Clinical trial results:
A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial to assess efficacy and safety of the herbal medicinal product Sinupret extract coated tablets in patients with chronic rhinosinusitis

Summary

EudraCT number	2015-001952-31
Trial protocol	DE
Global end of trial date	23 August 2017

Results information

Result version number	v1 (current)
This version publication date	06 January 2023
First version publication date	06 January 2023

Trial information

Trial identification

Sponsor protocol code	CRS-03

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bionorica SE
Sponsor organisation address	Kerschensteinerstraße 11-15, Neumarkt, Germany, 92318
Public contact	Head of cooperate communication, Bionorica SE, info@bionorica.de
Scientific contact	Head of Research and Development, Bionorica SE, research.development@bionorica.de

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	19 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2017
Global end of trial reached?	Yes
Global end of trial date	23 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the herbal medicinal product Sinupret extract versus placebo in the treatment of chronic rhinosinusitis (CRS) in adults.

Protection of trial subjects:

This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2016
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: 363
Country: Number of subjects enrolled	Germany: 209
Worldwide total number of subjects	572
EEA total number of subjects	572

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	489
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 624 patients were enrolled; of these, 51 were not randomized and not treated. In total, 573 (91.8% of the enrolled population) patients were randomized, of whom 1 patient was not treated. In total, 285 patients were randomized to treatment with Sinupret extract (test IMP) and 287 patients to treatment with placebo.

Pre-assignment

Screening details:

The trial consists of a screening phase of up to 2 weeks (V1 to V2). Patients were required to have CRS symptoms for more than 52 weeks prior to enrolment, diagnosis of CRS confirmed by an ENT-specialist, and severe symptoms at screening and baseline (MSS of at least 10 points).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo coated tablets

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet placebo three times a day.

Arm title	Sinupret extract

Arm description:

Sinupret extract coated tablet containing 160 mg native dry extract; 1 tablet tid.

Arm type	Experimental
Investigational medicinal product name	Sinupret extract
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Sinupret extract coated tablet containing 160 mg native dry extract; 1 tablet tid for 16 weeks.

Number of subjects in period 1	Placebo	Sinupret extract
Started	287	285
End of treatment	259	257
End of observation	255	252
Completed	255	252
Not completed	32	33
Adverse event, serious fatal	1	-
Consent withdrawn by subject	11	6
Extreme CRS-related pain symptomatology	2	3
Reasons not related to disease	1	1
Adverse event, non-fatal	11	10
Pregnancy	-	1
Non-compliance with study drug	1	2
Lost to follow-up	4	4
Progressive disease	1	4
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo coated tablets	
Reporting group title	Sinupret extract
Reporting group description:	
Sinupret extract coated tablet containing 160 mg native dry extract; 1 tablet tid.	

Reporting group values	Placebo	Sinupret extract	Total
Number of subjects	287	285	572
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	244	245	489
From 65-84 years	43	40	83
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	46.4	45.9	
standard deviation	± 14.73	± 14.06	-
Gender categorical			
Units: Subjects			
Female	168	164	332
Male	119	121	240

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo coated tablets	
Reporting group title	Sinupret extract
Reporting group description:	
Sinupret extract coated tablet containing 160 mg native dry extract; 1 tablet tid.	
Subject analysis set title	Sinupret extract - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients with at least one documented application of IMP and with at least one observed post-baseline value for the primary efficacy variable (MSSINV).	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients with at least one documented application of IMP and with at least one observed post-baseline value for the primary efficacy variable (MSSINV).	
Subject analysis set title	Sinupret extract - SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of trial medication; patients who were treated with more than one type of clinical trial medication by mistake were analyzed according to the clinical trial medication they received the longest.	
Subject analysis set title	Placebo - SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of trial medication; patients who were treated with more than one type of clinical trial medication by mistake were analyzed according to the clinical trial medication they received the longest.	
Subject analysis set title	Sinupret extract - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients from the FAS without major protocol deviations.	
Subject analysis set title	Placebo - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients from the FAS without major protocol deviations.	

Primary: MSS-INV

End point title	MSS-INV
End point description:	
The primary efficacy endpoint was the MSS-INV at V7.	
End point type	Primary
End point timeframe:	
After 12 weeks of treatment (Visit 7).	

End point values	Sinupret extract - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	279	283		
Units: Score points				
arithmetic mean (standard deviation)	5.4 (± 3.34)	5.6 (± 3.69)		

Statistical analyses

Statistical analysis title	Van Elteren test adjusted for centre
Comparison groups	Sinupret extract - FAS v Placebo - FAS
Number of subjects included in analysis	562
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3192
Method	Van Elteren test
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.45

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs ocurring between V2 (randomisation) and V8 (end of observation) are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Sinupret extract
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Sinupret extract	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 285 (1.05%)	5 / 287 (1.74%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Parathyroid tumour benign			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Meniere's disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Adjustment disorder with depressed mood			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hyperparathyroidism			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
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: 0 %

Non-serious adverse events	Sinupret extract	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 285 (39.65%)	116 / 287 (40.42%)	
Vascular disorders			
Circulatory collapse			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	2	
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			

Dental operation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Tooth extraction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Mucosal dryness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	2 / 287 (0.70%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			

Menstrual disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 285 (1.05%)	4 / 287 (1.39%)	
occurrences (all)	3	4	
Dysphonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	2 / 287 (0.70%)	
occurrences (all)	0	2	
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	1 / 287 (0.35%)	
occurrences (all)	2	1	
Nasal congestion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Nasal obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Noninfective bronchitis			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 285 (2.11%)	6 / 287 (2.09%)	
occurrences (all)	6	7	
Pharyngeal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	2 / 287 (0.70%)	
occurrences (all)	1	2	
Pharyngeal oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Pleurisy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Rhinalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 285 (1.05%)	3 / 287 (1.05%)	
occurrences (all)	3	3	
Throat irritation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract inflammation			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Product issues			
Device failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Blood alkaline phosphatase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Blood creatine increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Blood glucose increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Blood urea increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Body temperature decreased			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
C-reactive protein increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	2 / 287 (0.70%)	
occurrences (all)	0	2	
Eosinophil count increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 285 (1.05%)	2 / 287 (0.70%)	
occurrences (all)	3	2	
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Neutrophil count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Bone contusion			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Concussion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	0 / 287 (0.00%)	
occurrences (all)	2	0	
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Hand fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Humerus fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Ligament sprain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	2 / 287 (0.70%)	
occurrences (all)	2	2	
Muscle injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	

Nail injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Tendon rupture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Thermal burn			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Tooth fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	21 / 285 (7.37%)	14 / 287 (4.88%)	
occurrences (all)	27	17	
Migraine			

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	1 / 287 (0.35%)	
occurrences (all)	3	4	
Paraesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Radiculopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Sciatica			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Sensory disturbance			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Somnolence			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 285 (1.05%)	1 / 287 (0.35%)	
occurrences (all)	4	1	
Tension headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Trigeminal neuralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Microcytic anaemia			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Thrombocytosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear congestion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Ear discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	1 / 287 (0.35%)	
occurrences (all)	2	1	
Ear pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	1 / 287 (0.35%)	
occurrences (all)	2	1	
Tinnitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Vertigo			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 285 (0.70%)	1 / 287 (0.35%)	
occurrences (all)	3	1	
Eye disorders			
Eye pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	3	
Ocular hyperaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Abdominal distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	4 / 287 (1.39%)	
occurrences (all)	1	5	
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 285 (1.75%)	6 / 287 (2.09%)	
occurrences (all)	5	6	
Breath odour			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Colitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 285 (2.81%)	8 / 287 (2.79%)	
occurrences (all)	9	9	
Diverticulum intestinal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	3 / 287 (1.05%)	
occurrences (all)	2	3	
Dysphagia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Flatulence			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	2 / 287 (0.70%)	
occurrences (all)	0	2	
Food poisoning			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	1 / 287 (0.35%)	
occurrences (all)	2	1	
Gastric disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	

Gastritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Haematochezia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Lip swelling			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 285 (1.40%)	0 / 287 (0.00%)	
occurrences (all)	4	0	
Toothache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Vomiting			
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 285 (1.40%)	0 / 287 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 285 (2.81%)	0 / 287 (0.00%)	
occurrences (all)	8	0	
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	2 / 287 (0.70%)	
occurrences (all)	1	2	
Psoriasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Rash papular			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Rash pruritic			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Skin hypopigmentation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Skin odour abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Urticaria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Nephrolithiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Urine odour abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Back pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	2 / 287 (0.70%)	
occurrences (all)	0	2	
Musculoskeletal stiffness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	2 / 287 (0.70%)	
occurrences (all)	0	2	
Spinal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Infections and infestations			
Acute sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	2 / 287 (0.70%)	
occurrences (all)	1	2	
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 285 (1.05%)	2 / 287 (0.70%)	
occurrences (all)	3	2	
Bronchitis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Conjunctivitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Cystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 285 (1.05%)	4 / 287 (1.39%)	
occurrences (all)	3	4	
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Gastroenteritis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Haemophilus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	

Laryngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Nasal herpes			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Oral herpes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	2 / 287 (0.70%)	
occurrences (all)	1	2	
Pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	5 / 287 (1.74%)	
occurrences (all)	0	6	
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Respiratory tract infection viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 285 (0.70%)	0 / 287 (0.00%)	
occurrences (all)	2	0	
Rotavirus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Skin infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Soft tissue infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Tonsillitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 285 (2.11%)	4 / 287 (1.39%)	
occurrences (all)	7	4	
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 285 (1.05%)	0 / 287 (0.00%)	
occurrences (all)	3	0	
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	1 / 287 (0.35%)	
occurrences (all)	1	1	
Viral pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	29 / 285 (10.18%)	32 / 287 (11.15%)	
occurrences (all)	30	35	
Metabolism and nutrition disorders			
Fluid imbalance			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 285 (0.00%)	1 / 287 (0.35%)	
occurrences (all)	0	1	
Lactose intolerance			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 285 (0.35%)	0 / 287 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported