Clinical trial results:
Therapeutic effectiveness, safety and tolerability of Tonsilotren tablets in patients (6 to 60 years old) with chronic tonsillitis.
A randomized, international, multicenter, controlled clinical trial.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-001430-34
Trial protocol	DE ES
Global end of trial date	14 August 2015

Results information

Result version number	v1
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	10-TT-EP-003

Additional study identifiers

ISRCTN number	ISRCTN19016626
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG
Sponsor organisation address	Ottostraße 24, Karlsruhe, Germany, 76227
Public contact	Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG, Ottostrasse 24, D-76227 Karlsruhe, + 49(0)721 409301, info@dhu.com
Scientific contact	Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG, Ottostrasse 24, D-76227 Karlsruhe, + 49(0)721 409301, info@dhu.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the therapeutic effectiveness of Tonsilotren in the treatment of chronic tonsillitis when used in addition to conventional symptomatic treatment (test group) in comparison to conventional symptomatic treatment alone (control group).

Protection of trial subjects:

All patients were allowed to receive conventional symptomatic treatment, which were local antiseptics and/or anesthetics. Half of the patients received additionally Tonsilotren. Examinations performed consisted mainly of a physical examination, which included evaluation of chronic tonsillitis-specific symptoms at each visit and evaluation of acute complaints in the upper respiratory tract during additional visits in case the patients felt sick with acute complaints in the upper respiratory tract.
The physical examination did not differ significantly from a routine physical examination and did not involve any particular risk for the patient.
At the discretion of the investigator a throat swab (for a group A beta-hemolytic streptococci rapid test) could be performed. Patients were informed about the slight discomfort this test might cause via the patient informed consent.

Background therapy:

As conventional symptomatic treatment all patients were allowed to receive either local antiseptics and/or local anesthetics for the throat.

Evidence for comparator: -

Actual start date of recruitment	25 January 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	Spain: 31
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Ukraine: 171
Worldwide total number of subjects	256
EEA total number of subjects	85

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)	86
Adolescents (12-17 years)	51
Adults (18-64 years)	119
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited during a period of 13 months going from January 2013 until February 2014 inclusively. In Germany, patients were recruited at 5 ENT practices. In Spain, patients were recruited at 2 pediatrician and 4 general practitioners sites. In Ukraine, patients were recruited at 2 pediatrician, 1 general practitioner and 5 ENT sites.

Pre-assignment

Screening details:

A total of 258 patients gave their informed consent to participate to the trial. 2 of these 258 were screening failures (1 patient was too old, the other one took antibiotics during the 4 weeks before inclusion).
A total of 256 patients were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Test group

Arm description:

The test group received Tonsilotren tablets during Treatment Period I to III each for 8 weeks spread over 14 months and - if needed - conventional symptomatic treatment for chronic tonsillitis.

Arm type	Experimental
Investigational medicinal product name	Atropinum sulfuricum D5, Hepar sulfuris D3, Kalium bichromicum D4, Silicea D2 and Mercurius bijodatus D8.
Investigational medicinal product code	PR1
Other name	Tonsilotren ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tonsilotren was provided to the patients of the test group only. Separate blisters for children (<12 years) and adolescents / adults (≥12 years) were provided. All patients received Tonsilotren tablets during 3 treatment periods (TP I to III) each for 8 weeks: TP I and II were followed each by a 8 weeks follow-up period without Tonsilotren (FU I and II). TP III was followed by a 12 weeks FU III without Tonsilotren.
During the 3 TPs, children took 3 times a day 1 tablet of Tonsilotren whereas adolescents/adults took 3 times a day 2 tablets Tonsilotren.

Arm title	Control group

Arm description:

The control group was treated only with conventional symptomatic treatment if needed.

Arm type	Conventional symptomatic treatment

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Test group	Control group
Started	132	124
Visit 2 completed (Day 11±3)	130	121
Visit 3 completed (Week 8±1)	128	120
Visit 4 completed (Week 16±1)	125	120
Visit 5 completed (Week 24±1)	119	117
Visit 6 completed (Week 32±1)	105	103
Visit 7 completed (Week 40±1)	104	101
Visit 8 completed (Week 48±1)	98	94
Visit 9 completed (Week 60±1)	98	94
Completed	98	94
Not completed	34	30
Physician decision	1	-
Consent withdrawn by subject	7	4
Pregnancy	-	1
Military operations in Eastern part of Ukraine	13	14
Lost to follow-up	1	2
Tonsillectomy or any other surgery in the throat	1	1
Protocol deviation	11	8

Baseline characteristics

Reporting groups	
Reporting group title	Test group
Reporting group description:	
The test group received Tonsilotren tablets during Treatment Period I to III each for 8 weeks spread over 14 months and - if needed - conventional symptomatic treatment for chronic tonsillitis.	
Reporting group title	Control group
Reporting group description:	
The control group was treated only with conventional symptomatic treatment if needed.	

Reporting group values	Test group	Control group	Total
Number of subjects	132	124	256
Age categorical			
Units: Subjects			
Children (2-11 years)	45	41	86
Adolescents (12-17 years)	25	26	51
Adults (18-64 years)	62	57	119
Age continuous			
Age has been recorded as integer number value.			
Units: years			
median	15.5	16	
inter-quartile range (Q1-Q3)	9.5 to 32	9 to 31	-
Gender categorical			
Units: Subjects			
Female	86	70	156
Male	46	54	100
ATI baseline frequency			
Acute throat infections [ATIs] that occurred from 12 months prior to enrolment up to end of Treatment Period I are counted as baseline ATIs.			
Units: Subjects			
N=0	8	3	11
N=1	11	16	27
N=2	17	11	28
N=3	61	51	112
N=4	26	25	51
N=5	6	14	20
N=6	3	2	5
N=7	0	1	1
N=8	0	1	1

End points

End points reporting groups

Reporting group title	Test group
Reporting group description:	
The test group received Tonsilotren tablets during Treatment Period I to III each for 8 weeks spread over 14 months and - if needed - conventional symptomatic treatment for chronic tonsillitis.	
Reporting group title	Control group
Reporting group description:	
The control group was treated only with conventional symptomatic treatment if needed.	
Subject analysis set title	Test group - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Test group patients without major protocol violations are included in the 'Test group - PP' Analysis subset.	
Subject analysis set title	Control group - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Control group patients without major protocol violations are included in the 'Control group - PP' Analysis subset.	
Subject analysis set title	ATI events - Test group
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
This analysis set consists of 'ATI events' rather than individual patients. All ATI Events documented between Visit 1 and Termination Visit within test group ITT patients are included in this group. [Note: There were 92 ATI events recorded for 50 test group patients.]	
Subject analysis set title	ATI events - Control group
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
This analysis set consists of 'ATI events' rather than individual patients. All ATI Events documented between Visit 1 and Termination Visit within control group ITT patients are included in this group. [Note: There were 189 ATI events recorded for 87 control group patients.]	

Primary: Number of documented ATIs

End point title	Number of documented ATIs
End point description:	
End point type	Primary
End point timeframe:	
Basis are event occurrences observed beyond Visit 3 until the end of study. (Note that any ATI event occurrences prior to Visit 3 have been added to baseline ATI frequencies.)	

End point values	Test group	Control group	Test group - PP	Control group - PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	128[1]	120[2]	103	70
Units: ATI events				
No event	86	45	67	26
One event	28	39	25	22

Two events	10	16	8	9
Three events	0	12	0	10
Four events	2	3	1	1
Five events	0	2	0	1
Six events	2	2	2	1
Seven events	0	1	0	0

Notes:

[1] - Only patients continued beyond Visit 3.

[2] - Only patients continued beyond Visit 3.

Attachments (see zip file)	Estimated Overall Survival Curve/Figure_1__.png

Statistical analyses

Statistical analysis title	Modeling the time between consecutive ATIs

Statistical analysis description:

An extension of a survival model based on the Cox proportional hazards approach was applied.
Multiple ATI events per patient within observational period (if there were any) contributed to proportional means model, which included baseline ATI frequency as further covariable [which was not shown to be statistically significant].
Presented results refer to the treatment arm related effect.

Comparison groups	Test group v Control group
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0001
Method	Proportional means model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4463
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2971
upper limit	0.6705

Notes:

[3] - Analysis followed an exploratory rather than confirmatory approach.
Presented Hazard ratio [HR] refers to 'Hazard for test group compared to control group'.

Statistical analysis title	Modeling the time between consecutive ATIs - PP

Statistical analysis description:

Basis: Per-protocol patients

An extension of a survival model based on the Cox proportional hazards approach was applied.
Multiple ATI events per patient within observational period (if there were any) contributed to proportional means model, which included baseline ATI frequency as further covariable [which was not shown to be statistically significant].
Presented results refer to the treatment arm related effect.

Comparison groups	Test group - PP v Control group - PP
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.001
Method	Proportional means model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4618

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2919
upper limit	0.7308

Notes:

[4] - Analysis followed an exploratory rather than confirmatory approach.
Presented Hazard ratio [HR] refers to 'Hazard for test group compared to control group'.

Statistical analysis title	Proportions of patients with at least 1 ATI

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding binary categorization of patients with either 'No ATI event' or 'At least one ATI event' observed within considered timeframe.

Comparison groups	Test group v Control group
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001 [6]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-29.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.57
upper limit	-17.81

Notes:

[5] - Analysis followed an exploratory rather than confirmatory approach.

[6] - The presented risk difference refers to the difference of proportions [%] of patients with at least one ATI event considering 'Test - Control'. I.e. a negative value indicates less patients with ATI in test group compared to control group.

Statistical analysis title	Proportions of patients with at least 1 ATI - PP

Statistical analysis description:

Basis: Per-protocol patients

Analysis is based on comparison of treatment arms regarding binary categorization of patients with either 'No ATI event' or 'At least one ATI event' observed within considered timeframe.

Comparison groups	Test group - PP v Control group - PP
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0003 [8]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-27.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.5
upper limit	-13.31

Notes:

[7] - Analysis followed an exploratory rather than confirmatory approach.

[8] - The presented risk difference refers to the difference of proportions [%] of patients with at least one ATI event considering 'Test - Control'. I.e. a negative value indicates less patients with ATI in test group compared to control group.

Statistical analysis title	Sensitivity model: Poisson regression

Statistical analysis description:

Analysis of ATI event occurrences in terms of count-data has been additionally assessed via Poisson regression modelling. As a result event rates (Test=0.5927 [events/year] | Control=1.3457[events/year]) and 'estimated time to event' (Test=615.8 [days] | Control=271.2[days]), respectively, have been calculated from estimated treatment specific least

Comparison groups	Control group v Test group
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.0002 [10]
Method	Poisson Regression [GEE]
Parameter estimate	Risk ratio (RR)
Point estimate	0.4404
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2867
upper limit	0.6765

Notes:

[9] - Analysis followed an exploratory rather than confirmatory approach. Poisson regression model was intended as a sensitivity analysis.
[10] - Relative risk [RR] refers to 'Test/Control'. I.e. the statistically significant finding and referring RR value below '1' indicates less ATI in test group compared to control group. Thus, sensitivity analysis confirms primary analysis findings.

Secondary: Standardized number of days with any chronic tonsillitis symptom - per diary period

End point title	Standardized number of days with any chronic tonsillitis symptom - per diary period

End point description:

Patients were asked to report their suffering of chronic tonsillitis symptoms on a weekly basis restrospectively for each day in a diary. The standardized number of days, which is the ratio of days with presence of any symptom divided by the total number of days recorderd in a diary period, was evaluated.

End point type	Secondary

End point timeframe:

Following diary periods are considered (the number of patients differs between periods - depending on individual drop out [see subject disposition]):
T I: V1 to V3
FU I: V3 to V4
T II: V4 to V5
FU II: V5 to V6
T III: V6 to V7
FU III: V7 to V9

End point values	Test group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131[11]	123[12]		
Units: proportion of total diary days				
median (inter-quartile range (Q1-Q3))				
Diary period T I	0.214 (0.107 to 0.436)	0.393 (0.224 to 0.615)		
Diary period FU I	0.179 (0.092 to 0.276)	0.328 (0.179 to 0.589)		
Diary period T II	0.143 (0.081 to 0.229)	0.298 (0.148 to 0.576)		
Diary period FU II	0.113 (0.054 to 0.246)	0.268 (0.107 to 0.582)		
Diary period T III	0.107 (0.052 to 0.2)	0.21 (0.1 to 0.5)		
Diary period FU III	0.113 (0.057 to 0.2)	0.227 (0.1 to 0.529)		

Notes:

[11] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between diary periods.
[12] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between diary periods.

Statistical analyses

Statistical analysis title	Diary period 'T I' - days with any symptom

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented suffering from any chronic tonsillitis symptoms as obtained from patients' diaries.

Basis: Diary period T I (Visit 1 to Visit 3)
Number of patients with data in this period: 254 (Test group:131 | Control group: 123).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001 [14]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of location shift
Point estimate	-0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.202
upper limit	-0.079

Notes:

[13] - Analysis followed an exploratory rather than confirmatory approach.

[14] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from any chronic tonsillitis symptoms.

Statistical analysis title	Diary period 'FU I' - days with any symptom

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented suffering from any chronic tonsillitis symptoms as obtained from patients' diaries.

Basis: Diary period FU I (Visit 3 to Visit 4)
Number of patients with data in this period: 248 (Test group:128 | Control group: 120).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.0001 [16]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of location shift
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.212
upper limit	-0.095

Notes:

[15] - Analysis followed an exploratory rather than confirmatory approach.

[16] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from any chronic tonsillitis symptoms.

Statistical analysis title	Diary period 'T II' - days with any symptom

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented suffering from any chronic tonsillitis symptoms as obtained from patients' diaries.

Basis: Diary period T II (Visit 4 to Visit 5)
Number of patients with data in this period: 241 (Test group:124 | Control group: 117).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.0001 [18]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of location shift
Point estimate	-0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	-0.089

Notes:

[17] - Analysis followed an exploratory rather than confirmatory approach.

[18] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from any chronic tonsillitis symptoms.

Statistical analysis title	Diary period 'FU II' - days with any symptom

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented suffering from any chronic tonsillitis symptoms as obtained from patients' diaries.

Basis: Diary period FU II (Visit 5 to Visit 6)
Number of patients with data in this period: 230 (Test group:115| Control group: 115).

Comparison groups	Test group v Control group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	< 0.0001 [20]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of location shift
Point estimate	-0.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	-0.069

Notes:

[19] - Analysis followed an exploratory rather than confirmatory approach.

[20] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from any chronic tonsillitis symptoms.

Statistical analysis title	Diary period 'T III' - days with any symptom

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented suffering from any chronic tonsillitis symptoms as obtained from patients' diaries.

Basis: Diary period T III (Visit 6 to Visit 7)
Number of patients with data in this period: 226 (Test group:114 | Control group: 112).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	< 0.0001 [22]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of location shift
Point estimate	-0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.164
upper limit	-0.054

Notes:

[21] - Analysis followed an exploratory rather than confirmatory approach.

[22] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from any chronic tonsillitis symptoms.

Statistical analysis title	Diary period 'FU III' - days with any symptom

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented suffering from any chronic tonsillitis symptoms as obtained from patients' diaries.

Basis: Diary period FU III (Visit 7 to Visit 9)
Number of patients with data in this period: 211 (Test group:107 | Control group: 104).

Comparison groups	Test group v Control group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.0001 [24]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of location shift
Point estimate	-0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.181
upper limit	-0.062

Notes:

[23] - Analysis followed an exploratory rather than confirmatory approach.

[24] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from any chronic tonsillitis symptoms.

Secondary: Number of documented upper respiratory tract infections [URTIs]

End point title	Number of documented upper respiratory tract infections [URTIs]

End point description:

End point type	Secondary

End point timeframe:

Basis are event occurrences observed beyond Visit 3 until the end of study. (Note that any URTI event occurrences prior to Visit 3 have been added to baseline URTI frequencies.)

End point values	Test group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[25]	120[26]		
Units: URTI events				
No event	101	71		
One event	21	34		
Two events	3	12		
Three events	3	2		
Four events	0	1		

Notes:

[25] - Only patients continued beyond Visit 3.

[26] - Only patients continued beyond Visit 3.

Statistical analyses

Statistical analysis title	Proportions of patients with at least 1 URTI

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding binary categorization of patients with either 'No URTI event' or 'At least one URTI event' observed within considered timeframe.

Comparison groups	Test group v Control group

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.0008 [28]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.02
upper limit	-8.46

Notes:

[27] - Analysis followed an exploratory rather than confirmatory approach.

[28] - The presented risk difference refers to the difference of proportions [%] of patients with at least one URTI event considering 'Test -Control'. I.e. a negative value indicates less patients with URTI in test group compared to control group.

Secondary: Presence / Absence of chronic tonsillitis symptoms per visit (investigators assessment)

End point title	Presence / Absence of chronic tonsillitis symptoms per visit (investigators assessment)

End point description:

During the study, the following 7 chronic tonsillitis-specific symptoms were evaluated by the investigator by checking the presence and intensity (3-items scale: absent, mild, severe) at each regular study visit (Visit 1 [Baseline Visit] to Visit 9):
• Difficulties in swallowing / sore throat;
• Bad breath and / or taste in mouth (halitosis);
• Hyperemia of the anterior palatine arches;
• Edema of angle where the anterior and posterior palatine arches join each other;
• Caseous purulent plug and / or purulent exudates in the tonsillar crypts;
• Friable tonsils or indurated tonsils or scarred adhesions between the tonsils and the palatine arches;
• Enlarged submandibular lymph nodes.

Presented "number of present symptoms at visit" does not refer to the symptom intensities but sums up the number of symptoms recorded to be present within a patient.

End point type	Secondary

End point timeframe:

All regular study visits.

Note: Data presented for "Visit 9" refers to either regular Visit 9 (Week 60±1) or early Termination Visit.

End point values	Test group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131[29]	123[30]		
Units: Number of present symptoms at visit				
Visit 1: No symptoms	0	0		
Visit 1: 1 symptom	0	0		
Visit 1: 2 symptoms	0	0		
Visit 1: 3 symptoms	3	2		
Visit 1: 4 symptoms	12	12		
Visit 1: 5 symptoms	22	29		

Visit 1: 6 symptoms	36	30		
Visit 1: 7 symptoms	57	50		
Visit 2: No symptoms	1	0		
Visit 2: 1 symptom	3	1		
Visit 2: 2 symptoms	7	3		
Visit 2: 3 symptoms	11	12		
Visit 2: 4 symptoms	13	13		
Visit 2: 5 symptoms	43	26		
Visit 2: 6 symptoms	25	23		
Visit 2: 7 symptoms	27	43		
Visit 3: No symptoms	2	1		
Visit 3: 1 symptom	9	6		
Visit 3: 2 symptoms	13	5		
Visit 3: 3 symptoms	32	14		
Visit 3: 4 symptoms	23	10		
Visit 3: 5 symptoms	16	19		
Visit 3: 6 symptoms	14	17		
Visit 3: 7 symptoms	19	48		
Visit 4: No symptoms	2	1		
Visit 4: 1 symptom	11	4		
Visit 4: 2 symptoms	16	2		
Visit 4: 3 symptoms	27	19		
Visit 4: 4 symptoms	21	15		
Visit 4: 5 symptoms	16	16		
Visit 4: 6 symptoms	13	10		
Visit 4: 7 symptoms	19	53		
Visit 5: No symptoms	3	0		
Visit 5: 1 symptom	11	4		
Visit 5: 2 symptoms	43	13		
Visit 5: 3 symptoms	26	10		
Visit 5: 4 symptoms	16	18		
Visit 5: 5 symptoms	10	14		
Visit 5: 6 symptoms	5	14		
Visit 5: 7 symptoms	5	44		
Visit 6: No symptoms	4	0		
Visit 6: 1 symptom	7	0		
Visit 6: 2 symptoms	29	10		
Visit 6: 3 symptoms	23	12		
Visit 6: 4 symptoms	14	13		
Visit 6: 5 symptoms	7	22		
Visit 6: 6 symptoms	7	12		
Visit 6: 7 symptoms	14	34		
Visit 7: No symptoms	25	3		
Visit 7: 1 symptom	8	3		
Visit 7: 2 symptoms	29	10		
Visit 7: 3 symptoms	13	12		
Visit 7: 4 symptoms	9	14		
Visit 7: 5 symptoms	14	15		
Visit 7: 6 symptoms	3	18		
Visit 7: 7 symptoms	3	26		
Visit 8: No symptoms	23	1		
Visit 8: 1 symptom	8	1		

Visit 8: 2 symptoms	22	6		
Visit 8: 3 symptoms	14	9		
Visit 8: 4 symptoms	10	9		
Visit 8: 5 symptoms	12	17		
Visit 8: 6 symptoms	7	21		
Visit 8: 7 symptoms	2	30		
Visit 9: No symptoms	21	3		
Visit 9: 1 symptom	23	4		
Visit 9: 2 symptoms	32	13		
Visit 9: 3 symptoms	20	10		
Visit 9: 4 symptoms	15	28		
Visit 9: 5 symptoms	10	7		
Visit 9: 6 symptoms	5	15		
Visit 9: 7 symptoms	5	43		

Notes:

[29] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between visits.
[30] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between visits.

Statistical analyses

Statistical analysis title	Visit 1: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 1 records
Number considered patients with symptom assessment data at this visit: 253 (Test group: 130 | Control group: 123).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.463 [32]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[31] - Analysis followed an exploratory rather than confirmatory approach.

[32] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. No statistically significant could be detected at current visit.

Statistical analysis title	Visit 2: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 2 records
Number considered patients with symptom assessment data at this visit: 251 (Test group: 130 | Control group: 121).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.0214 [34]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[33] - Analysis followed an exploratory rather than confirmatory approach.

[34] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Statistical analysis title	Visit 3: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 3 records
Number considered patients with symptom assessment data at this visit: 248 (Test group: 128 | Control group: 120).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	< 0.0001 [36]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-1

Notes:

[35] - Analysis followed an exploratory rather than confirmatory approach.

[36] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Statistical analysis title	Visit 4: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 4 records
Number considered patients with symptom assessment data at this visit: 245 (Test group: 125 | Control group: 120).

Comparison groups	Test group v Control group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.0001 [38]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-1

Notes:

[37] - Analysis followed an exploratory rather than confirmatory approach.

[38] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Statistical analysis title	Visit 5: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 5 records
Number considered patients with symptom assessment data at this visit: 236 (Test group: 119 | Control group: 117).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	< 0.0001 [40]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-2

Notes:

[39] - Analysis followed an exploratory rather than confirmatory approach.

[40] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Statistical analysis title	Visit 6: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 6 records
Number considered patients with symptom assessment data at this visit: 208 (Test group: 105 | Control group: 103).

Comparison groups	Test group v Control group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	< 0.0001 [42]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-1

Notes:

[41] - Analysis followed an exploratory rather than confirmatory approach.

[42] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Statistical analysis title	Visit 7: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 7 records
Number considered patients with symptom assessment data at this visit: 205 (Test group: 104 | Control group: 101).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	< 0.0001 [44]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-2

Notes:

[43] - Analysis followed an exploratory rather than confirmatory approach.

[44] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Statistical analysis title	Visit 8: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 8 records
Number considered patients with symptom assessment data at this visit: 192 (Test group: 98| Control group: 94).

Comparison groups	Test group v Control group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	< 0.0001 [46]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-2

Notes:

[45] - Analysis followed an exploratory rather than confirmatory approach.

[46] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Statistical analysis title	Visit 9: Number of present symptoms

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of present symptoms at visit as determined by the treating physician.
Basis: Visit 9 records [Regular visit (Week 60±1) or early Termination Visit]
Number considered patients with symptom assessment data at this visit: 254 (Test group: 131| Control group: 123).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	< 0.0001 [48]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-2

Notes:

[47] - Analysis followed an exploratory rather than confirmatory approach.

[48] - The presented location shift refers to the difference in number of present symptoms 'Test - Control'. A p-value <0.05 indicates statistically significant differences. There is a lower number of present symptoms in test group compared to control group.

Secondary: ATI treated with antibiotics

End point title	ATI treated with antibiotics

End point description:

Within observed ATI events, distinction has been made with respect to 'treatment with antibiotics'. Basis for this analysis are (i) recorded ATI events as well as (ii) patients with at least one ATI event.
[Note: In case of multiple ATI Events per patient, a patient has been counted as 'treated with antibiotics' (due to ATI), if there was at least one of his/her ATIs treated with antibiotics.]

End point type	Secondary

End point timeframe:

Whole study period (i.e. from Day 0 until Termination Visit).

End point values	Test group	Control group	ATI events - Test group	ATI events - Control group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50[49]	87[50]	92	189
Units: Patients | Events				
Treated with antibiotics	26	59	34	110
No antibiotic treatment applied	24	28	58	79

Notes:

[49] - Only patients with at least one ATI event are considered.

[50] - Only patients with at least one ATI event are considered.

Statistical analyses

Statistical analysis title	ATI events treated with antibiotics

Statistical analysis description:

Analysis is based on comparison of treatment arms' ATI events regarding binary categorization of events with either 'No antibiotic treatment applied" or 'Antibiotic treatment'.

Comparison groups	ATI events - Test group v ATI events - Control group
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.0008 [52]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.36
upper limit	-9.13

Notes:

[51] - Analysis followed an exploratory rather than confirmatory approach.

[52] - Risk difference refers to the difference of proportions [%] of ATI events "treated with antibiotics" considering the direction 'Test -Control'. I.e. a negative value indicates less events treated with antibiotics in test compared to control group.

Statistical analysis title	Patients with ATI treated with antibiotics

Statistical analysis description:

Analysis is based on comparison of patients with at least one ATI event. The proportions of patients with 'at least one ATI with antibiotic treatment' and 'All ATI events not treated with antibiotics" are compared between treatment arms.

Comparison groups	Test group v Control group
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.0663 [54]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-15.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.79
upper limit	1.16

Notes:

[53] - Analysis followed an exploratory rather than confirmatory approach.

[54] - Presented risk difference refers to the difference of proportions [%] of "patient with at least 1 ATI treated with antibiotics" 'Test -Control'. The difference is not statistically significant at alpha=0.05 level.

Secondary: ATI treated with analgesics

End point title	ATI treated with analgesics

End point description:

Within observed ATI events, distinction has been made with respect to 'treatment with analgesics'. Basis for this analysis are (i) recorded ATI events as well as (ii) patients with at least one ATI event. [Note: In case of multiple ATI events per patient, a patient has been counted as 'treated with analgesics' (due to ATI), if there was at least one of his/her ATIs treated with analgesics.]

End point type	Secondary

End point timeframe:

Whole study period (i.e. from Day 0 until Termination Visit).

End point values	Test group	Control group	ATI events - Test group	ATI events - Control group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50[55]	87[56]	92	189
Units: Patients | Events				
Treated with analgesics	34	67	57	125
No analgesic treatment applied	16	20	35	64

Notes:

[55] - Only patients with at least one ATI event are considered.

[56] - Only patients with at least one ATI event are considered.

Statistical analyses

Statistical analysis title	ATI events treated with analgesics

Statistical analysis description:

Analysis is based on comparison of treatment arms' ATI events regarding binary categorization of events with either 'No analgesic treatment applied" or 'Analgesic treatment'.

Comparison groups	ATI events - Test group v ATI events - Control group
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	= 0.4911 [58]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.18
upper limit	7.82

Notes:

[57] - Analysis followed an exploratory rather than confirmatory approach.

[58] - Presented risk difference refers to the difference of proportions [%] of ATI events "treated with analgesics" considering the direction 'Test -Control'. No statistically significant difference was detected.

Statistical analysis title	Patients with ATI treated with analgesics

Statistical analysis description:

Analysis is based on comparison of patients with at least one ATI event. The proportions of patients with 'at least one ATI with analgesic treatment' and 'All ATI events not treated with analgesics" are compared between treatment arms.

Comparison groups	Test group v Control group
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.2486 [60]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.68
upper limit	6.65

Notes:

[59] - Analysis followed an exploratory rather than confirmatory approach.

[60] - Presented risk difference refers to the difference of proportions [%] of "patient with at least 1 ATI treated with analgesics" 'Test -Control'. The difference is not statistically significant at alpha=0.05 level.

Secondary: Number of days with consumption of analgesics due to ATI

End point title	Number of days with consumption of analgesics due to ATI

End point description:

Within observed ATI events, distinction has been made with respect to 'treatment with analgesics' (see secondary endpoint "ATI treated with analgesics"). The number of days with consumption of analgesics has been evaluated, based on the documented start and end dates of documented analgesics consumption within ATI event occurrence.

End point type	Secondary

End point timeframe:

Whole study period (i.e. from Day 0 until Termination Visit).

End point values	ATI events - Test group	ATI events - Control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[61]	125[62]		
Units: Days				
median (inter-quartile range (Q1-Q3))	5 (3 to 6)	5 (4 to 7)		

Notes:

[61] - Only "treated" events are considered.

[62] - Only "treated" events are considered.

Statistical analyses

Statistical analysis title	Days with consumption of analgesics due to ATI

Statistical analysis description:

The number of days treated with analgesics due to ATI has been compared between test and control group ATI event occurrences, where only ATI events treated with analgesics have been considered (Test group: 57 | Control group: 125).

Comparison groups	ATI events - Control group v ATI events - Test group
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	= 0.4802 [64]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of location shift
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[63] - Analysis followed an exploratory rather than confirmatory approach.

[64] - The presented location shift refers to the difference 'Test -Control'. No statistically significant differences between treatment arms could be detected.

Secondary: Standardized number of days with impact on performance of normal daily activity

End point title	Standardized number of days with impact on performance of normal daily activity

End point description:

Patients were asked to report impact on performance of normal daily activities by chronic tonsillitis symptoms on a weekly basis restrospectively for each day in a diary. The standardized number of days, which is the ratio of days with impact on normal daily activitiy divided by the total number of days recorderd in a diary period, was evaluated.

End point type	Secondary

End point timeframe:

Following diary periods are considered (the number of patients differs between periods - depending on individual drop out [see subject disposition]):
T I: V1 to V3
FU I: V3 to V4
T II: V4 to V5
FU II: V5 to V6
T III: V6 to V7
FU III: V7 to V9

End point values	Test group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131[65]	123[66]		
Units: proportion of total diary days				
median (inter-quartile range (Q1-Q3))				
Diary period T I	0.018 (0 to 0.054)	0.082 (0.018 to 0.179)		
Diary period FU I	0 (0 to 0.036)	0.055 (0 to 0.135)		
Diary period T II	0 (0 to 0.018)	0.018 (0 to 0.143)		

Diary period FU II	0 (0 to 0.018)	0 (0 to 0.096)		
Diary period T III	0 (0 to 0)	0 (0 to 0.088)		
Diary period FU III	0 (0 to 0.021)	0.022 (0 to 0.1)		

Notes:

[65] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between diary periods.
[66] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between diary periods.

Statistical analyses

Statistical analysis title	Period 'T I' - days with impact on daily activity

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented impact on daily activity due to chronic tonsillitis symptoms as obtained from patients' diaries.
Basis: Diary period T I (Visit 1 to Visit 3) Number of patients with data in this period: 254 (Test group: 131 | Control group: 123).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	< 0.0001 [68]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.071
upper limit	-0.021

Notes:

[67] - Analysis followed an exploratory rather than confirmatory approach.

[68] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from impact on daily activities due to symptoms.

Statistical analysis title	Period 'FU I' - days with impact on daily activity

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented impact on daily activity due to chronic tonsillitis symptoms as obtained from patients' diaries.
Basis: Diary period FU I (Visit 3 to Visit 4) Number of patients with data in this period: 248 (Test group: 128 | Control group: 120).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	< 0.0001 [70]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-0.036

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.054
upper limit	-0.017

Notes:

[69] - Analysis followed an exploratory rather than confirmatory approach.

[70] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from impact on daily activities due to symptoms.

Statistical analysis title	Period 'T II' - days with impact on daily activity

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented impact on daily activity due to chronic tonsillitis symptoms as obtained from patients' diaries.
Basis: Diary period T II (Visit 4 to Visit 5) Number of patients with data in this period: 241 (Test group: 124 | Control group: 117).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	< 0.0001 [72]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0

Notes:

[71] - Analysis followed an exploratory rather than confirmatory approach.

[72] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from impact on daily activities due to symptoms.

Statistical analysis title	Period 'FU II'- days with impact on daily activity

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented impact on daily activity due to chronic tonsillitis symptoms as obtained from patients' diaries.
Basis: Diary period FU II (Visit 5 to Visit 6) Number of patients with data in this period: 230 (Test group: 115 | Control group: 115).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.0007 [74]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0003
upper limit	0

Notes:

[73] - Analysis followed an exploratory rather than confirmatory approach.

[74] - The statistically significant finding and referring Wilcoxon mean scores (Test=102.4 | Control=128.6) values indicate patients in test group less frequently suffering from impact on daily activities due to symptoms, although location shift is "0".

Statistical analysis title	Period 'T III'- days with impact on daily activity

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented impact on daily activity due to chronic tonsillitis symptoms as obtained from patients' diaries.
Basis: Diary period T III (Visit 6 to Visit 7) Number of patients with data in this period: 226 (Test group: 114 | Control group: 112).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[75]
P-value	< 0.0001 [76]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[75] - Analysis followed an exploratory rather than confirmatory approach.

[76] - The statistically significant finding and referring Wilcoxon mean scores (Test=97.2 | Control=130.1) values indicate patients in test group less frequently suffering from impact on daily activities due to symptoms, although location shift is "0".

Statistical analysis title	Period 'FU III'-days with impact on daily activity

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the fraction of days with documented impact on daily activity due to chronic tonsillitis symptoms as obtained from patients' diaries.
Basis: Diary period FU III (Visit 7 to Visit 9) Number of patients with data in this period: 211 (Test group: 107 | Control group: 104).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	< 0.0001 [78]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges Lehman estimate of Location Shift
Point estimate	-0.007

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0

Notes:

[77] - Analysis followed an exploratory rather than confirmatory approach.

[78] - The presented location shift refers to the difference 'Test -Control'. I.e. the statistically significant finding and referring negative value indicate patients in test group less frequently suffering from impact on daily activities due to symptoms.

Secondary: Patient's quality of life

End point title	Patient's quality of life

End point description:

Quality of life was assessed by the patient at each regular visit except Visit 2 using a 5-point rating scale (items: "Very good", "Good", "Moderate", "Poor" and "Very poor").
Presented evaluation is related to binary categorization of patients' assessments into categories "At least good" (i.e. summarizing answers: "very good" and "good") and "Moderate or worse" (i.e. summarizing answers: "moderate ", "poor" and "very poor").

End point type	Secondary

End point timeframe:

All regular study visits (except Visit 2).

Note: Data presented for "Visit 9" refers to either regular Visit 9 (Week 60±1) or early Termination Visit

End point values	Test group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131[79]	123[80]		
Units: Patients				
Visit 1: Very good or good	20	18		
Visit 1: Moderate or poor or very poor	110	105		
Visit 3: Very good or good	103	36		
Visit 3: Moderate or poor or very poor	25	84		
Visit 4: Very good or good	108	36		
Visit 4: Moderate or poor or very poor	17	84		
Visit 5: Very good or good	109	35		
Visit 5: Moderate or poor or very poor	10	82		
Visit 6: Very good or good	99	51		
Visit 6: Moderate or poor or very poor	6	52		
Visit 7: Very good or good	98	48		
Visit 7: Moderate or poor or very poor	6	53		
Visit 8: Very good or good	95	40		
Visit 8: Moderate or poor or very poor	3	54		
Visit 9: Very good or good	123	46		
Visit 9: Moderate or poor or very poor	8	77		

Notes:

[79] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between visits.
[80] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between visits.

Statistical analyses

Statistical analysis title	Visit 1: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality of life [QoL] being "At least good".

Basis: Visit 1 records
Number considered patients with symptom assessment data at this visit: 253 (Test group: 130 | Control group: 123).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[81]
P-value	= 0.8674 [82]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.05
upper limit	9.55

Notes:

[81] - Analysis followed an exploratory rather than confirmatory approach.

[82] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. No statistically significant difference was detected for current visit.

Statistical analysis title	Visit 3: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality of life [QoL] being "At least good".

Basis: Visit 3 records
Number considered patients with symptom assessment data at this visit: 248 (Test group: 128 | Control group: 120).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[83]
P-value	< 0.0001 [84]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	50.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.77
upper limit	61.16

Notes:

[83] - Analysis followed an exploratory rather than confirmatory approach.

[84] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. I.e. a positive value indicates more patients with "very good" or "good" QoL in test group compared to control group.

Statistical analysis title	Visit 4: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality of life [QoL] being "At least good".

Basis: Visit 4 records
Number considered patients with symptom assessment data at this visit: 245 (Test group: 125 | Control group: 120).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[85]
P-value	< 0.0001 [86]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	56.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.23
upper limit	66.57

Notes:

[85] - Analysis followed an exploratory rather than confirmatory approach.

[86] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. I.e. a positive value indicates more patients with "very good" or "good" QoL in test group compared to control group.

Statistical analysis title	Visit 5: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality of life [QoL] being "At least good".

Basis: Visit 5 records
Number considered patients with symptom assessment data at this visit: 236 (Test group: 119 | Control group: 117).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[87]
P-value	< 0.0001 [88]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	61.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	52
upper limit	71.36

Notes:

[87] - Analysis followed an exploratory rather than confirmatory approach.

[88] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. I.e. a positive value indicates more patients with "very good" or "good" QoL in test group compared to control group.

Statistical analysis title	Visit 6: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality

of life [QoL] being "At least good".

Basis: Visit 6 records
Number considered patients with symptom assessment data at this visit: 208 (Test group: 105 | Control group: 103).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[89]
P-value	< 0.0001 [90]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	44.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.14
upper limit	55.4

Notes:

[89] - Analysis followed an exploratory rather than confirmatory approach.

[90] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. I.e. a positive value indicates more patients with "very good" or "good" QoL in test group compared to control group.

Statistical analysis title	Visit 7: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality of life [QoL] being "At least good".

Basis: Visit 7 records
Number considered patients with symptom assessment data at this visit: 205 (Test group: 104 | Control group: 101).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[91]
P-value	< 0.0001 [92]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	46.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.99
upper limit	57.43

Notes:

[91] - Analysis followed an exploratory rather than confirmatory approach.

[92] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. I.e. a positive value indicates more patients with "very good" or "good" QoL in test group compared to control group.

Statistical analysis title	Visit 8: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality of life [QoL] being "At least good".

Basis: Visit 8 records

Number considered patients with symptom assessment data at this visit: 192 (Test Group: 98 | Control Group: 94).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[93]
P-value	< 0.0001 [94]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	54.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	43.82
upper limit	64.95

Notes:

[93] - Analysis followed an exploratory rather than confirmatory approach.

[94] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. I.e. a positive value indicates more patients with "very good" or "good" QoL in test group compared to control group.

Statistical analysis title	Visit 9: quality of life

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the number of patients rating their quality of life [QoL] being "At least good".

Basis: Visit 9 records [Regular visit (Week 60±1) or early Termination Visit]
Number considered patients with symptom assessment data at this visit: 254 (Test group: 131 | Control group: 123).

Comparison groups	Test group v Control group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[95]
P-value	< 0.0001 [96]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	56.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.01
upper limit	65.98

Notes:

[95] - Analysis followed an exploratory rather than confirmatory approach.

[96] - The presented risk difference refers to the difference of proportions [%] of patients with "At least good" self-rating of QoL. I.e. a positive value indicates more patients with "very good" or "good" QoL in test group compared to control group.

Secondary: Treatment Outcome according to integrative medicine outcome scale [IMOS]

End point title	Treatment Outcome according to integrative medicine outcome scale [IMOS]

End point description:

Global judgement of the treatment outcome by IMOS (5-point rating scale) was done by both the investigator and the patient each separately in comparison to Visit 1 at each regular post-baseline visit except for Visit 2.

IMOS items are "Complete recovery", "Major improvement", "Slight to moderate improvement", "No change" and "Deterioration".

Presented evaluation is related to binary categorization of patients' assessments into categories "At least major improvement" (i.e. summarizing answers: "Complete recovery" and "Major improvement") and "Less than major improvement" (i.e. summarizing the remaining three categories). Distinction is made between patients' and investigators' IMOS ratings.

End point type	Secondary

End point timeframe:

All regular post-baseline study visits (except Visit 2).

Note: Data presented for "Visit 9" refers to either regular Visit 9 (Week 60±1) or early Termination Visit.

End point values	Test group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131[97]	123[98]		
Units: Patients				
Visit 3: At least major improvement [Patient]	88	9		
Visit 3: Less than major improvement [Patient]	40	109		
Visit 4: At least major improvement [Patient]	82	7		
Visit 4: Less than major improvement [Patient]	43	113		
Visit 5: At least major improvement [Patient]	95	18		
Visit 5: Less than major improvement [Patient]	24	99		
Visit 6: At least major improvement [Patient]	82	15		
Visit 6: Less than major improvement [Patient]	23	88		
Visit 7: At least major improvement [Patient]	89	14		
Visit 7: Less than major improvement [Patient]	15	87		
Visit 8: At least major improvement [Patient]	82	15		
Visit 8: Less than major improvement [Patient]	16	79		
Visit 9: At least major improvement [Patient]	110	14		
Visit 9: Less than major improvement [Patient]	18	108		
Visit 3: At least major improvement [Investigator]	80	8		
Visit 3: Less than major improvement [Investigator	48	110		
Visit 4: At least major improvement [Investigator]	81	6		
Visit 4: Less than major improvement [Investigator	44	114		
Visit 5: At least major improvement [Investigator]	95	18		
Visit 5: Less than major improvement [Investigator	24	99		

Visit 6: At least major improvement [Investigator]	82	11		
Visit 6: Less than major improvement [Investigator	23	92		
Visit 7: At least major improvement [Investigator]	91	11		
Visit 7: Less than major improvement [Investigator	13	90		
Visit 8: At least major improvement [Investigator]	84	11		
Visit 8: Less than major improvement [Investigator	14	83		
Visit 9: At least major improvement [Investigator]	110	8		
Visit 9: Less than major improvement [Investigator	18	114		

Notes:

[97] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between visits.
[98] - 1 Patient excluded due to no post-baseline data.
Number of patients varies between visits.

Statistical analyses

Statistical analysis title	Visit 3: IMOS [Patients' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 3 records
Number considered patients with IMOS assessment data at this visit: 246 (Test group: 128 | Control group: 118)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[99]
P-value	< 0.0001 [100]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	61.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.77
upper limit	70.47

Notes:

[99] - Analysis followed an exploratory rather than confirmatory approach.

[100] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 4: IMOS [Patients' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 4 records
Number considered patients with IMOS assessment data at this visit: 245 (Test group: 125 | Control group: 120)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[101]
P-value	< 0.0001 [102]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	59.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.44
upper limit	69.09

Notes:

[101] - Analysis followed an exploratory rather than confirmatory approach.

[102] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 5: IMOS [Patients' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 5 records
Number considered patients with IMOS assessment data at this visit: 236 (Test group: 119 | Control group: 117)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[103]
P-value	< 0.0001 [104]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	64.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.72
upper limit	74.18

Notes:

[103] - Analysis followed an exploratory rather than confirmatory approach.

[104] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 6: IMOS [Patients' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 6 records
Number considered patients with IMOS assessment data at this visit: 208 (Test group: 105 | Control group: 103)

Comparison groups	Control group v Test group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[105]
P-value	< 0.0001 [106]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	63.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.09
upper limit	73.97

Notes:

[105] - Analysis followed an exploratory rather than confirmatory approach.

[106] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 7: IMOS [Patients' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 7 records
Number considered patients with IMOS assessment data at this visit: 205 (Test group: 104 | Control group: 101)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[107]
P-value	< 0.0001 [108]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	71.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	62.18
upper limit	81.26

Notes:

[107] - Analysis followed an exploratory rather than confirmatory approach.

[108] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 8: IMOS [Patients' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 8 records
Number considered patients with IMOS assessment data at this visit: 192 (Test group: 98 | Control group: 94)

Comparison groups	Control group v Test group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[109]
P-value	< 0.0001 [110]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	67.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.31
upper limit	78.13

Notes:

[109] - Analysis followed an exploratory rather than confirmatory approach.

[110] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 9: IMOS [Patients' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 9 records (either regular Visit 9 (Week 60±1) or early Termination Visit)
Number considered patients with IMOS assessment data at this visit: 250 (Test group: 128 | Control group: 122)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[111]
P-value	< 0.0001 [112]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	74.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	66.2
upper limit	82.72

Notes:

[111] - Analysis followed an exploratory rather than confirmatory approach.

[112] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 3: IMOS [Investigators' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 3 records
Number considered patients with IMOS assessment data at this visit: 246 (Test group: 128 | Control group: 118)

Comparison groups	Control group v Test group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[113]
P-value	< 0.0001 [114]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	55.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.19
upper limit	65.26

Notes:

[113] - Analysis followed an exploratory rather than confirmatory approach.

[114] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 4: IMOS [Investigators' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 4 records
Number considered patients with IMOS assessment data at this visit: 245 (Test group: 125 | Control group: 120)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[115]
P-value	< 0.0001 [116]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	59.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.56
upper limit	69.04

Notes:

[115] - Analysis followed an exploratory rather than confirmatory approach.

[116] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 5: IMOS [Investigators' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 5 records
Number considered patients with IMOS assessment data at this visit: 236 (Test group: 119 | Control group: 117)

Comparison groups	Control group v Test group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[117]
P-value	< 0.0001 [118]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	64.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.72
upper limit	74.18

Notes:

[117] - Analysis followed an exploratory rather than confirmatory approach.

[118] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 6: IMOS [Investigators' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 6 records
Number considered patients with IMOS assessment data at this visit: 208 (Test group: 105 | Control group: 103)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[119]
P-value	< 0.0001 [120]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	67.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.51
upper limit	77.32

Notes:

[119] - Analysis followed an exploratory rather than confirmatory approach.

[120] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 7: IMOS [Investigators' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 7 records
Number considered patients with IMOS assessment data at this visit: 205 (Test group: 104 | Control group: 101)

Comparison groups	Control group v Test group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[121]
P-value	< 0.0001 [122]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	76.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	67.82
upper limit	85.4

Notes:

[121] - Analysis followed an exploratory rather than confirmatory approach.

[122] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 8: IMOS [Investigators' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 8 records
Number considered patients with IMOS assessment data at this visit: 192 (Test group: 98 | Control group: 94)

Comparison groups	Control group v Test group
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[123]
P-value	< 0.0001 [124]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	74
Confidence interval	
level	95 %
sides	2-sided
lower limit	64.51
upper limit	83.51

Notes:

[123] - Analysis followed an exploratory rather than confirmatory approach.

[124] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Statistical analysis title	Visit 9: IMOS [Investigators' assessments]

Statistical analysis description:

Analysis is based on comparison of treatment arms regarding the proportion of patients with IMOS "At least major improvement" rating.

Basis: Visit 9 records (either regular Visit 9 (Week 60±1) or early Termination Visit)
Number considered patients with IMOS assessment data at this visit: 250 (Test group: 128 | Control group: 122)

Comparison groups	Control group v Test group

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[125]
P-value	< 0.0001 [126]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	79.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	71.93
upper limit	86.83

Notes:

[125] - Analysis followed an exploratory rather than confirmatory approach.

[126] - The presented risk difference refers to the difference of proportions [%] of patients with "At least least major improvement" IMOS rating. I.e. a positive value indicates more patients with better outcome category in test group compared to control.

Secondary: Global Assessment of Tolerability by Investigator and Patient

End point title	Global Assessment of Tolerability by Investigator and

End point description:

Assessment of tolerability of treatment has been done for test group patients after each of the three active treatment periods. Assessment has been done separately by patients and physicians on a 5-point verbal rating scale (items: "Very good", "Good", "Moderate", "Poor" and "Very poor").

Presented evaluation is related to binary categorization of assessments into categories "At least good" (i.e. summarizing "Very good" and "Good") and "Moderate or worse" (i.e. summarizing answers: "Moderate ", "Poor" and "Very poor").

End point type	Secondary

End point timeframe:

Visit 3 (Week 8 [+/- 1 week])
Visit 5 (Week 24 [+/- 1 week])
Visit 7 (Week 40 [+/- 1 week])
Early Termination Visit (if applicable)

Notes:

[127] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint has only been evaluated in the test group.

End point values	Test group			
Subject group type	Reporting group			
Number of subjects analysed	132[128]			
Units: Patients				
Visit 3: At least good [Patient]	126			
Visit 3: Moderate or worse [Patient]	2			
Visit 5: At least good [Patient]	118			
Visit 5: Moderate or worse [Patient]	0			
Visit 7: At least good [Patient]	100			
Visit 7: Moderate or worse [Patient]	0			
Early Term.Visit: At least good [Patient]	3			
Early Term.Visit: Moderate or worse [Patient]	1			
Visit 3: At least good [Investigator]	126			

Visit 3: Moderate or worse [Investigator]	2			
Visit 5: At least good [Investigator]	118			
Visit 5: Moderate or worse [Investigator]	0			
Visit 7: At least good [Investigator]	100			
Visit 7: Moderate or worse [Investigator]	0			
Early Term.Visit: At least good [Investigator]	2			
Early Term.Visit: Moderate or worse [Investigator]	2			

Notes:

[128] - Number of patients varies between visits.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Whole study period.

Adverse event reporting additional description:

As ATI and URTI occurrences were expected in the evaluated population and were part of efficacy analysis they were not regarded in the AE / SAE evaluation. Therefore events coded as J02, J03, J00, J06, J09, J10 and J01 (according to ICD-10) are not presented within the adverse event evaluation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Test Group

Reporting group description:

The test group received Tonsilotren tablets during Treatment Period I to III each for 8 weeks and - if needed - conventional symptomatic treatment for chronic tonsillitis.

Reporting group title	Control group

Reporting group description:

The control group was treated only with conventional symptomatic treatment if needed.

Serious adverse events	Test Group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 132 (3.03%)	3 / 124 (2.42%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 132 (0.76%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			

subjects affected / exposed	0 / 132 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 132 (0.76%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 132 (0.76%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Test Group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 132 (40.91%)	59 / 124 (47.58%)	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 132 (11.36%)	13 / 124 (10.48%)	
occurrences (all)	55	22	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	6 / 132 (4.55%)	2 / 124 (1.61%)	
occurrences (all)	8	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 132 (2.27%)	4 / 124 (3.23%)	
occurrences (all)	5	4	

Rhinitis allergic			
subjects affected / exposed	1 / 132 (0.76%)	5 / 124 (4.03%)	
occurrences (all)	1	8	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 132 (3.79%)	1 / 124 (0.81%)	
occurrences (all)	9	2	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	8 / 132 (6.06%)	12 / 124 (9.68%)	
occurrences (all)	9	14	
Bronchitis			
subjects affected / exposed	3 / 132 (2.27%)	9 / 124 (7.26%)	
occurrences (all)	3	9	
Otitis externa			
subjects affected / exposed	5 / 132 (3.79%)	1 / 124 (0.81%)	
occurrences (all)	12	1	
Sinusitis			
subjects affected / exposed	0 / 132 (0.00%)	5 / 124 (4.03%)	
occurrences (all)	0	7	
Laryngitis			
subjects affected / exposed	0 / 132 (0.00%)	4 / 124 (3.23%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2012	This amendment was implemented in Germany because of following German's ethics committee's (EC) request: 1. Sequential recruitment of patients: first 80 adult patients had to be recruited. Minors could only be recruited after the data of 80 adults who had passed the first 2 treatment cycles were presented to the German EC. This step was not required though as only 54 patients (adults) were recruited in total in Germany. 2. Specification of the study centers qualification: restriction to ear-nose-throat specialists.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported