Clinical trial results:
Double-blind, randomised, placebo-controlled study evaluating the efficacy and Safety of Tavipec® capsules in acute Rhinosinusitis
A prospective, multi-centre, parallel group, interventional clinical phase IV study

Summary

EudraCT number	2013-002977-23
Trial protocol	AT PL
Global end of trial date	24 December 2016

Results information

Result version number	v1 (current)
This version publication date	31 July 2022
First version publication date	31 July 2022
Summary attachment (see zip file)	TAV02-13_Synospsis_Final Study Report (Synospsis_TAV02-13.pdf)

Trial information

Trial identification

Sponsor protocol code	TAV2-13

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pharmazeutische Fabrik Montavit Ges.m.b.H.
Sponsor organisation address	Salzbergstraße 96, Absam, Austria, 6067
Public contact	Head of the Clinical Trial Department, Montavit Head Quarter Mag. Gabriele Zacke, 0043 0522357926234, gabriele.zacke@montavit.com
Scientific contact	Head of the Clinical Trial Department, Montavit Head Quarter Mag. Gabriele Zacke, 0043 0522357926234, gabriele.zacke@montavit.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2016
Global end of trial reached?	Yes
Global end of trial date	24 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Mean difference of an investigator-evaluated Major Symptom Score (MSS) of 20% between the verum group and the placebo group after 4 days of full medication dose

Protection of trial subjects:

Acute rhinosinusitis is generally a self-limiting disease and care for acute rhinosinusitis is primarily supportive and aims on alleviation of symptoms.
Therefore, no problems of ethics, acceptability, and feasibility are assumed to arise from the use of a placebo-concurrent control group.
Patients were advised about re-consulting at any time during the study if there was a significant worsening of symptoms or occurrence of complications. For safety reason, these subjects would have been deemed clinical failures and promptly scheduled for a treatment failure visit.
A close monitoring of patients was done. After baseline next evaluation was performed following four days of treatment, so the detection of a possible worsening of the clinical condition has been guaranteed. In case of treatment failure at this time point, treatment would have been discontinued.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	04 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	Poland: 222
Country: Number of subjects enrolled	Austria: 46
Worldwide total number of subjects	268
EEA total number of subjects	268

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	251
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between Jan 2014 and Oct 2016 in 4 study sites in Austria and in 6 study sites in Poland by general practitioner, specialist of ENT or by hospital doctors from ENT clinics.
Moreover, recruitment advertising campaigns in Vienna and Innsbruck were carried out (e.g. posters and postcards, which were released by ECs).

Pre-assignment

Screening details:

There was no screening period as it was an acute treatment.
Only patients suffering from uncomplicated acute viral rhinosinusitis with onset of first symptoms within two days before start of treatment were recruited.
In summery, 288 patients were assessed for eligibility (safety group) of which 20 patients were excluded after inclusion (n= 268).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The IMPs were supplied in a double blind way. Each patient received a medication bottle with capsules. In the placebo group the bottles contained placebo identical in appearance, shape and taste to verum, being indistinguishable from their respective active investigational drug. Neither the labelled bottle nor the capsules of the placebo and the verum group differ. Moreover, Investigators received an emergency envelope of each patient.
During the conduct of the trial no unblinding was performed

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

In summary 288 patients were assessed and randomised.
Placebo (n = 141)
9 patients were excluded after inclusion:
- Not meeting inclusion criteria (n = 7)
- Not allowed concomitant medication (n = 1)
- No pregnancy test done (n = 1)

Arm type	Placebo
Investigational medicinal product name	Placebo capsules, enteric-coated
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsules with gastroresistant coating were filled with medium-chain triglycerides. Patients were instructed to swallow placebo capsules as a whole with some liquid, 30 minutes before a meal. The application was three times daily two capsules (2-2-2)

Arm title	Tavipec

Arm description:

In summary 288 patients were assessed and randomised.
Tavipec group (n = 147)
11 patients were excluded after inclusion:
- Not meeting inclusion criteria (n = 8)
- Not allowed concomitant medication (n = 1)

- Use of expired drug (n = 1)
- No pregnancy test done (n = 1)

Arm type	Active comparator
Investigational medicinal product name	Tavipec® capsule, enteric-coated
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tavipec capsules with gastroresistant coating contained 150 mg Spicae aetheroleum (per capsule) as the active ingredient. Patients were instructed to swallow Tavipec capsules as a whole with some liquid, 30 minutes before a meal. The application was three times daily two capsules (2-2-2)

Number of subjects in period 1	Placebo	Tavipec
Started	132	136
Follow-up	132	136
PP Analysis day 5	125	128
PP Analysis day 8	116	122
Completed	116	122
Not completed	16	14
Consent withdrawn by subject	9	8
Adverse event, non-fatal	-	1
Need for antibiotic treatment	6	5
Retrospective data entry	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

In summary 288 patients were was assessed for eligibility and randomised (Tavipec = 147 patients / Placebo = 141 patients). This number of patients was considered as Safety population (Safety analysis). 11 patients were excluded after Inclusion in the Tavipec group (n = 136) and 9 patients were excluded after Inclusion in the Placebo group (n = 132). This was considered as intended-to-treat (ITT) population, which received allocated intervention at least once.

Reporting group values	Overall trial	Total	
Number of subjects	268	268	
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 Units: years			
arithmetic mean	39.4020		
full range (min-max)	18 to 74	-	
Gender categorical Units: Subjects			
Female	150	150	
Male	118	118	
Weight Units: kg			
arithmetic mean	74,0493		
full range (min-max)	44,20 to 136	-	
Height Units: cm			
arithmetic mean	172.26		
full range (min-max)	154 to 196	-	
Body temperature Units: °C			
arithmetic mean	37.1412		
full range (min-max)	34.20 to 38.20	-	
Onset of rhinosinusitis Units: day			
arithmetic mean	2.2351		
standard deviation	± 0.73487	-	

MSS at baseline			
MSS = major symptom score			
Units: MSS			
arithmetic mean	8.6866		
standard deviation	± 1.29775	-	

Subject analysis sets

Subject analysis set title	Placebo group
Subject analysis set type	Intention-to-treat
Subject analysis set description: Received allocated intervention at least once (ITT-population)	
Subject analysis set title	Tavipec group
Subject analysis set type	Intention-to-treat
Subject analysis set description: Received allocated intervention at least once (ITT-population)	

Reporting group values	Placebo group	Tavipec group	
Number of subjects	132	136	
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 Units: years			
arithmetic mean	40.447	38,3897	
full range (min-max)	18 to 74	18 to 72	
Gender categorical Units: Subjects			
Female	70	80	
Male	62	56	
Weight Units: kg			
arithmetic mean	73.9129	74.1816	
full range (min-max)	48.00 to 118.00	44.20 to 136.00	
Height Units: cm			
arithmetic mean	171.92	172.60	
full range (min-max)	154 to 190	156 to 196	
Body temperature Units: °C			
arithmetic mean	37.0908	37.1897	
full range (min-max)	34.20 to 38.20	34.80 to 38.20	

Onset of rhinosinusitis Units: day arithmetic mean standard deviation	 2.2045 ± 0.72826	 2.2647 ± 0.74272	
MSS at baseline			
MSS = major symptom score			
Units: MSS arithmetic mean standard deviation	 8.6288 ± 1.32161	 8.7426 ± 1.27655	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

In summary 288 patients were assessed and randomised.
Placebo (n = 141)
9 patients were excluded after inclusion:
- Not meeting inclusion criteria (n = 7)
- Not allowed concomitant medication (n = 1)
- No pregnancy test done (n = 1)

Reporting group title	Tavipec

Reporting group description:

In summary 288 patients were assessed and randomised.
Tavipec group (n = 147)
11 patients were excluded after inclusion:
- Not meeting inclusion criteria (n = 8)
- Not allowed concomitant medication (n = 1)
- Use of expired drug (n = 1)
- No pregnancy test done (n = 1)

Subject analysis set title	Placebo group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Received allocated intervention at least once (ITT-population)

Subject analysis set title	Tavipec group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Received allocated intervention at least once (ITT-population)

Primary: Mean difference of an investigator-evaluated MSS between the verum group and the placebo group after 4 days of full medication dose (PP day 5)

End point title	Mean difference of an investigator-evaluated MSS between the verum group and the placebo group after 4 days of full medication dose (PP day 5)

End point description:

Primary efficacy evaluation was the mean difference of an investigator-evaluated MSS (of >5 and <12 (of a maximum 15 score points)) of 20 % between the verum and placebo group after 4 days of full medication dose.
During a 4-day treatment course the MSS improved by a mean of 3,7266 and 3,0800 score points in the Tavipec and placebo group, respectively in the PP day 5 population. Resulting in a difference between both groups of 0,6466 score points. The difference between both groups in terms of improvement was in favour of Tavipec, however reached no statistical significance.

End point type	Primary

End point timeframe:

Assessed after 4 days of full medication dose (PP day 5)

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125[1]	128[2]		
Units: MSS				
arithmetic mean (standard deviation)				
MSS Diff	3.080 (± 2.52)	3.727 (± 2.04)		

Notes:

[1] - PP-population

[2] - PP-population

Statistical analyses

Statistical analysis title	2-sided (α= 5%) Mann-Whitney test (rank-sum test)

Statistical analysis description:

Primary efficacy parameter was the mean difference of an investigator-evaluated Major Symptom Score (of >5 & <12 (of max. 15 score points)) of 20% between the Tavipec and Placebo group after 4 days of full medication dose. A sum sore from signs and symptoms was formed (0= none, 1 = mild, 2 = moderate, 3 = severe), comparing changes from baseline in both treatment groups.

Comparison groups	Placebo group v Tavipec group
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[3] - The main efficacy variable is quantitative, however, not necessarily normally distributed; therefore a two-sided (α= 5%) Mann-Whitney test (rank-sum test) was applied to test the following hypothesis (null hypothesis):
H0: μ MSS (day 5) placebo = μ MSS (day 5) verum
H1: μ MSS (day 5) placebo ≠ μ MSS (day 5) verum

Secondary: Mean difference of an investigator-evaluated MSS between the verum group and the placebo group after 7 days of full medication dose (PP day 8)

End point title	Mean difference of an investigator-evaluated MSS between the verum group and the placebo group after 7 days of full medication dose (PP day 8)

End point description:

After 7 days of full medication dose the mean change of MSS from baseline was 6.1885 score points in the Tavipec group and 5.0689 score points in the placebo group. The Mann-Whitney test shows a significance level of p = 0.049. Thus it can be concluded that the MSS at day 8 for the Tavipec group is significantly lower than in the placebo group. Taking the aimed 20 % difference into account the significance level decreases to p = 0.893

End point type	Secondary

End point timeframe:

Assessed after 7 days of full medication dose (PP day 8)

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116[4]	122[5]		
Units: MSS				
arithmetic mean (standard deviation)				
MSS day 0	8.5948 (± 1.29197)	8.7295 (± 1.27944)		
MSS day 7	3.5259 (± 2.83905)	2.5410 (± 1.76816)		

Notes:

[4] - PP-population day 8

[5] - PP-population day 8

Statistical analyses

Statistical analysis title	2-sided (α= 5%) Mann-Whitney test (rank-sum test)
Comparison groups	Tavipec group v Placebo group
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 4 days of full medication dose (PP day 5)

End point title	Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 4 days of full medication dose (PP day 5)

End point description:

During a 4-day treatment course the adapted MSS dropped from 10.4375 and 10.3280 score points in the Tavipec and placebo group, respectively at baseline to 5.9531 and 6.7040 score points at day 5, corresponding to an improvement of 4.4844 and 3.6240 score points in those patients. The difference between both groups in terms of improvement was in favour of Tavipec, however reached no statistical significance (p = 0.065). Taking the aimed 20 % difference into account, the significance level decrease to p = 0.456.

End point type	Secondary

End point timeframe:

Assessed after 4 days of full medication dose (PP day 5).

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125[6]	128[7]		
Units: MSS				
arithmetic mean (standard deviation)				
adapted MSS day 0	10.3280 (± 1.58509)	10.4375 (± 1.44042)		
adapted MSS day 5	6.7040 (± 3.26028)	5.9531 (± 2.58968)		

Notes:

[6] - PP-population (day 5)

[7] - PP-population (day 5)

Statistical analyses

Statistical analysis title	2-sided (α= 5%) Mann-Whitney test (rank-sum test)
Comparison groups	Tavipec group v Placebo group
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 7 days of full medication dose

End point title	Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 7 days of full medication dose

End point description:

As a secondary efficacy parameter the mean difference of an adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 7 days of full medication dose was evaluated. The analysis was performed on the PP-day 8 population, consisting of 238 subjects (122 Tavipec group, 116 placebo group).
The difference of the adapted MSS (day 0 and day 8) was 7.4590 score points in the verum group and 5.9741 score points in the placebo group. The Mann-Whitney test shows significance level of p = 0.040 and it can be concluded that the adapted MSS at day 8 for the verum group is significantly lower than in the placebo group. Taking the aimed 20 % difference into account, the significance level decreased to p = 0.770.

End point type	Secondary

End point timeframe:

Assessed after after 7 days of full medication dose

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116[8]	122[9]		
Units: MSS				
arithmetic mean (standard deviation)				
Adapted MSS day 0	10.2500 (± 1.55968)	10.4590 (± 1.46670)		
Adapted MSS day 8	4.2759 (± 3.49555)	3.0000 (± 2.10862)		

Notes:

[8] - PP-population day 8

[9] - PP-population day 8

Statistical analyses

Statistical analysis title	2-sided (α= 5%) Mann-Whitney test (rank-sum test)
Comparison groups	Tavipec group v Placebo group
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Global impact of disease on QOL as assessed by patient

End point title	Global impact of disease on QOL as assessed by patient

End point description:

Patients were asked to rate the impact of symptoms on their quality of life on a verbal rating scale (VRS) ranging from 0 (not troublesome) to 10 (worst thinkable troublesome). Valuations from 0-3, 4-7 and 8-10 indicating mild, moderate and severe impact.
The mean QoL score dropped from 6.84 at baseline to 3.60 after 4 days of full medication dose and to 1.60 score points after 7 days of full medication dose in the Tavipec group and from 6.91 at baseline, to 4.59 and 3.04 in the placebo group. The Mann-Whitney test shows a significane level of p = 0.0000027678 at day 5 and p=0,0000000051 at day 8 and therefore it can be concluded that the QoL score in the Tavipec group is significantly lower than for the placebo group after 4 and 7 days of full medication dose.

Below, the results for day 0 and day 5 are shown. Complete Results are attachment.

End point type	Secondary

End point timeframe:

Assessed after 4 and 7 days of full medication dose

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125[10]	128[11]		
Units: QOL score				
arithmetic mean (standard deviation)				
QoL day 0	6.91 (± 1.556)	6.84 (± 1.673)		
QoL day 5	4.59 (± 1.972)	3.60 (± 1.638)		

Notes:

[10] - PP-population day 8

[11] - PP-population (day 0 and day 5)

Attachments (see zip file)	TAV02-13_Results sec. endpint_QoL/TAV02-13_Results sec.

Statistical analyses

Statistical analysis title	2-sided (α= 5%) Mann-Whitney test (rank-sum test)
Comparison groups	Placebo group v Tavipec group

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: % of patients with improvement of health-related QOL score as revealed by SNOT-22 by at least ten score points

End point title	% of patients with improvement of health-related QOL score as revealed by SNOT-22 by at least ten score points

End point description:

Patients were asked to fill in the SNOT-22 questionnaire, a disease-specific, health-related quality-of-life-test comprising 22 items. Patients rated the severity of symptoms on a 6-point (0-5) Likert-scale, giving a total score ranging between 0 and 110 by summing up all the symptoms. Higher score indicating greater rhinosinusitis-related health burden. Below the results for SNOT-22 score points at day 0 and day 5 are shown. Complete results of % of patients with improvement of health-related QOL score as revealed by SNOT-22 by at least ten score points are shown in the attachment.

End point type	Secondary

End point timeframe:

Assessed after 4 and 7 days of full medication dose

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	128		
Units: SNOT score points				
arithmetic mean (standard deviation)				
SNOT-22 day 0	43.5323 (± 19.05722)	27.5484 (± 18.90126)		
SNOT-22 day 5	46.6641 (± 19.05495)	24.2734 (± 15.12141)		

Attachments (see zip file)	TAV02-13_Results sec. endpoint_SNOT-22/TAV02-13_Results

Statistical analyses

Statistical analysis title	2-sided (α= 5%) Mann-Whitney test (rank-sum test)
Comparison groups	Placebo group v Tavipec group
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Chi-Square for SNOT-22
Statistical analysis description: Chi-Square tests for categorical variables	
Comparison groups	Placebo group v Tavipec group
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs assessed by the investigator have to be reported to Montavit by e-mail within 30 days from receipt.
All SAEs have to be reported at latest within 24 hours of the first awareness of the event.

Adverse event reporting additional description:

At each visit, all AEs either reported by the patient or observed by the investigator were evaluated and recorded into the CRF. Each AE was described by its duration, frequency, severity, its relationship to the trial medication, its influence on administration or study medication and a possible requirement of therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo group
Reporting group description: -	
Reporting group title	Tavipec group

Reporting group description: -

Serious adverse events	Placebo group	Tavipec group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 141 (0.00%)	0 / 147 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo group	Tavipec group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 141 (5.67%)	26 / 147 (17.69%)	
Investigations			
Blood pressure increased	Additional description: Investigations (cardiac and vascular) Relationship to IMP: unlikely Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache	Additional description: Relationship to IMP: possibly (n=1), unlikely (n=1) Severity: mild (n=1), moderate (n=1)		

subjects affected / exposed	0 / 141 (0.00%)	2 / 147 (1.36%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Vertigo	Additional description: Relationship to IMP: Unlikely Severity: mild Relationship to Placebo: Unrelated Severity: moderate		
subjects affected / exposed	1 / 141 (0.71%)	1 / 147 (0.68%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Relationship to IMP: probably Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Nausea	Additional description: Relationship to IMP: possibly (n = 4) Severity: mild (n = 2), moderate (n = 2) Relationship to Placebo: possibly (n = 1) Severity: mild (n = 1)		
subjects affected / exposed	1 / 141 (0.71%)	4 / 147 (2.72%)	
occurrences (all)	1	4	
Abdominal pain	Additional description: Relationship to IMP: possibly (n = 13), unrelated (n = 1) Severity: mild (n = 7), moderate (n = 6), severe (n = 1) Relationship to Placebo: possibly (n = 2), unrelated (n = 1) Severity: mild (n = 3)		
subjects affected / exposed	3 / 141 (2.13%)	14 / 147 (9.52%)	
occurrences (all)	3	14	
Appendicitis	Additional description: Relationship to IMP: unrelated Severity: moderate		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Diarrhoea	Additional description: Relationship to IMP: possibly Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Breath odour	Additional description: Relationship to IMP: possibly Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Dysgeusia	Additional description: Relationship to IMP: probably Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Feeling of fullness in abdomen	Additional description: Relationship to Placebo: unlikely Severity: mild		

subjects affected / exposed	1 / 141 (0.71%)	0 / 147 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Menstrual discomfort	Additional description: Relationship to IMP: unrelated Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Additional description: Relationship to Placebo: unlikely Severity: mild		
subjects affected / exposed	1 / 141 (0.71%)	0 / 147 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Mental disorder	Additional description: Relationship to IMP: unrelated Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Sleep disturbance	Additional description: Relationship to Placebo: unlikely Severity: moderate		
subjects affected / exposed	1 / 141 (0.71%)	0 / 147 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Tonsillitis	Additional description: Relationship to IMP: unrelated Severity: mild		
subjects affected / exposed	0 / 141 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Herpes virus infection	Additional description: Relationship to Placebo: unrelated Severity: mild		
subjects affected / exposed	1 / 141 (0.71%)	0 / 147 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2014	Additional study sites and centres in order to not fail to recruit to the original target within the specified time, it was decided to include additional study sites. Before site initiation visit 8 study centres withdrew their consent to participate after having been approved by the ethics committee, due to high administrative effort of conducting a clinical trial. The study was extended to Poland and six study centres have been included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

n.a

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31210177