reporting group description:	
Placebo spray, a single application (4 nebulizations).	

Reporting group values	Benzydamine	Placebo	Total
Number of subjects	99	102	201
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)	95	99	194
Adolescents (12-17 years)	4	3	7
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	8.8	8.7	
standard deviation	± 1.8	± 1.7	-
Gender categorical Units: Subjects			
Female	47	57	104
Male	52	45	97

End points

End points reporting groups

Reporting group title	Benzydamine
Reporting group description:	
Benzydamnine 0,15 % spray, a single application (4 nebulizations).	
Reporting group title	Placebo
Reporting group description:	
Placebo spray, a single application (4 nebulizations).	

Primary: SPID Child ITT population

End point title	SPID Child ITT population
End point description:	
Sum of Pain Intensity Difference Score (SPID) of the Children's Sore Throat Pain Thermometer scale by the child. CSTPT is a vertical 21 point (200 mm) VAS anchored on the bottom by the sentence "IT DOESN'T HURT AT ALL" and at the top "IT HURTS A LOT", divided at 1 cm intervals from 0 to 20.	
End point type	Primary
End point timeframe:	
Baseline and then after 15, 30, 45, 60 and 90 minutes from the study medications administrations.	

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: mm				
arithmetic mean (standard deviation)	-3919.1 (± 2629.7)	-4127.7 (± 2495.6)		

Statistical analyses

Statistical analysis title	SPID child: Benzydamine- Placebo/ITT
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7041 [1]
Method	ANOVA

Notes:

[1] - Not significant

Primary: SPID Child PP population

End point title	SPID Child PP population
End point description:	
Sum of Pain Intensity Difference Score (SPID) of the Children's Sore Throat Pain Thermometer scale by	

the child. CSTPT is a vertical 21 point (200 mm) VAS anchored on the bottom by the sentence "IT DOESN'T HURT AT ALL" and at the top "IT HURTS A LOT", divided at 1 cm intervals from 0 to 20.

End point type	Primary

End point timeframe:

Baseline and after 15, 30, 45, 60 and 90 minutes from the study medications administrations.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: mm				
arithmetic mean (standard deviation)	-3855.9 (± 2696.8)	-4276.5 (± 2567.2)		

Statistical analyses

Statistical analysis title	SPID child: Benzydamine-Placebo/PP
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7277 [2]
Method	ANOVA

Notes:

[2] - Not significant

Secondary: SPID Parent ITT population

End point title	SPID Parent ITT population

End point description:

Sum of Pain Intensity Difference Score (SPID) of the Children's Sore Throat Pain Intensity scale by the parent. This scale is a horizontal VAS presented as a line (100 mm in length) anchored by word descriptors at each end: on the left by thesentence "NO PAIN", and on the right "VERY SEVERE PAIN".

End point type	Secondary

End point timeframe:

Baseline and then after 15, 30, 45, 60 and 90 minutes from the study medications administrations.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: mm				
arithmetic mean (standard deviation)	-1830.7 (± 1202.5)	-1922.9 (± 1387.1)		

Statistical analyses

Statistical analysis title	SPID parent : Benzydamine- Placebo/ITT
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7041 [3]
Method	ANOVA

Notes:

[3] - Not significant

Secondary: SPID Investigator ITT population

End point title	SPID Investigator ITT population

End point description:

Sum of Pain Intensity Difference Score (SPID) of the Children's Sore Throat Pain Intensity scale by the investigator. This scale is a horizontal VAS presented as a line (100 mm in length) anchored by word descriptors at each end: on the left by the sentence "NO PAIN", and on the right "VERY SEVERE PAIN".

End point type	Secondary

End point timeframe:

Baseline and then after 15, 30, 45, 60 and 90 minutes from the study medications administrations.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: mm				
arithmetic mean (standard deviation)	-1902.5 (± 1012.1)	-1895.7 (± 1176.8)		

Statistical analyses

Statistical analysis title	SPID investigator: Benzydamine- Placebo/ITT
Comparison groups	Benzydamine v Placebo

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7303 [4]
Method	ANOVA

Notes:

[4] - Not significant

Secondary: TOTPAR Child ITT population

End point title	TOTPAR Child ITT population

End point description:

Children's Sore Throat Relief was estimated as the area under the pain relief versus time curve (TOTPAR). At all fixed times, the child was also asked to indicate pain intensity using the horizontal scale to rate the sore throat relief, consisting of 5 cartoon faces ranging from a tearful face for "NO RELIEF " on the left to a smiling face for "COMPLETE RELIEF " on the right.

End point type	Secondary

End point timeframe:

After 15, 30, 45, 60 and 90 minutes from the study medications administrations.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: score on a scale				
arithmetic mean (standard deviation)	214.1 (± 65.1)	217.3 (± 65.6)		

Statistical analyses

Statistical analysis title	TOTPAR: Benzydamine-Placebo/ITT
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9082 [5]
Method	ANOVA

Notes:

[5] - Not significant

Secondary: SPID Parent PP population

End point title	SPID Parent PP population

End point description:

Sum of Pain Intensity Difference Score (SPID) of the Children's Sore Throat Pain Intensity Scale by the parent. This scale is a horizontal VAS presented as a line (100 mm in length) anchored by word descriptors at each end: on the left by the sentence "NO PAIN", and on the right "VERY SEVERE PAIN".

End point type	Secondary

End point timeframe:

Baseline and after 15, 30, 45, 60 and 90 minutes from the study medications administrations.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: mm				
arithmetic mean (standard deviation)	-1738.5 (± 1254.5)	-1984.6 (± 1460.5)		

Statistical analyses

Statistical analysis title	SPID parent : Benzydamine- Placebo/PP
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7708 [6]
Method	ANOVA

Notes:

[6] - Not significant

Secondary: SPID Investigator PP population

End point title	SPID Investigator PP population

End point description:

Sum of Pain Intensity Difference Score (SPID) of the Children's Sore Throat Pain Intensity scale by the investigator. This scale is a horizontal VAS presented as a line (100 mm in length) anchored by word descriptors at each end: on the left by the sentence "NO PAIN", and on the right "VERY SEVERE PAIN".

End point type	Secondary

End point timeframe:

Baseline and after 15, 30, 45, 60 and 90 minutes from the study medications administrations.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: mm				
arithmetic mean (standard deviation)	-1894.2 (± 1055.7)	-1963.8 (± 1248.2)		

Statistical analyses

Statistical analysis title	SPID investigator : Benzydamine- Placebo/PP
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5945 [7]
Method	ANOVA

Notes:

[7] - Not significant

Secondary: TOTPAR Child PP population

End point title	TOTPAR Child PP population

End point description:

Children's Sore Throat Relief was estimated as the area under the pain relief versus time curve (TOTPAR). At all fixed times, the child was also asked to indicate pain intensity using the horizontal scale to rate the sore throat relief, consisting of 5 cartoon faces ranging from a tearful face for "NO RELIEF " on the left to a smiling face for "COMPLETE RELIEF " on the right.

End point type	Secondary

End point timeframe:

After 15, 30, 45, 60 and 90 minutes from the study medications administrations.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: score on a scale				
arithmetic mean (standard deviation)	214.1 (± 69.5)	220.5 (± 68.5)		

Statistical analyses

Statistical analysis title	TOTPAR: Benzydamine-Placebo/PP
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8113 [8]
Method	ANOVA

Notes:

[8] - Not significant

Secondary: Tolerability evaluation Investigator/ good 90 minutes

End point title	Tolerability evaluation Investigator/ good 90 minutes

End point description:

A global tolerability rating was expressed by the Investigator through a 5-point categorical scale (very good, good, fair, poor and very poor).

End point type	Secondary

End point timeframe:
after 90 minutes and 4 days post-treatment

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	1	0		

Statistical analyses

Statistical analysis title	Tolerabiliy evaluation investigator
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3173 [9]
Method	Cochran-Mantel-Haenszel

Notes:
[9] - Not significant

Secondary: Tolerability evaluation Investigator/very good 90 minutes

End point title	Tolerability evaluation Investigator/very good 90 minutes

End point description:
A global tolerability rating was expressed by the Investigator through a 5-point categorical scale (very good, good, fair, poor and very poor).

End point type	Secondary

End point timeframe:
after 90 minutes and 4 days post-treatment

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	99	100		

Statistical analyses

Statistical analysis title	Tolerabiliy evaluation investigator
Comparison groups	Benzydamine v Placebo

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3173 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - Not significant

Secondary: Tolerability evaluation Investigator/ good Day 4

End point title	Tolerability evaluation Investigator/ good Day 4

End point description:

A global tolerability rating was expressed by the Investigator through a 5-point categorical scale (very good, good, fair, poor and very poor).

End point type	Secondary

End point timeframe:

after 90 minutes and 4 days post-treatment

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	0	1		

Statistical analyses

Statistical analysis title	Tolerabiliy evaluation investigator
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3173 [11]
Method	Cochran-Mantel-Haenszel

Notes:

[11] - Not significant

Secondary: Tolerability evaluation Investigator/ very good Day 4

End point title	Tolerability evaluation Investigator/ very good Day 4

End point description:

A global tolerability rating was expressed by the Investigator through a 5-point categorical scale (very good, good, fair, poor and very poor).

End point type	Secondary

End point timeframe:

after 90 minutes and 4 days post-treatment

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	100	99		

Statistical analyses

Statistical analysis title	Tolerabiliy evaluation investigator
Comparison groups	Benzydamine v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3173 [12]
Method	Cochran-Mantel-Haenszel

Notes:

[12] - Not significant

Secondary: Taste evaluation Child- Fresh

End point title	Taste evaluation Child- Fresh

End point description:

The Investigator asked the children the taste of the administered formulation, in terms of fresh (yes/no), sweet (yes/no), bitter (yes/no), and a global assessment in terms of good or bad. Only positive answers are reported.

End point type	Secondary

End point timeframe:

After the first administration and before the first efficacy assessment.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	88.9	88.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Taste evaluation Child- Sweet

End point title	Taste evaluation Child- Sweet

End point description:

The Investigator asked the children the taste of the administered formulation, in terms of fresh (yes/no), sweet (yes/no), bitter (yes/no), and a global assessment in terms of good or bad. Only positive answers are reported.

End point type	Secondary

End point timeframe:

After the first administration and before the first efficacy assessment.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	67.7	66.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Taste evaluation Child- Bitter

End point title	Taste evaluation Child- Bitter

End point description:

The Investigator asked the children the taste of the administered formulation, in terms of fresh (yes/no), sweet (yes/no), bitter (yes/no), and a global assessment in terms of good or bad. Only positive answers are reported.

End point type	Secondary

End point timeframe:

After the first administration and before the first efficacy assessment.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	12.1	14.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Taste evaluation Child- Global assessment- Good

End point title	Taste evaluation Child- Global assessment- Good

End point description:

The Investigator asked the children the taste of the administered formulation, in terms of global assessment in terms of good or bad.

End point type	Secondary

End point timeframe:

After the first administration and before the first efficacy assessment.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	90.9	93.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Taste evaluation Child- Global assessment- Bad

End point title	Taste evaluation Child- Global assessment- Bad

End point description:

The Investigator asked the children the taste of the administered formulation, in terms of global assessment in terms of good or bad.

End point type	Secondary

End point timeframe:

After the first administration and before the first efficacy assessment.

End point values	Benzydamine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: percent				
number (not applicable)	9.1	6.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to the final visit (day 4)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Benzydamine
Reporting group description: -	

Serious adverse events	Placebo	Benzydamine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 102 (0.00%)	0 / 99 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	Benzydamine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 102 (12.75%)	12 / 99 (12.12%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 102 (6.86%)	7 / 99 (7.07%)	
occurrences (all)	7	7	

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