Clinical trial results:
A multicentre, randomized, double-blind, placebo-controlled, parallel group study to assess efficacy and safety of two dosages of a herbal medicinal product (dry extract BNO 1016) in patients with chronic rhinosinusitis

Summary

EudraCT number	2011-003623-35
Trial protocol	PL DE CZ BE
Global end of trial date	03 April 2014

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-02

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	22 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of two dosages (240 mg and 480 mg per day) of a herbal medicinal product (BNO 1016) compared with placebo in the treatment of chronic rhinosinusitis 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	01 September 2012
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: 465
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Czechia: 158
Country: Number of subjects enrolled	Germany: 279
Worldwide total number of subjects	929
EEA total number of subjects	929

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)	828

From 65 to 84 years	101
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of 1190 patients screened at visit 1, 929 patients were randomised at visit 2 and received investigational treatment (27 patients at 2 sites in Belgium; 158 patients at 16 sites in the Czech Republic, 279 patients at 27 sites in Germany, and 465 patients at 22 sites in Poland).

Pre-assignment

Screening details:

The clinical trial comprised a screening phase of up to two weeks (Visit 1 – Visit 2). At Visit 1, patients were consecutively screened for fulfilling the criteria of a Chronic Rhino Sinusitis [CRS] at the trial sites. Patients with nasal polyps were excluded. An allergic origin of CRS was ruled out by skin testing (Prick test).

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.
Active Ingredients: None
Mode of Administration: Oral

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:

3 x 2 placebo tablets per day

Arm title	BNO 1016 240mg

Arm description:

Mode of Administration: Oral
Dose: 240 mg BNO 1016 (low dose verum group): one 80 mg CT of BNO 1016 plus one matching placebo CT three times daily (tid)

Arm type	Experimental
Investigational medicinal product name	BNO 1016 coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Mode of Administration: Oral
Dose: 240 mg BNO 1016 (low dose verum group): one 80 mg CT of BNO 1016 plus one matching placebo CT three times daily (tid)

Arm title	BNO 1016 480mg

Arm description:

480 mg BNO 1016 (high dose verum group): two 80 mg CT of BNO 1016 tid

Arm type	Experimental
Investigational medicinal product name	BNO 1016 coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Mode of Administration: Oral
Dose: 480 mg BNO 1016 (high dose verum group): two 80 mg CT of BNO 1016 tid

Number of subjects in period 1[1]	Placebo	BNO 1016 240mg	BNO 1016 480mg
Started	303	309	303
End of treatment	287	293	280
End of observation	281	289	275
Completed	281	289	275
Not completed	22	20	28
Consent withdrawn by subject	5	6	7
Appearance of exclusion criterion 16	1	-	1
Adverse event, non-fatal	5	5	9
Appearance of exclusion criterion 19	1	-	-
Poor compliance	2	-	1
Pregnancy	1	-	-
No specific reason characterized by patient	1	-	-
Lost to follow-up	1	3	1
Not permitted concomicant medication	5	4	7
Harmful situation for the patient	-	1	-
Health resort	-	-	1
Lack of efficacy	-	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Reasons for excluding patients after the screening period, 14 out of 929, were not documented in detail. Thus, patients of the full analysis set (n=915) are reported only.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo coated tablets. Active Ingredients: None Mode of Administration: Oral	
Reporting group title	BNO 1016 240mg
Reporting group description:	
Mode of Administration: Oral Dose: 240 mg BNO 1016 (low dose verum group): one 80 mg CT of BNO 1016 plus one matching placebo CT three times daily (tid)	
Reporting group title	BNO 1016 480mg
Reporting group description:	
480 mg BNO 1016 (high dose verum group): two 80 mg CT of BNO 1016 tid	

Reporting group values	Placebo	BNO 1016 240mg	BNO 1016 480mg
Number of subjects	303	309	303
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	44.0	43.8	45.1
standard deviation	± 14.4	± 14.7	± 15.3
Gender categorical Units: Subjects			
Female	195	175	192
Male	108	134	111

Reporting group values	Total		
Number of subjects	915		
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			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	562		
Male	353		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo coated tablets. Active Ingredients: None Mode of Administration: Oral	
Reporting group title	BNO 1016 240mg
Reporting group description:	
Mode of Administration: Oral Dose: 240 mg BNO 1016 (low dose verum group): one 80 mg CT of BNO 1016 plus one matching placebo CT three times daily (tid)	
Reporting group title	BNO 1016 480mg
Reporting group description:	
480 mg BNO 1016 (high dose verum group): two 80 mg CT of BNO 1016 tid	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS for the efficacy analyses included all randomised patients with at least one documented application of trial medication (BNO 1016 or placebo) and post-baseline MSS data.	
Subject analysis set title	BNO 1016 240mg - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS for the efficacy analyses included all randomised patients with at least one documented application of trial medication (BNO 1016 or placebo) and post-baseline MSS data.	
Subject analysis set title	BNO 1016 480mg - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS for the efficacy analyses included all randomised patients with at least one documented application of trial medication (BNO 1016 or placebo) and post-baseline MSS data.	
Subject analysis set title	Placebo - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS for the efficacy analyses included all FAS patients who did not show protocol deviations which could have had a relevant influence on the assessment of the primary endpoint. Patients who prematurely discontinued the trial due to premature termination caused by AE, lack of efficacy or any other reason which could have been associated with lack of efficacy or safety, were also allocated to the PPS if relevant protocol violations did not occur.	
Subject analysis set title	BNO 1016 240mg - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS for the efficacy analyses included all FAS patients who did not show protocol deviations which could have had a relevant influence on the assessment of the primary endpoint. Patients who prematurely discontinued the trial due to premature termination caused by AE, lack of efficacy or any other reason which could have been associated with lack of efficacy or safety, were also allocated to the PPS if relevant protocol violations did not occur.	
Subject analysis set title	BNO 1016 480mg - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS for the efficacy analyses included all FAS patients who did not show protocol deviations which could have had a relevant influence on the assessment of the primary endpoint. Patients who prematurely discontinued the trial due to premature termination caused by AE, lack of efficacy or any other reason	

which could have been associated with lack of efficacy or safety, were also allocated to the PPS if relevant protocol violations did not occur.

Subject analysis set title	Placebo - SES
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population described by the SES included all randomised patients with at least one documented application of trial medication (BNO 1016 or placebo) and any post-baseline safety data.

Subject analysis set title	BNO 1016 240mg - SES
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population described by the SES included all randomised patients with at least one documented application of trial medication (BNO 1016 or placebo) and any post-baseline safety data.

Subject analysis set title	BNO 1016 480mg - SES
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population described by the SES included all randomised patients with at least one documented application of trial medication (BNO 1016 or placebo) and any post-baseline safety data.

Subject analysis set title	Placebo - mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mFAS for sensitivity analysis of the primary endpoint included all randomised patients with at least one documented application of trial medication regardless whether they had any post-baseline MSS data documented or not.

Subject analysis set title	BNO 1016 240mg - mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mFAS for sensitivity analysis of the primary endpoint included all randomised patients with at least one documented application of trial medication regardless whether they had any post-baseline MSS data documented or not.

Subject analysis set title	BNO 1016 480mg - mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mFAS for sensitivity analysis of the primary endpoint included all randomised patients with at least one documented application of trial medication regardless whether they had any post-baseline MSS data documented or not.

Primary: MSS-INV

End point title	MSS-INV

End point description:

The average over V5 and V6 for the MSS-INV was calculated as arithmetic mean of 2 investigator ratings (score V5 + score V6 divided by 2).

End point type	Primary

End point timeframe:

Treatment week 8 (V5) until week 12 (V6) after treatment start

End point values	Placebo	BNO 1016 240mg	BNO 1016 480mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	285	293	278	
Units: Score points				
arithmetic mean (standard deviation)	5.3 (± 3.0)	5.1 (± 2.5)	5.1 (± 2.4)	

Statistical analyses

Statistical analysis title	Wilcoxon Mann-Whitney test adjusted for "Centre"
Comparison groups	Placebo v BNO 1016 480mg
Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9649
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.0449
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.045
upper limit	1.956
Variability estimate	Standard error of the mean
Dispersion value	1.021

Statistical analysis title	Wilcoxon Mann-Whitney test adjusted for "Centre"
Comparison groups	Placebo v BNO 1016 240mg
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7252
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	0.356
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.361
upper limit	2.343
Variability estimate	Standard error of the mean
Dispersion value	1.014

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs occurring between V2 (randomisation) and V7 (end of observation) are reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	BNO 1016 240mg
Reporting group description: -	
Reporting group title	BNO 1016 480mg
Reporting group description: -	

Serious adverse events	Placebo	BNO 1016 240mg	BNO 1016 480mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 306 (1.31%)	8 / 318 (2.52%)	4 / 305 (1.31%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatobiliary disorders			
Liver disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal and urinary disorders			
Renal colic			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	BNO 1016 240mg	BNO 1016 480mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 306 (62.09%)	181 / 318 (56.92%)	174 / 305 (57.05%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Benign bone neoplasm			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Skin papilloma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1
Varicophlebitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Hernia repair			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Mole excision			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Peripheral nerve operation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Scar excision			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Tooth extraction			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	2
Chills			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	2 / 318 (0.63%)	1 / 305 (0.33%)
occurrences (all)	1	3	1
Chronic fatigue syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	2	0
Face oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Facial pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Hangover			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Influenza like illness			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 306 (0.98%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	3	0	0
Mucosal dryness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 306 (1.31%)	2 / 318 (0.63%)	2 / 305 (0.66%)
occurrences (all)	4	2	2
Spinal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1
Immune system disorders			
Hypersensitivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Balanitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Cervical polyp			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Cervix inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Dysmenorrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	2 / 318 (0.63%)	1 / 305 (0.33%)
occurrences (all)	2	2	1
Menorrhagia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Menstrual disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Vaginal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	0	2	0
Chronic obstructive pulmonary disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Cough			
alternative assessment type: Non-systematic			

subjects affected / exposed	17 / 306 (5.56%)	2 / 318 (0.63%)	2 / 305 (0.66%)
occurrences (all)	24	2	2
Dysphonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	3 / 318 (0.94%)	2 / 305 (0.66%)
occurrences (all)	0	3	2
Increased upper airway secretion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	2	0	1
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 306 (1.96%)	4 / 318 (1.26%)	3 / 305 (0.98%)
occurrences (all)	7	4	5
Rhinorrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	3	2	1
Sneezing			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Agitation			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Compensation neurosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	1	3	1
Sleep disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	2 / 305 (0.66%)
occurrences (all)	1	1	2
Arthroscopy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Blood albumin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Blood alkaline phosphatase abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Blood creatine increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Blood pressure decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	2 / 305 (0.66%)
occurrences (all)	0	2	2
Blood urea increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Blood urine present			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1

Gamma-glutamyltransferase abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 306 (0.98%)	2 / 318 (0.63%)	1 / 305 (0.33%)
occurrences (all)	3	2	1
Haematocrit decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1
Hepatic enzyme abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	0	2	0
Hepatic enzyme increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	1	1	1
Platelet count abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Contusion			

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	2	2	0
Epicondylitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Forearm fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	2	0	0
Joint injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Ligament rupture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Limb injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	0 / 318 (0.00%)	2 / 305 (0.66%)
occurrences (all)	2	0	2
Lip injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Skin injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	2 / 305 (0.66%)
occurrences (all)	0	0	2
Palpitations			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Supraventricular tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Aphonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Cervical root pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Cervicobrachial syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	1	1	1
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	68 / 306 (22.22%)	50 / 318 (15.72%)	44 / 305 (14.43%)
occurrences (all)	138	82	75
Migraine			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	3 / 318 (0.94%)	1 / 305 (0.33%)
occurrences (all)	1	4	1
Paraesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Sciatica			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	2	0	0
Tension headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1
Iron deficiency anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Leukocytosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Cerumen impaction			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Ear pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	0	2	0
Eustachian tube dysfunction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Tinnitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Vertigo			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	2 / 318 (0.63%)	1 / 305 (0.33%)
occurrences (all)	1	3	1
Eye disorders			
Conjunctival haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Conjunctivitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis allergic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Eye pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Glaucoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Hypermetropia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Visual impairment			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	1	0	1
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	3 / 318 (0.94%)	2 / 305 (0.66%)
occurrences (all)	2	4	2
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 306 (1.63%)	4 / 318 (1.26%)	4 / 305 (1.31%)
occurrences (all)	5	5	4
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 306 (1.31%)	6 / 318 (1.89%)	5 / 305 (1.64%)
occurrences (all)	4	7	6
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	5 / 318 (1.57%)	2 / 305 (0.66%)
occurrences (all)	2	5	2
Epigastric discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	1	2	0
Flatulence			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Food poisoning			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Frequent bowel movements			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Gastritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	2 / 305 (0.66%)
occurrences (all)	1	1	2
Gastrointestinal hypermotility			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 306 (1.31%)	4 / 318 (1.26%)	0 / 305 (0.00%)
occurrences (all)	4	4	0
Glossitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Glossodynia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Haemorrhoids			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Lip swelling			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	2	0	0
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 306 (0.98%)	3 / 318 (0.94%)	2 / 305 (0.66%)
occurrences (all)	4	3	2
Oedema mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Oral pruritus			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	0	2	0
Tooth disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Toothache			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	3	1	1
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	1 / 305 (0.33%)
occurrences (all)	0	2	1
Hepatobiliary disorders			
Cholelithiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Drug-induced liver injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Hyperbilirubinaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Acne			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Dermal cyst			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Dermatitis allergic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	1	1	0
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Heat rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Palmar erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0

Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	3 / 305 (0.98%)
occurrences (all)	1	1	3
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 306 (0.98%)	3 / 318 (0.94%)	3 / 305 (0.98%)
occurrences (all)	3	4	3
Rash erythematous			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Rash pruritic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Swelling face			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Urticaria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Haematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1
Leukocyturia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Hypothyroidism			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	2 / 305 (0.66%)
occurrences (all)	0	6	2
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 306 (1.31%)	3 / 318 (0.94%)	2 / 305 (0.66%)
occurrences (all)	8	3	3
Bursitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Joint effusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	0	2	0
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	2 / 305 (0.66%)
occurrences (all)	0	0	2
Neck pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	2	1	0
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Rheumatic fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Temporomandibular joint syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1

Infections and infestations			
Acute sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	3 / 318 (0.94%)	1 / 305 (0.33%)
occurrences (all)	0	5	1
Arthritis infective			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 306 (1.96%)	3 / 318 (0.94%)	10 / 305 (3.28%)
occurrences (all)	6	3	10
Cystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Ear infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	1	1	0
Erysipelas			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	3 / 318 (0.94%)	0 / 305 (0.00%)
occurrences (all)	2	3	0
Gastroenteritis rotavirus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Gastroenteritis viral			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal bacterial infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Gastrointestinal infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1
Gastrointestinal viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Gingivitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Herpes simplex			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Herpes virus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	2	1	1
Herpes zoster			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	1	0	1
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	1	0	1

Laryngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	3	1	1
Localised infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	0 / 305 (0.00%)
occurrences (all)	0	2	0
Mastitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	121 / 306 (39.54%)	99 / 318 (31.13%)	102 / 305 (33.44%)
occurrences (all)	195	149	167
Oral herpes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	3 / 318 (0.94%)	0 / 305 (0.00%)
occurrences (all)	2	3	0
Otitis externa bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Otitis media			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	4 / 305 (1.31%)
occurrences (all)	0	0	4
Otitis media acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Otitis media chronic			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 306 (1.96%)	8 / 318 (2.52%)	8 / 305 (2.62%)
occurrences (all)	6	8	9
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 306 (0.65%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	2	1	0
Pyelonephritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Rash pustular			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	1 / 305 (0.33%)
occurrences (all)	0	1	1
Tracheitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	0 / 318 (0.00%)	0 / 305 (0.00%)
occurrences (all)	1	0	0

Tracheobronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 306 (1.63%)	10 / 318 (3.14%)	3 / 305 (0.98%)
occurrences (all)	5	13	3
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	2 / 318 (0.63%)	1 / 305 (0.33%)
occurrences (all)	0	2	1
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	0	1	0
Viral pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	1	2	0
Viral upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	1 / 318 (0.31%)	3 / 305 (0.98%)
occurrences (all)	0	1	3
Vulvovaginal mycotic infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Diabetes mellitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 306 (0.33%)	1 / 318 (0.31%)	0 / 305 (0.00%)
occurrences (all)	1	1	0
Increased appetite			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1
Polydipsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 306 (0.00%)	0 / 318 (0.00%)	1 / 305 (0.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2013	The substantial amendment covered the following changes: - A new exclusion criterion "Patients with gastric or duodenal ulcer" was added due to safety relevant changes in the IB update. - The definition of an AE was modified to clarify that worsening or deterioration of CRS symptoms would not be recorded as AE unless it resulted in a condition considered "serious". - Based on the results of the blinded interim analysis, the sample size was increased from initially 771 to 900 patients. Accordingly, the number of patients that were to be screened was increased from 1000 to 1200 patients. - The date for Last Patient Last Visit (LPLV) was postponed from Q3/Q4 2013 to Q1/2014 due to slow patient recruitment. The amendment was substantial since the changes affected safety issues and an increase in sample size. Safety-relevant changes were due to an update of IB Version 4.0 which made reference to an outdated version of the German. Version 5.0 of the IB became effective on 15 APR 2013. The increase in sample since was based on the results of the preplanned interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported