EU Clinical Trials Register

Clinical trial results:

A COMPARISON OF THERAPEUTIC EQUIVALENCE BETWEEN THE TEST AND THE REFERENCE FORMULATION OF FIXED COMBINATION OF CETYLPYRIDINIUM CHLORIDE 1.0 mg/BENZYDAMINE HYDROCHLORIDE 3 mg IN SUBJECTS WITH SORE THROAT ASSOCIATED WITH UPPER RESPIRATORY TRACT INFECTIONS

Summary

EudraCT number	2013-002970-32
Trial protocol	SI
Global end of trial date	27 February 2014

Results information

Result version number	v1 (current)
This version publication date	11 August 2016
First version publication date	11 August 2016
Summary attachment (see zip file)	KKL072012_ClinicalTrialResults_synopsis (KKL072012_ClinicalTrialResults_synopsis_250516.docx)

Trial information

Trial identification

Sponsor protocol code	KKL072012

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Krka d. d.
Sponsor organisation address	Šmarješka cesta 6, Novo mesto, Slovenia, 8501
Public contact	Info točka raziskave, KRKA, tovarna zdravil, d. d., Novo mesto, 00386 14751489, marko.boh@krka.biz
Scientific contact	Info točka raziskave, KRKA, tovarna zdravil, d. d., Novo mesto, 00386 14751489, marko.boh@krka.biz

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	27 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2014
Global end of trial reached?	Yes
Global end of trial date	27 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- to demonstrate the equivalence of the treatment effect between   test and reference product in terms of the sore throat pain intensity difference at the predefined time point compared to baseline .
_WIthin the main objective a superiority of the treatment effect of both test and reference treatment over placebo treatment is to be demonstrated in terms of sore throat pain intensity difference at the predefined time point compared to baseline.

Protection of trial subjects:

Due to the placebo control but also for the cases of active treatient inactivity, an option of rescue medication was provided to each subject. In this respect , each subject received a number of Paracetamol tablets 500 mg to fit the treatment period with the recomended dosing schedule of maximal 4 x 500 mg daily. Subjects also had an option to request for rescue medication during 3 hour efficacy assessment at the clinical site.

Background therapy:

No background therapy for the tested indication was allowed

Evidence for comparator:

According to the legal basis of classical generic application, we performed therapeutic equivalence study to the originator reference product; classical bioequivalence study was not possible due to insufficient systemic absorbtion of the investigational medicinal product.

Actual start date of recruitment	18 November 2013
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	Slovenia: 1
Country: Number of subjects enrolled	Russian Federation: 290
Worldwide total number of subjects	291
EEA total number of subjects	1

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)	290
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were 291 subjects screened; all of them were also enrolled. There were no drop-outs during the assessment period at Visit 1. Altogether 290 patients were enrolled in Russian Federation and one subject in Slovenia. First patient in date: 18.11.2013. Last patient out date: 27.2.2014

Pre-assignment

Screening details:

Basic screening criteria were the history of sore throat of 6 days or less, the adult age with the upper limit of completed 65 years and the ability to read and understand how to use the methodological tool for pain assessment.
All subjects that were screened were also enrolled.

Period 1

Period 1 title	SIngle dose assessment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

We were only able to ensure the complete blind for Tested Investigational Medicinal Product (TIMP) and placebo due to techical difficulties related to local application (long time oral dissolution). TIMP and placebo were Identical with regard to all of the features including appearance, shape, smell, and taste, as well as the size, colour and shape of the blisters. None of the IMPs were present on the national market so subjects were not familiar with the IMP's appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Subjects in this arm have been taking placebo during the entire trial duration.

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

Dosage and administration details:

In this period, the initial single dose was applied. The instructions were given to dissolve the lozenge in the mouth , by putting it on the tongue and left to be dissolved. Chewing, crushing or swallowing of the lozenge was not allowed, while the saliva could be swallowed.

Arm title	Group B

Arm description:

Subjects in this arm were administered the reference medicinal product manufactured by the originator of the product.

Arm type	Active comparator
Investigational medicinal product name	benzydamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg
Investigational medicinal product code	
Other name	Gola action
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oropharyngeal use

Dosage and administration details:

In this period, the initial single dose was applied. The instructions were given to dissolve the orodispersible tablet in the mouth , by putting it on the tongue and left to be dissolved. Chewing, crushing or swallowing of the orodispersible tablet   was not allowed, while the saliva could be swallowed.

Arm title	Group C

Arm description:

All the subjects in this arm were administered tested investigational medicinal product.

Arm type	Experimental
Investigational medicinal product name	benzydamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg
Investigational medicinal product code	
Other name	Septolete Total, Septabene
Pharmaceutical forms	Lozenge
Routes of administration	Oropharyngeal use

Dosage and administration details:

In this period, the initial single dose was applied. The instructions were given to dissolve the lozenge in the mouth , by putting it on the tongue and left to be dissolved. Chewing, crushing or swallowing of the lozenge   was not allowed, while the saliva could be swallowed.

Number of subjects in period 1	Group A	Group B	Group C
Started	57	116	118
Completed	57	116	118

Period 2

Period 2 title	Therapy follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The blinding was assured similarly to Period I, i.e. Placebo had the same appearance as TIMP. Besides, none of the products was at the market of any of the participating countries at the time of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

All the subjects in this arm have been taking placebo as in the period I.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Lozenge
Routes of administration	Oropharyngeal use

Dosage and administration details:

In this period, subjects were taking the IMP according to the planned Schedule (4 times daily each 3 hours). The instructions were given to dissolve the lozenge in the mouth , by putting it on the tongue and left to be dissolved. Chewing, crushing or swallowing of the lozenge was not allowed, while the saliva could be swallowed.

Arm title	Group B

Arm description:

Subjects in this arm were administered the reference medicinal product manufactured by the originator of the product.

Arm type	Active comparator
Investigational medicinal product name	benzydamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg
Investigational medicinal product code	
Other name	Gola action
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oropharyngeal use

Dosage and administration details:

In this period, the initial single dose was applied. The instructions were given to dissolve the orodispersible tablet in the mouth , by putting it on the tongue and left to be dissolved. Chewing, crushing or swallowing of the orodispersible tablet was not allowed, while the saliva could be swallowed.

Arm title	Group C

Arm description:

All the subjects in this arm were administered tested investigational medicinal product.

Arm type	Experimental
Investigational medicinal product name	benzydamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg
Investigational medicinal product code	
Other name	Septolete Total, Septabene
Pharmaceutical forms	Lozenge
Routes of administration	Oropharyngeal use

Dosage and administration details:

In this period, subjects were taking the IMP according to the planned Schedule (4 times daily each 3 hours). The instructions were given to dissolve the lozenge in the mouth , by putting it on the tongue and left to be dissolved. Chewing, crushing or swallowing of the lozenge was not allowed, while the saliva could be swallowed.

Number of subjects in period 2	Group A	Group B	Group C
Started	57	116	118
Completed	37	51	54
Not completed	20	65	64
Complete disease resolution	-	62	63
condition completely resolved	18	-	-
Lost to follow-up	-	1	-

Protocol deviation	1	1	1
non-allowed concomitant therapy indicated	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	Group A
Reporting group description:	
Subjects in this arm have been taking placebo during the entire trial duration.	
Reporting group title	Group B
Reporting group description:	
Subjects in this arm were administered the reference medicinal product manufactured by the originator of the product.	
Reporting group title	Group C
Reporting group description:	
All the subjects in this arm were administered tested investigational medicinal product.	

Reporting group values	Group A	Group B	Group C
Number of subjects	57	116	118
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			
A descriptive statistics of the subject mean age per treatment group was calculated. The population set analysed was full analysis set. A comparative analysis of baseline characteristics did not show any differences between the treatment arms.			
Units: years			
arithmetic mean	39.9	40.5	38.5
standard deviation	± 10.8	± 12.23	± 11.07
Gender categorical			
The descriptive statistics for FAS analsysis has been made on the percentage of gender categories per treatment group. The comparison between the treatment groups did not show any significant differences. FAS analysis has been performed.			
Units: Subjects			
Female	37	74	87
Male	20	42	31
concomitant therapy for current URTI			
The descriptive statistics about subjects who have been taking any medication for the current upper respiratory tract infection (URTI). In all of the subjects the therapy has been withdrawn in time with respect to the protocol. The distribution among the treatment groups was relatively even.			
Units: Subjects			
concomitant therapy	9	18	26
no concomitant therapy	48	98	92

body weight			
A descriptive statistics has been made for body weight at baseline per treatment group with between group comparison. No significant differences were identified. FAS analysis has been done.			
Units: kg			
arithmetic mean	73.2	72.8	70.5
standard deviation	± 13.81	± 14.59	± 13.3
body temperature			
Descriptive statistics has been made for mean body temperature per treatment group with the intergroup comparison. there were no significant differences between the treatment groups in mean body temperature. FAS analysis has been done.			
Units: Celsius Degrees			
arithmetic mean	37.48	37.48	37.48
standard deviation	± 0.33	± 0.38	± 0.38
TPA score			
Tonsillo-pharingitis assessment (TPA) is a method of the assessment of the upper respiratory tract infection signs. Five parameters are assessed including body temperature, oropharyngeal status and status of local lymph nodes. The examination results are transformed into score with the maximum of 10 points. A descriptive statistics on the mean TPA score and comparison between the treatment groups were done and showed no significant differences.			
Units: points			
arithmetic mean	5.1	5.1	5.2
standard deviation	± 0.91	± 1.05	± 0.85
Sore throat pain intensitiy			
Abreviaiton: STPI The pain intensity is measured by the pain Visual analogue scale, which is completed by the subjects and evaluated by the investigator. It also denotes basic inclusion criterion.			
Units: mm			
arithmetic mean	80	78.2	77.6
standard deviation	± 10.28	± 10.02	± 9.89

Reporting group values	Total		
Number of subjects	291		
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			
A descriptive statistics of the subject mean age per treatment group was calculated. The population set analysed was full analysis set. A comparative analysis of baseline characteristics did not show any differences between the treatment arms.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
The descriptive statistics for FAS analsysis has been made on the percentage of gender categories per treatment group. The comparison between the treatment groups did not show any significant			

differences. FAS analysis has been performed.			
Units: Subjects			
Female	198		
Male	93		
concomitant therapy for current URTI			
The descriptive statistics about subjects who have been taking any medication for the current upper respiratory tract infection (URTI). In all of the subjects the therapy has been withdrawn in time with respect to the protocol. The distribution among the treatment groups was relatively even.			
Units: Subjects			
concomitant therapy	53		
no concomitant therapy	238		
body weight			
A descriptive statistics has been made for body weight at baseline per treatment group with between group comparison. No significant differences were identified. FAS analysis has been done.			
Units: kg			
arithmetic mean			
standard deviation	-		
body temperature			
Descriptive statistics has been made for mean body temperature per treatment group with the intergroup comparison. there were no significant differences between the treatment groups in mean body temperature. FAS analysis has been done.			
Units: Celsius Degrees			
arithmetic mean			
standard deviation	-		
TPA score			
Tonsillo-pharingitis assessment (TPA) is a method of the assessment of the upper respiratory tract infection signs. Five parameters are assessed including body temperature, oropharyngeal status and status of local lymph nodes. The examination results are transformed into score with the maximum of 10 points. A descriptive statistics on the mean TPA score and comparison between the treatment groups were done and showed no significant differences.			
Units: points			
arithmetic mean			
standard deviation	-		
Sore throat pain intensitiy			
Abreviaiton: STPI The pain intensity is measured by the pain Visual analogue scale, which is completed by the subjects and evaluated by the investigator. It also denotes basic inclusion criterion.			
Units: mm			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set (FAS) included all subjects who were randomised and have received minimally one dose of the study medication regardless of protocol violations or premature discontinuation status. The FAS analysis of efficacy was a supportive analysis to per protocol set analysis for the primary efficacy endpoint and was used for all secondary and tertiary efficacy endpoints analysis and safety analysis.

Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol (PP) set was defined as all randomized subjects entirely consistent with the protocol who

received the initial IMP dose and had all assessments for all efficacy endpoints during the 3-hour measurement procedure at Visit 1. The major protocol violations for which subjects would be excluded from the PP set will represent violations that may impact the efficacy endpoints for which equivalence comparisons are being made. The decision towhich subjects to exclude from the PP set was made prior to breaking the blind.

PP set was used for the primary endpoint analysis.

Reporting group values	Full analysis set	Per protocol set	
Number of subjects	291	288	
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			
A descriptive statistics of the subject mean age per treatment group was calculated. The population set analysed was full analysis set. A comparative analysis of baseline characteristics did not show any differences between the treatment arms.			
Units: years			
arithmetic mean	39.6	39.5	
standard deviation	± 11.49	± 11.51	
Gender categorical			
The descriptive statistics for FAS analsysis has been made on the percentage of gender categories per treatment group. The comparison between the treatment groups did not show any significant differences. FAS analysis has been performed.			
Units: Subjects			
Female	198	195	
Male	93	93	
concomitant therapy for current URTI			
The descriptive statistics about subjects who have been taking any medication for the current upper respiratory tract infection (URTI). In all of the subjects the therapy has been withdrawn in time with respect to the protocol. The distribution among the treatment groups was relatively even.			
Units: Subjects			
concomitant therapy	53		
no concomitant therapy	239		
body weight			
A descriptive statistics has been made for body weight at baseline per treatment group with between group comparison. No significant differences were identified. FAS analysis has been done.			
Units: kg			
arithmetic mean	71.9	72.1	
standard deviation	± 13.9	± 13.9	
body temperature			
Descriptive statistics has been made for mean body temperature per treatment group with the intergroup comparison. there were no significant differences between the treatment groups in mean body temperature. FAS analysis has been done.			
Units: Celsius Degrees			
arithmetic mean	37.48	37.49	

standard deviation	± 0.37	± 0.36	
TPA score			

Tonsillo-pharingitis assessment (TPA) is a method of the assessment of the upper respiratory tract infection signs. Five parameters are assessed including body temperature, oropharyngeal status and status of local lymph nodes. The examination results are transformed into score with the maximum of 10 points.
A descriptive statistics on the mean TPA score and comparison between the treatment groups were done and showed no significant differences.

Units: points			
arithmetic mean	5.1	5.1	
standard deviation	± 0.94	± 0.95	
Sore throat pain intensitiy			

Abreviaiton: STPI
The pain intensity is measured by the pain Visual analogue scale, which is completed by the subjects and evaluated by the investigator. It also denotes basic inclusion criterion.

Units: mm			
arithmetic mean	78.3	78.5	
standard deviation	± 10.02	± 9.93	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	
Subjects in this arm have been taking placebo during the entire trial duration.	
Reporting group title	Group B
Reporting group description:	
Subjects in this arm were administered the reference medicinal product manufactured by the originator of the product.	
Reporting group title	Group C
Reporting group description:	
All the subjects in this arm were administered tested investigational medicinal product.	
Reporting group title	Group A
Reporting group description:	
All the subjects in this arm have been taking placebo as in the period I.	
Reporting group title	Group B
Reporting group description:	
Subjects in this arm were administered the reference medicinal product manufactured by the originator of the product.	
Reporting group title	Group C
Reporting group description:	
All the subjects in this arm were administered tested investigational medicinal product.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS) included all subjects who were randomised and have received minimally one dose of the study medication regardless of protocol violations or premature discontinuation status. The FAS analysis of efficacy was a supportive analysis to per protocol set analysis for the primary efficacy endpoint and was used for all secondary and tertiary efficacy endpoints analysis and safety analysis.	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol (PP) set was defined as all randomized subjects entirely consistent with the protocol who received the initial IMP dose and had all assessments for all efficacy endpoints during the 3-hour measurement procedure at Visit 1. The major protocol violations for which subjects would be excluded from the PP set will represent violations that may impact the efficacy endpoints for which equivalence comparisons are being made. The decision towhich subjects to exclude from the PP set was made prior to breaking the blind. PP set was used for the primary endpoint analysis.	

Primary: Difference in sore throat pain intensity at 1 hour PP

End point title	Difference in sore throat pain intensity at 1 hour PP
End point description:	
The endpoint is a difference in sore throat pain intensity (STPI) between baseline just before the IMP administration and 1 hour after the IMP administration. It was calculated by the statistician. The STPI scores were assessed by the visual analogue scale (VAS), a 100 mm horizontal line with the left end named " not sore" (0 mm) and right end named " very sore" . The subject is instructed to put a perpendicular mark on the VAS according to the current level of sore throat. Thereafter, the investigator measures the distance from the left end to the perpendicular mark. The measurement at baseline is later subtracted from the 1-hour measurement by the study statistician and the result for primary endpoint obtained.	
End point type	Primary
End point timeframe:	
The endpoint is based on a two STPI measurements when administered a single initial dose of the IMP: 1. baseline measurement at time 0 h	

End point values	Group A	Group B	Group C	Per protocol set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	115	116	288
Units: mm				
arithmetic mean (standard deviation)	22.4 (± 21.36)	40 (± 26.15)	42.6 (± 26.77)	37.6 (± 26.57)

Attachments (see zip file)	Box plot for primary
	Box plot for primary efficacy endpoint (FAS)
	Table: primary endpoint (FAS)
	Table: Primary endpoint (PP)

Statistical analyses

Statistical analysis title	Primary efficacy endpoint equivalence analysis PP

Statistical analysis description:

Assessment of null and alternative hypothesys is based on a two-sided 95% confidence interval for the treatment difference. It was concluded that TIMP is equivalent to RIMP if the lower and upper bounds of the 95% confidence interval for the treatment difference lie entirely within $(-\delta, \delta)$ interval.
The equivalence margin for the STPID1h is 13 mm of VAS score.

Comparison groups	Group B v Group C
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.244 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.087
upper limit	8.161
Variability estimate	Standard error of the mean
Dispersion value	2.603

Notes:

[1] - Statistically, this study is based on equivalence design. The null hypothesis for the primary efficacy endpoint is inequivalence between TIMP and RIMP, and the alternative hypothesis is equivalence defined by pre-specified equivalence margin (δ). In order to achieve essay sensitivity, both active treatment should have been superior to placebo. The latter has been subject in the separate analysis.
[2] - The P level was higher than standard threshold for alpha error of 0.05. This demonstrated lack of non-equivalence between the treatments. The equivalence was established by means of 95% CI.

Statistical analysis title	Primary endpoint superiority analysis RIMP PP

Statistical analysis description:

The analysis of the superiority of two active treatments over placebo is carried out to establish assay sensitivity of the equivalence analysis. Assessment of null and alternative hypotheses is based on a two-sided 95% confidence interval for the treatment difference between placebo and both reference (RIMP) and test (TIMP) investigational medicinal product.

Comparison groups	Group A v Group B
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	19.766
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.458
upper limit	26.074
Variability estimate	Standard error of the mean
Dispersion value	3.204

Notes:

[3] - This is a superiority analysis to establish significant superiority of the RIMP against the placebo treatment. The null hypothesis for the primary efficacy endpoint is the lack of difference between placebo and active treatments. In case of its rejection, the alternative hypothesis is accepted of the RIMP superiority over placebo.

[4] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated significant difference between RIMP and placebo.

Statistical analysis title	Primary endpoint superiority analysis TIMP PP

Statistical analysis description:

The analysis of the superiority of two active treatments over placebo is carried out to establish assay sensitivity of the equivalence analysis. Assessment of null and alternative hypotheses is based on a two-sided 95% confidence interval for the treatment difference between placebo and both reference (RIMP) and test (TIMP) investigational medicinal product.

Comparison groups	Group A v Group C
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	22.803
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.496
upper limit	29.11
Variability estimate	Standard error of the mean
Dispersion value	3.204

Notes:

[5] - This is a superiority analysis to establish significant superiority of the TIMP against the placebo treatment. The null hypothesis for the primary efficacy endpoint is the lack of difference between placebo and active treatments. In case of its rejection, the alternative hypothesis is accepted of the TIMP superiority over placebo.

[6] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error

which demonstrated significant difference between TIMP and placebo.

Primary: Difference in sore throat pain intensity at 1 hour ITT

End point title	Difference in sore throat pain intensity at 1 hour ITT

End point description:

The endpoint is a difference in sore throat pain intensity (STPI) between baseline just before the IMP administration and 1 hour after the IMP administration. It was calculated by the statistician. The STPI scores were assessed by the visual analogue scale (VAS), a 100 mm horizontal line with the left end named " not sore" (0 mm) and right end named " very sore" . The subject is instructed to put a perpendicular mark on the VAS according to the current level of sore throat. Thereafter, the investigator measures the distance from the left end to the perpendicular mark. The measurement at baseline is later subtracted from the 1-hour measurement by the study statistician and the result for primary endpoint obtained.

End point type	Primary

End point timeframe:

The endpoint is based on a two STPI measurements when administered a single initial dose of the IMP:
1. baseline measurement at time 0 h
2. measurement at 1 h post IMP administration

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: mm				
arithmetic mean (standard deviation)	22.4 (± 21.36)	39.7 (± 26.21)	42.6 (± 26.79)	37.5 (± 26.6)

Statistical analyses

Statistical analysis title	Primary efficacy endpoint equivalence analysis ITT

Statistical analysis description:

Assessment of null and alternative hypothesys is based on a two-sided 95% confidence interval for the treatment difference. It was concluded that TIMP is equivalent to RIMP if the lower and upper bounds of the 95% confidence interval for the treatment difference lie lie entirely within (−δ, δ) interval.
The equivalence margin for the STPID1h is 13 mm of VAS score.

Comparison groups	Group C v Group B
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.194 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.378
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.731
upper limit	8.487

Variability estimate	Standard error of the mean
Dispersion value	2.595

Notes:

[7] - Statistically, this study is based on equivalence design. The null hypothesis for the primary efficacy endpoint is inequivalence between TIMP and RIMP, and the alternative hypothesis is equivalence defined by pre-specified equivalence margin (δ). In order to achieve essay sensitivity, both active treatment should have been superior to placebo. The latter has been subject in the separate analysis.

[8] - The P level was higher than standard threshold for alpha error of 0.05. This demonstrated lack of non-equivalence between the treatments. The equivalence was established by means of 95% CI.

Statistical analysis title	Primary endpoint superiority analysis TIMP ITT

Statistical analysis description:

The analysis of the superiority of two active treatments over placebo is carried out to establish assay sensitivity of the equivalence analysis. Assessment of null and alternative hypotheses is based on a two-sided 95% confidence interval for the treatment difference between placebo and both reference (RIMP) and test (TIMP) investigational medicinal product.

Comparison groups	Group C v Group A
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001 [10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	23.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.788
upper limit	29.44
Variability estimate	Standard error of the mean
Dispersion value	3.213

Notes:

[9] - This is a superiority analysis to establish significant superiority of the TIMP against the placebo treatment. The null hypothesis for the primary efficacy endpoint is the lack of difference between placebo and active treatments. In case of its rejection, the alternative hypothesis is accepted of the TIMP superiority over placebo.

[10] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated significant difference between RIMP and placebo.

Statistical analysis title	Primary endpoint superiority analysis RIMP ITT

Statistical analysis description:

The analysis of the superiority of two active treatments over placebo is carried out to establish assay sensitivity of the equivalence analysis. Assessment of null and alternative hypotheses is based on a two-sided 95% confidence interval for the treatment difference between placebo and both reference (RIMP) and test (TIMP) investigational medicinal product.

Comparison groups	Group A v Group B
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	19.736

Confidence interval	
level	95 %
sides	2-sided
lower limit	13.401
upper limit	26.071
Variability estimate	Standard error of the mean
Dispersion value	3.218

Notes:

[11] - This is a superiority analysis to establish significant superiority of the RIMP against the placebo treatment. The null hypothesis for the primary efficacy endpoint is the lack of difference between placebo and active treatments. In case of its rejection, the alternative hypothesis is accepted of the RIMP superiority over placebo.

[12] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated significant difference between RIMP and placebo.

Secondary: Difference in sore throat pain intensity at 2 h

End point title	Difference in sore throat pain intensity at 2 h

End point description:

The endpoint is a difference in sore throat pain intensity (STPI) between baseline just before the IMP administration and 2 hours after the IMP administration. It was calculated by the statistician. The STPI scores were assessed by the visual analogue scale (VAS), a 100 mm horizontal line with the left end named " not sore" (0 mm) and right end named " very sore" . The subject is instructed to put a perpendicular mark on the VAS according to the current level of sore throat. Thereafter, the investigator measures the distance from the left end to the perpendicular mark. The measurement at baseline is later subtracted from the result at 2 hours by the study statistician and the result for primary endpoint obtained.

End point type	Secondary

End point timeframe:

The endpoint is based on a two STPI measurements when administered a single initial dose of the IMP:
1. baseline measurement at time 0 h
2. measurement at 2 h post IMP administation

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: mm				
arithmetic mean (standard error)	14.07 (± 2.856)	28.03 (± 2.044)	34.63 (± 2.043)	29.19 (± 1.42)

Attachments (see zip file)	Table: secondary endpoint (STPID 2h)

Statistical analyses

Statistical analysis title	Secondary endpoint STPID2h analysis TIMPvsRIMP

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The equivalence analysis has been applied to comparison between active treatments including also a superiority analysis of both active treatments against placebo. This analysis was not relevant for the equivalence demonstration.

Comparison groups	Group B v Group C

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	equivalence[13]
P-value	= 0.014 [14]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.596
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.323
upper limit	11.868
Variability estimate	Standard error of the mean
Dispersion value	2.678

Notes:

[13] - Statistically, the STPID2h is based on equivalence design including superiority of both active treatments over placebo and equivalence between the two active treatments.
This analysis section reports the comparative analysis between test IMP and reference IMP.

[14] - The p-value indicates statistically significant difference between TIMP and RIMP since the p value is lower than conventional 0.05. The difference is in favour of the test IMP effect.

Statistical analysis title	Secondary endpoint STPID2h analysis TIMPvsPlacebo

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis has been applied to provide a comparison between both active treatments against placebo. This analysis was not relevant for the equivalence demonstration.

Comparison groups	Group A v Group C
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001 [16]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	20.556
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.028
upper limit	27.084
Variability estimate	Standard error of the mean
Dispersion value	3.316

Notes:

[15] - Statistically, this secondary efficacy endpoint analysis is based on superiority of both active treatments over placebo and equivalence between the two active treatments.
This analysis section reports the comparative analysis between test IMP and placebo.

[16] - The p-value indicates statistically significant difference between TIMP and placebo since the p value is lower than conventional 0.05. The difference is in favour of the test IMP effect.

Statistical analysis title	Secondary endpoint STPID2h analysis RIMPvsPlacebo

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis has been applied to provide a comparison between both active treatments against placebo. This analysis was not relevant for the equivalence demonstration.

Comparison groups	Group A v Group B

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001 [18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	13.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.422
upper limit	20.498
Variability estimate	Standard error of the mean
Dispersion value	3.321

Notes:

[17] - Statistically, this secondary efficacy endpoint analysis is based on superiority of both active treatments over placebo and equivalence between the two active treatments.
This analysis section reports the comparative analysis between reference IMP and placebo.

[18] - The p-value indicates statistically significant difference between RIMP and placebosince the p value is lower than conventional 0.05. The difference is in favour of the reference IMP effect.

Secondary: Difference in sore throat pain intensity at 3 h

End point title	Difference in sore throat pain intensity at 3 h

End point description:

The endpoint is a difference in sore throat pain intensity (STPI) between baseline just before the IMP administration and 1 hour after the IMP administration. It was calculated by the statistician. The STPI scores were assessed by the visual analogue scale (VAS), a 100 mm horizontal line with the left end named "not sore" (0 mm) and right end named " very sore" . The subject is instructed to put a perpendicular mark on the VAS according to the current level of sore throat. Thereafter, the investigator measures the distance from the left end to the perpendicular mark. The measurement at baseline is later subtracted from the 1-hour measurement by the study statistician and the result for primary endpoint obtained

End point type	Secondary

End point timeframe:

The endpoint is based on a two STPI measurements when administered a single initial dose of the IMP:
1. baseline measurement at time 0 h
2. measurement at 3 h post IMP administration

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: mm				
arithmetic mean (standard error)	13.03 (± 2.677)	20.96 (± 1.916)	28.8 (± 1.915)	21.64 (± 1.37)

Attachments (see zip file)	Table: secondary endpoint (STPID 3h)

Statistical analyses

Statistical analysis title	Secondary endpoint STPID3h analysis TIMPvsRIMP

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The equivalence analysis has been applied to comparison between active treatments including also a superiority analysis of both active treatments against placebo. This analysis was not relevant for the equivalence demonstration.

Comparison groups	Group C v Group B
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	equivalence[19]
P-value	= 0.002 [20]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.848
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.906
upper limit	12.791
Variability estimate	Standard error of the mean
Dispersion value	2.511

Notes:

[19] - Statistically, the STPID3h is based on equivalence design including superiority of both active treatments over placebo and equivalence assessment between the two active treatments.
This analysis section reports the comparative analysis between test IMP and reference IMP.

[20] - The p-value indicates statistically significant difference between TIMP and RIMP since the p value is lower than conventional 0.05. The difference is in favour of the test IMP effect.

Statistical analysis title	Secondary endpoint STPID3h analysis TIMPvsPlacebo

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis has been applied to provide a comparison between both active treatments against placebo. This analysis was not relevant for the equivalence demonstration.

Comparison groups	Group C v Group A
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.001 [22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	15.774
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.654
upper limit	21.893
Variability estimate	Standard error of the mean
Dispersion value	3.109

Notes:

[21] - Statistically, this secondary efficacy endpoint analysis is based on superiority of both active treatments over placebo and equivalence between the two active treatments.
This analysis section reports the comparative analysis between test IMP and placebo.

[22] - The p-value indicates statistically significant difference between TIMP and RIMP since the p value is lower than conventional 0.05. The difference is in favour of the test IMP effect.

Statistical analysis title	Secondary endpoint STPID3h analysis RIMPvs Placebo
Statistical analysis description:	
Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis has been applied to provide a comparison between both active treatments against placebo. This analysis was not relevant for the equivalence demonstration.	
Comparison groups	Group A v Group B
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.011 [24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.925
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.797
upper limit	14.054
Variability estimate	Standard error of the mean
Dispersion value	3.113

Notes:

[23] - Statistically, this secondary efficacy endpoint analysis is based on superiority of both active treatments over placebo and equivalence between the two active treatments.
This analysis section reports the comparative analysis between reference IMP and placebo.

[24] - The p-value indicates statistically significant difference between TIMP and RIMP since the p value is lower than conventional 0.05. The difference is in favour of the test IMP effect.

Secondary: Total pain relief over the time interval 15 -180 min after the IMP administration

End point title	Total pain relief over the time interval 15 -180 min after the IMP administration
End point description:	
Total pain relief over the time interval 15 -180 min after the IMP administration (TOTPAR 15-180min) is the endpoint that assesses pain relief over the over the 15-min to 3-hour interval after the administration of IMP. TOTPAR 15-180min was computed for each subject as the area under the curve of the pain relief scores (measured by a 7-point pain relief scale), according to the trapezoidal rule.	
End point type	Secondary
End point timeframe:	
Altogether 12 measurements were made in the intervals of 15 minutes from 15 min up to 180 min after the single dose of the tested drugs.	

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: point				
arithmetic mean (standard error)	263.465 (± 27.317)	437.338 (± 19.554)	473.984 (± 19.541)	434.897 (± 12.959)

Attachments (see zip file)	Table: secondary endpoint (TOTPAR)

Statistical analyses

Statistical analysis title	TOTPAR 15-180 min statistical analysis TIMPvsRIMP

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis has been applied to provide a comparison between both active IMP against placebo as well as to investigate the differences between the two active IMPs. It was analyzed based on ANCOVA model including clinical site and treatment as main effects, and baseline pain intensity score as a covariate.

Comparison groups	Group C v Group B
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.154 [26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	36.646
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.791
upper limit	87.084
Variability estimate	Standard error of the mean
Dispersion value	25.622

Notes:

[25] - Statistically, this secondary efficacy endpoint analysis is based on superiority of both active treatments over placebo and absence of any significant difference between the two active IMPs. This analysis section reports the comparative analysis between both active IMPs.

[26] - The P value is higher than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated lack of significant difference between RIMP and TIMP.

Statistical analysis title	TOTPAR 15-180 min statistical analysis TIMPvsPlac

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis has been applied to provide a comparison between both active IMP against placebo as well as to investigate the differences between the two active IMPs. It was analyzed based on ANCOVA model including clinical site and treatment as main effects, and baseline pain intensity score as a covariate.

Comparison groups	Group C v Group A

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.001 [28]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	210.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	148.068
upper limit	272.971
Variability estimate	Standard error of the mean
Dispersion value	31.725

Notes:

[27] - Statistically, this secondary efficacy endpoint analysis is based on superiority of both active treatments over placebo and absence of any significant difference   between the two active IMPs. This analysis section reports the comparative analysis between TIMP and placebo.

[28] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated significant difference between TIMP and placebo.

Statistical analysis title	TOTPAR 15-180 min statistical analysis RIMPvsPlac

Statistical analysis description:

Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis has been applied to provide a comparison between both active IMP against placebo as well as to investigate the differences between the two active IMPs. It was analyzed based on ANCOVA model including clinical site and treatment as main effects, and baseline pain intensity score as a covariate.

Comparison groups	Group A v Group B
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	< 0.001 [30]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	173.873
Confidence interval	
level	95 %
sides	2-sided
lower limit	111.329
upper limit	236.417
Variability estimate	Standard error of the mean
Dispersion value	31.772

Notes:

[29] - Statistically, this secondary efficacy endpoint analysis is based on superiority of both active treatments over placebo and absence of any significant difference   between the two active IMPs. This analysis section reports the comparative analysis between RIMP and placebo.

[30] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated significant difference between TIMP and placebo.

Secondary: Percent of responders after the initial single IMP dose

End point title	Percent of responders after the initial single IMP dose

End point description:

% RESP is defined as the share of subjects who respond to the therapy with respect to the total number of subjects taking the same IMP. The responder criterion is related to minimal clinically significant change in sore throat pain intensity (STPI) at one, two and three hours after the IMP administration. This change is defined as the reduction of 13 mm or more of the STPI value at the Visual analogue scale.

End point type	Secondary

End point timeframe:

The endpoint was assessed at the end of the three hour time interval after a single dose of the IMPs.

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: subjects	16	55	70	141

Attachments (see zip file)	Crosstabulation: secondary endpoint (% RESP)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint percent responders 1

Statistical analysis description:

The endpoint was analyzed by means of the Chi-square and the pairwise Chi-square test with corresponding 95% confidence intervals.

Comparison groups	Group B v Group C
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.068 [32]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-11.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.6
upper limit	0.79

Notes:

[31] - Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. This section includes the comparison between two active treatments. In the analysis results the TIMP value has been subtracted from the RIMP value.

[32] - The P value for the difference between the two active treatment groups demonstrates lack of significant difference between the two groups.

Statistical analysis title	Secondary efficacy endpoint percent responders 2

Statistical analysis description:

The endpoint was analyzed by means of the Chi-square and the pairwise Chi-square test with corresponding 95% confidence intervals.

Comparison groups	Group A v Group C

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.001 [34]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-31.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.9
upper limit	-16.6

Notes:

[33] - Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis of both active treatments against placebo was to be demonstrated and the comparison between the two active group investigated. The type of analysis corresponds to the statistical nature of the endpoint. This section includes comparison between Test IMP and placebo.

[34] - The P value for the difference between Test IMP and placebo demonstrates superiority of the Test IMP over placebo.

Statistical analysis title	Secondary efficacy endpoint percent responders 3

Statistical analysis description:

The endpoint was analyzed by means of the Chi-square and the pairwise Chi-square test with corresponding 95% confidence intervals.

Comparison groups	Group A v Group B
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.015 [36]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-19.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.1
upper limit	-4.56

Notes:

[35] - Assessment of null and alternative hypothesis is based on a two-sided 95% confidence interval for the treatment difference. The superiority analysis of both active treatments against placebo was to be demonstrated and the comparison between the two active group investigated. The type of analysis corresponds to the statistical nature of the endpoint. This section includes comparison between Reference IMP and placebo.

[36] - The P value for the difference between Reference IMP and placebo demonstrates superiority of the Reference IMP over placebo.

Secondary: Time to Sore Throat Pain relief (TSTPAR)

End point title	Time to Sore Throat Pain relief (TSTPAR)

End point description:

Time to Sore Throat Pain relief (TSTPAR) is defined as the time in minutes to a minimal sore throat pain relief (STPAR). The minimal STPAR is defined as a relief of at least 1 point on the STPAR scale. In order for the minimal STPAR to be confirmed it has to be followed by at least 3-point score at the each of the following two measurements.

End point type	Secondary

End point timeframe:

Time to Sore Throat Pain relief (TSTPAR) Was assessed within the 3 hours after the single dose IMP administration.

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: minutes				
arithmetic mean (standard error)	97.6 (± 10.2)	48.5 (± 5.4)	46 (± 5.2)	57.1 (± 3.8)

Statistical analyses

Statistical analysis title	TSTPAR comparative analysis TIMPvs Placebo

Statistical analysis description:

TSTPAR was analyzed using survival analysis method. The Kaplan-Meier method was used to derive the median time to sore throat pain relief (TSTPAR) with 95% confidence intervals for each treatment group. The log-rank test was used to determine the statistical significance of treatment group differences in the distribution of time to event. For subjects who has not experienced onset of pain relief within 3 hours after dosing, time to onset was right censored and set to 3 hours.

Comparison groups	Group A v Group C
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.001 [38]
Method	Logrank
Parameter estimate	Mean difference (final values)

Notes:

[37] - The survival analysis seemed most appropriate method for the endpoint related to the time to the event. The analysis was used to investigate differences between the treatments in terms of the onset of the effect.
This part of analysis presents a comparison between TIMP and placebo.

[38] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated significant difference between TIMP and placebo.

Statistical analysis title	TSTPAR comparative analysis RIMPvs Placebo

Statistical analysis description:

TSTPAR was analyzed using survival analysis method. The Kaplan-Meier method was used to derive the median time to sore throat pain relief (TSTPAR) with 95% confidence intervals for each treatment group. The log-rank test was used to determine the statistical significance of treatment group differences in the distribution of time to event. For subjects who has not experienced onset of pain relief within 3 hours after dosing, time to onset was right censored and set to 3 hours.

Comparison groups	Group A v Group B
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	< 0.001 [40]
Method	Logrank
Parameter estimate	Mean difference (final values)

Notes:

[39] - The survival analysis seemed most appropriate method for the endpoint related to the time to the event. The analysis was used to investigate differences between the treatments in terms of the onset of the effect. This part of analysis presents a comparicon between RIMP and placebo.

[40] - The P value is lower than conventional 0.05 threshold for the statistical relevance of alpha error which demonstrated significant difference between RIMP and placebo.

Other pre-specified: Percent subjects complete disease resolution (%RESOL)

End point title	Percent subjects complete disease resolution (%RESOL)

End point description:

Patients were defined as having conpletely resolved condition by fullfilling the following criteria:
o   The Tonsilopharyngitis Assessment (TPA) score of 1 or less
o   The score of 6 on the Sore Throat Pain Release (STPAR) scale
o   The score of 0 millimetres on the pain intensity visual analogue scale (VAS)

End point type	Other pre-specified

End point timeframe:

The end point has been evaluated 4 days and 7 days after the therapy initiation. In this report, only 7-day data are presented.

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: Subjects	57	116	118	291

Attachments (see zip file)	Table: tertiary endpoint (%RESOL)

Statistical analyses

Statistical analysis title	% RESOL comparative analysis part 1

Statistical analysis description:

Pearson chi-square test has been used to carry out parwise comparisons between the treatment groups.

Comparison groups	Group A v Group C
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.001 [42]
Method	Chi-squared
Parameter estimate	Percent count
Point estimate	-22.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.8
upper limit	-8.84

Notes:

[41] - The analysis type fits the statistical profile of the endpoint including the normality of the distribution.
In a nutshell, a superiority of both active IMPs over placebo was tested and also the absence of

superiority of any of the active treatments over another was investigated.
This part contains the results of comparison between placebo and Test IMP (TIMP).
[42] - The p value has confirmed the superiority of TIMP over placebo.

Statistical analysis title	% RESOL comparative analysis part 2
Statistical analysis description:	
Pearson chi-square test has been used to carry out parwise comparisons between the treatment groups.	
Comparison groups	Group A v Group B
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.037 [44]
Method	Chi-squared
Parameter estimate	Percent count
Point estimate	-14.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.53
upper limit	-0.2

Notes:

[43] - The analysis type fits the statistical profile of the endpoint including the normality of the distribution.
In a nutshell, a superiority of both active IMPs over placebo was tested and also the absence of superiority of any of the active treatments over another was investigated.
This part contains the results of comparison between placebo and reference IMP.
[44] - The p value has confirmed the superiority of reference IMP over placebo.

Statistical analysis title	% RESOL comparative analysis part 3
Statistical analysis description:	
Pearson chi-square test has been used to carry out parwise comparisons between the treatment groups.	
Comparison groups	Group B v Group C
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.088 [46]
Method	Chi-squared
Parameter estimate	Percent count
Point estimate	-7.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.05
upper limit	1.15

Notes:

[45] - The analysis type fits the statistical profile of the endpoint including the normality of the distribution.
In a nutshell, a superiority of both active IMPs over placebo was tested and also the absence of superiority of any of the active treatments over another was investigated.
This part contains the results of comparison between both active IMPs.
[46] - The p value has confirmed the absence of a significant difference between the two active IMPs.

Other pre-specified: Percent rescue medication users (%SRM)

End point title	Percent rescue medication users (%SRM)

End point description:

% SRM is defined as the share of subjects who had to take the rescue medication (paracetamol 500 mg up to 4 times daily) at least once during the treatment with respect to the total number of subjects having been taking the same IMP.
%SRM have been assessed at Visit 2 and Visit 3. The patients were defined as rescue medication users if they have taken at least one dose of rescue medication during the 4-day or 7-day follow-up.

End point type	Other pre-specified

End point timeframe:

The end point has been evaluated 4 days and 7 days after the therapy initiation.

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: subjects	12	25	17	54

Attachments (see zip file)	Table:tertiary endpoint (% SRM)

Statistical analyses

Statistical analysis title	% SRM comparative analysis

Statistical analysis description:

Pearson chi-square test has been used to comparisons between the three treatment groups.

Comparison groups	Group A v Group B v Group C
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.322 [48]
Method	Chi-squared

Notes:

[47] - The analysis type fits the statistical profile of the endpoint including the normality of the distribution.
In a nutshell, the differences betrween the three groups were tested in a single statistical procedure.
[48] - The p value has confirmed the lack of significant difference between the three groups

Other pre-specified: Tonsilopharyngitis assessment score (TPAS)

End point title	Tonsilopharyngitis assessment score (TPAS)

End point description:

Tonsilopharyngitis assessment (TPA) is a method of the upper respiratory tract infection signs. It contains five categories, scored with the ratings from 0 to 2. The ratings are summed up to yield the TPAS. The range of TPAS is 0 - 10 points.

End point type	Other pre-specified

End point timeframe:

The endpoint was assessed after 7-day and/or 4-day therapy. Subjects who have already finished the treatment after 4 days, were included into the end-therapy analysis with TPAS values obtained after 4 days. Here, only end therapy analysis is presented.

End point values	Group A	Group B	Group C	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	57	116	118	291
Units: points				
arithmetic mean (standard deviation)	0.8 (± 1.33)	0.5 (± 0.96)	0.3 (± 0.63)	0.5 (± 0.95)

Attachments (see zip file)	Figure: Tertiary endpoint ,

Statistical analyses

Statistical analysis title	Tonsilopharingitis assessment score (TPAS) Part 1

Statistical analysis description:

TPAS was analysed by the non-parametric one way ANOVA. In this part, comparison between TIMP and RIMP is reported

Comparison groups	Group B v Group C
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.013 [50]
Method	ANOVA

Notes:

[49] - The analysis has been chosen with regard to the statistical nature of the endpoint including the distribution type.
[50] - The p - value is smaller as the conventional 0.05 indicating the significant difference between TIMP and RIMP.

Statistical analysis title	Tonsilopharingitis assessment score (TPAS) part 2

Statistical analysis description:

TPAS was analysed by the non-parametric one way ANOVA. In this part, comparison between RIMP and placebo is reported.

Comparison groups	Group A v Group B
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.294 [52]
Method	ANOVA

Notes:

[51] - The analysis has been chosen with regard to the statistical nature of the endpoint including the distribution type.
[52] - The p - value is greater as the conventional 0.05 indicating no significant difference between RIMP and placebo.

Statistical analysis title	Tonsilopharingitis assessment score (TPAS) part 3

Statistical analysis description:

TPAS was analysed by the non-parametric one way ANOVA. In this part, comparison between TIMP and placebo is reported.

Comparison groups	Group A v Group C

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.003 [54]
Method	ANOVA

Notes:

[53] - The analysis has been chosen with regard to the statistical nature of the endpoint including the distribution type.

[54] - The p - value is greater as the conventional 0.05 indicating no significant difference between RIMP and placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) were recorded along entire trial i.e. after a single dose and later up to 7 days of therapy.

Adverse event reporting additional description:

All AE were stratified into drug-related (adverse reactions- AR) and not related to IMP. Only AR were analysed thoroughly. Interview and physical inspection were used for safety assessment. AE were reported according to drug relatedness, severity, seriousness, time to onset, frequency, a requirement for the treatment, and expectedness.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Group A_placebo

Reporting group description:

This group has been taking placebo along the entire follow-up period.

Reporting group title	Group C- TIMP

Reporting group description:

This Group of patients has been taking reference IMP along the entire trial follow - up up to 7 days. They have taken at least one dose of the IMP.

Reporting group title	Group B - RIMP

Reporting group description:

This Group of patients has been taking reference IMP along the entire trial follow - up up to 7 days. They have taken at least one dose of the IMP.

Serious adverse events	Group A_placebo	Group C- TIMP	Group B - RIMP
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 57 (0.00%)	0 / 118 (0.00%)	0 / 116 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Group A_placebo	Group C- TIMP	Group B - RIMP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 57 (3.51%)	3 / 118 (2.54%)	5 / 116 (4.31%)
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 118 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1

Dry mouth			
subjects affected / exposed	0 / 57 (0.00%)	2 / 118 (1.69%)	0 / 116 (0.00%)
occurrences (all)	0	2	0
Heartburn			
subjects affected / exposed	0 / 57 (0.00%)	1 / 118 (0.85%)	0 / 116 (0.00%)
occurrences (all)	0	1	0
Meteorism			
subjects affected / exposed	1 / 57 (1.75%)	0 / 118 (0.00%)	0 / 116 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 118 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1
Numbness of tongue			
subjects affected / exposed	0 / 57 (0.00%)	0 / 118 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1
Parageusia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 118 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1
Stomach pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 118 (0.00%)	1 / 116 (0.86%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Erythema facial			
subjects affected / exposed	1 / 57 (1.75%)	0 / 118 (0.00%)	0 / 116 (0.00%)
occurrences (all)	1	0	0

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