



Clinical trial results:

Clinical trial for examination of efficacy and safety of ANGOCIN® Anti-Infekt N versus placebo in the continuous prophylaxis of chronically recurring uncomplicated cystitis

Summary

EudraCT number	2013-004653-25
Trial protocol	DE
Global end of trial date	15 August 2019

Results information

Result version number	v1 (current)
This version publication date	03 March 2023
First version publication date	03 March 2023

Trial information

Trial identification

Sponsor protocol code	Repha_1362
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Repha GmbH
Sponsor organisation address	Alt-Godshorn 87, Langenhagen, Germany, 30855
Public contact	Clinical Research, Mediconomics GmbH, 0049 05115609980, info@mediconomics.com
Scientific contact	Clinical Research, Mediconomics GmbH, 0049 05115609980, info@mediconomics.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2019
Global end of trial reached?	Yes
Global end of trial date	15 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Rates of first recurrences, observed during the six-month medicinal prophylaxis within the test group and the placebo group

Protection of trial subjects:

This clinical trial was conducted according to the specifications of the protocol, in compliance with the ethical principles of the Declaration of Helsinki as amended in 1996, § 42 para. 1 sentence 1 in conjunction with Art. 1 para. 3 of Directive 2001/20/EC in conjunction with Art. 3 para. 2 of Directive 2005/28/EC, and furthermore in strict compliance with the German Medicines Act (AMG), the German GCP Regulation (GCP-V) and the German Federal Data Protection Act (BDSG). This ensured that the rights, safety and welfare of patients were protected and that the results of the clinical trial were credible.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 224
Worldwide total number of subjects	224
EEA total number of subjects	224

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)	161
From 65 to 84 years	61
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Potential trial subjects were approached directly by the examiners at the test centres and asked about their willingness to participate.

Pre-assignment

Screening details:

After informed consent and sufficient time to think about it, patients who wanted to take part in the clinical trial signed a consent form. By giving written consent, patients were trial subjects. The examiner entered the patient in the Patient Identification Log and the Patient Enrolment Log and conducted the screening examination.

Period 1

Period 1 title	Relapse prophylaxis
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Blinding of investigator and patient was achieved by the following measures:

Verum and placebo did not differ visually,

There was no information on the name and strength of the study medication on the blisters and secondary packaging,

The study medication of the two study arms was labelled with the same batch designation and expiry date; traceability was ensured via the randomisation number and the manufacturing documentation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Investigational product

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Angocin Anti-Infekt N
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

3x 4 film-coated tablets daily

Arm title	Placebo
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Arm description: -

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

Dosage and administration details:

3 x 4 film-coated tablets daily

Number of subjects in period 1	Investigational product	Placebo
Started	115	109
Completed	113	108
Not completed	2	1
Consent withdrawn by subject	-	1
lost sample	2	-

Period 2

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

Blinding implementation details:

Blinding of investigator and patient was achieved by the following measures:

Verum and placebo did not differ visually,

There was no information on the name and strength of the study medication on the blisters and secondary packaging,

The study medication of the two study arms was labelled with the same batch designation and expiry date; traceability was ensured via the randomisation number and the manufacturing documentation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Medicinal product

Arm description:

Angocin Anti-Infekt N (however in this phase, no study medication was administered)

Arm type	Experimental
Investigational medicinal product name	Angocin Anti-Infekt N
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

3x 4 film-coated tablets daily

Arm title	Placebo
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Arm description:

Placebo (however in this phase, no study medication was administered)

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

Dosage and administration details:

3 x 4 film-coated tablets daily

Number of subjects in period 2 ^[1]	Medicinal product	Placebo
Started	51	29
Completed	37	24
Not completed	14	5
Relapse	14	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only those patients without relapse in the prophylaxis phase were continuing the follow-up phase

Baseline characteristics

Reporting groups

Reporting group title	Investigational product
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Investigational product	Placebo	Total
Number of subjects	115	109	224
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)	78	80	158
From 65-84 years	35	26	61
85 years and over	0	2	2
Not recorded	2	1	3
Gender categorical			
Units: Subjects			
Female	112	107	219
Male	3	2	5

End points

End points reporting groups

Reporting group title	Investigational product
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Medicinal product
Reporting group description:	
Angocin Anti-Infekt N (however in this phase, no study medication was administered)	
Reporting group title	Placebo
Reporting group description:	
Placebo (however in this phase, no study medication was administered)	

Primary: Relapse rate

End point title	Relapse rate
End point description:	
Rate of first relapses observed in the test group and the comparison group during the six-month drug relapse prophylaxis, determined as Kaplan-Meier estimator in the interval from 0 to 180 days. Relapses were defined as symptomatic infections (with a urophathogenic count of $\geq 10^3$ CFU/ml urine in pure culture confirmed by the central laboratory), as far as a urine culture was feasible. Only first relapses were recorded, i.e. for each patient only the first recurrence diagnosed after the start of prophylaxis.	
End point type	Primary
End point timeframe:	
0-180 days	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	108		
Units: number of patients	42	52		

Statistical analyses

Statistical analysis title	Relapse rate
Statistical analysis description:	
The rates were determined as Kaplan-Meier estimators (product limit estimators) over 180 days of the Kaplan-Meier plot. Recurrence rates were compared using the logrank test.	
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0333
Method	Logrank

Notes:

[1] - The rates were determined as Kaplan-Meier estimators (product limit estimators) over 180 days of the Kaplan-Meier plot.

Statistical analysis title	Relapse Rate Cox Regression
Comparison groups	Placebo v Investigational product
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Regression, Cox

Secondary: Relapse rate V4-V8

End point title	Relapse rate V4-V8
End point description:	Relapse rate during the relapse prophylaxis period Day 30 - Day 150
End point type	Secondary
End point timeframe:	Day 30 - Day 150

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	108		
Units: number of patients (percentage)				
Day 30	13	11		
Day 60	24	32		
Day 90	26	44		
Day 120	34	49		
Day 150	38	55		
Day 180	39	56		

Statistical analyses

Statistical analysis title	Relapse rates V4-V8
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.055 ^[3]
Method	Chi-squared

Notes:

[2] - cumulative results

[3] - only day 180

Secondary: Time without relapse

End point title	Time without relapse
End point description: The relapse-free time during the relapse prophylaxis phase (day 0 to 180) was calculated in quartiles using the log-rank test. The cumulative recurrence rate were compared with the quartiles.	
End point type	Secondary
End point timeframe: Day 0 - Day 180	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	108		
Units: quartile (25%)				
number (confidence interval 95%)	75 (42 to 111)	49 (39 to 63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse rate follow-up phase

End point title	Relapse rate follow-up phase
End point description: Of all patients who had not yet experienced a relapse at day 180, how many had a relapse within the next 180 days?	
End point type	Secondary
End point timeframe: Day 180 - Day 360	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	29		
Units: number of patients	14	5		

Statistical analyses

Statistical analysis title	Relapse rate FU
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3563
Method	Logrank

Secondary: Investigator's assessment at the end of the prophylaxis phase

End point title	Investigator's assessment at the end of the prophylaxis phase
End point description:	
End point type	Secondary
End point timeframe:	
At the end of the prophylaxis phase (Visit 9)	

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	108		
Units: number of patients				
Study medication not effective	9	8		
Study medication not meaningfully effective	13	13		
good efficacy	41	27		
very good efficacy	23	18		

Statistical analyses

Statistical analysis title	Investigator's assessment after prophylaxis phase
Comparison groups	Investigational product v Placebo

Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.817
Method	Chi-squared

Secondary: Investigator's assessment at the end of the follow-up phase

End point title	Investigator's assessment at the end of the follow-up phase
End point description:	Investigator's assessment as to how likely the study medication prevented a recurrent infection
End point type	Secondary
End point timeframe:	Within the 6 months after the prophylaxis phase

End point values	Investigational product	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	108		
Units: number of patients				
unlikely	7	1		
possibly	20	9		
likely	21	18		

Statistical analyses

Statistical analysis title	Investigator's assessment after follow-up phase
Comparison groups	Investigational product v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.142
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

To evaluate safety and tolerability, 'adverse events' were recorded during the treatment period and laboratory findings and vital signs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Angocin
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Angocin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 113 (4.42%)	6 / 108 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Catheterisation cardiac			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Removal of foreign body from joint			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urosepsis			

subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
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	Angocin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 113 (76.11%)	86 / 108 (79.63%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Adrenal neoplasm			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Adenoma thyroid			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Angiodysplasia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Flush hot			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Hypertonia			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Thrombophlebitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Varicose veins			

subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Peripheral nerve therapeutic procedures			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Limb operation			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Morning sickness			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Thirst			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	6 / 113 (5.31%)	2 / 108 (1.85%)	
occurrences (all)	6	2	

Pyrexia			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Sensation of foreign body			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Medical device site calcification			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Chills			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Swelling			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Suprapubic pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Drug intolerance			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Drug hypersensitivity			

subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	2 / 113 (1.77%) 2	0 / 108 (0.00%) 0	
Allergy to animal subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Reproductive system and breast disorders			
Atrophic vulvovaginitis subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Breast disorder subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	1 / 108 (0.93%) 1	
Dyspareunia subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Menopausal symptoms subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Ovarian cyst subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			

Asthma		
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)
occurrences (all)	1	2
Dyspnoea exertional		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Oropharyngeal blistering		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Dyspnoea		
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)
occurrences (all)	0	2
Tonsillar hypertrophy		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Laryngeal inflammation		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Nasal dryness		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Obstructive airways disorder		
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)
occurrences (all)	1	0
Rhinorrhoea		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Oropharyngeal pain		
subjects affected / exposed	3 / 113 (2.65%)	0 / 108 (0.00%)
occurrences (all)	3	0
Vocal cord inflammation		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Cough		
subjects affected / exposed	4 / 113 (3.54%)	1 / 108 (0.93%)
occurrences (all)	5	1

Psychiatric disorders			
Aversion			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Depression			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	2	
Depressed mood			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Post-traumatic stress disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences (all)	3	4	
Stress			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Compulsive conduct disorder			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Cyclothymic disorder			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 113 (2.65%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Blood urine present			

subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Blood pressure increased			
subjects affected / exposed	5 / 113 (4.42%)	0 / 108 (0.00%)	
occurrences (all)	7	0	
Blood pressure decreased			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Chlamydia test positive			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	4	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Weight increased			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Physical breast examination abnormal			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Urine output increased			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			

Epicondylitis		
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)
occurrences (all)	2	0
Wrist fracture		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Arthropod bite		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Ligament sprain		
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)
occurrences (all)	0	2
Thoracic vertebral end plate fracture		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Concussion		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Joint injury		
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)
occurrences (all)	1	1
Meniscus injury		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Fall		
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)
occurrences (all)	0	2
Procedural nausea		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Spinal column injury		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Contusion		
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)
occurrences (all)	1	1

Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Arrhythmia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Cardiovascular disorder			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Hypoaesthesia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Intercostal neuralgia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	13 / 113 (11.50%)	7 / 108 (6.48%)	
occurrences (all)	16	9	
Migraine			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences (all)	5	2	
Vertigo			
subjects affected / exposed	5 / 113 (4.42%)	2 / 108 (1.85%)	
occurrences (all)	5	3	
headache tension			

subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Tardive dyskinesia subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 113 (1.77%) 3	1 / 108 (0.93%) 1	
Tinnitus subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 2	0 / 108 (0.00%) 0	
Sudden hearing loss subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 2	0 / 108 (0.00%) 0	
Eye inflammation subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Gastrointestinal disorders Faeces hard subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Faeces discoloured subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	2 / 108 (1.85%) 4	
Nausea subjects affected / exposed occurrences (all)	10 / 113 (8.85%) 13	14 / 108 (12.96%) 18	
Gingival bleeding subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Toothache			

subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)
occurrences (all)	1	2
Abdominal pain		
subjects affected / exposed	2 / 113 (1.77%)	9 / 108 (8.33%)
occurrences (all)	4	9
Abdominal discomfort		
subjects affected / exposed	6 / 113 (5.31%)	8 / 108 (7.41%)
occurrences (all)	6	12
Eructation		
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)
occurrences (all)	1	2
Abdominal distension		
subjects affected / exposed	6 / 113 (5.31%)	6 / 108 (5.56%)
occurrences (all)	7	8
Retching		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Diarrhoea		
subjects affected / exposed	13 / 113 (11.50%)	12 / 108 (11.11%)
occurrences (all)	14	16
Duodenitis		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Dysbiosis		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Dyspepsia		
subjects affected / exposed	2 / 113 (1.77%)	5 / 108 (4.63%)
occurrences (all)	7	6
Enteritis		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Vomiting		
subjects affected / exposed	4 / 113 (3.54%)	0 / 108 (0.00%)
occurrences (all)	4	0
Flatulence		

subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Gastrointestinal pain			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Hiatus hernia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Noninfective gingivitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	10 / 113 (8.85%)	6 / 108 (5.56%)	
occurrences (all)	15	7	
Abdominal pain lower			
subjects affected / exposed	1 / 113 (0.88%)	4 / 108 (3.70%)	
occurrences (all)	1	4	
Stomatitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	

Skin burning sensation subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Decubitus ulcer subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
hyperhidrosis subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	1 / 108 (0.93%) 1	
Pityriasis rosea subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	3 / 108 (2.78%) 3	
Generalised pruritus subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Stasis dermatitis subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Dry skin subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 113 (5.31%) 6	3 / 108 (2.78%) 4	
Arthritis reactive subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Muscle spasms			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Periarthritis		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Tendon pain		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Arthritis		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Joint swelling		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Limb discomfort		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Coccydynia		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Myalgia		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Osteoarthritis		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Plantar fasciitis		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Rheumatoid arthritis		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Rotator cuff syndrome		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Back pain		

subjects affected / exposed	12 / 113 (10.62%)	10 / 108 (9.26%)	
occurrences (all)	13	13	
Pain in extremity			
subjects affected / exposed	3 / 113 (2.65%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Tenosynovitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	3	
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	21 / 113 (18.58%)	17 / 108 (15.74%)	
occurrences (all)	21	18	
respiratory tract infection			
subjects affected / exposed	4 / 113 (3.54%)	2 / 108 (1.85%)	
occurrences (all)	4	2	
Rash pustular			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Bacterial vaginosis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	4 / 113 (3.54%)	0 / 108 (0.00%)	
occurrences (all)	4	0	
Candida infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Clostridial infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	

Diverticulitis		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
fungal skin infection		
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)
occurrences (all)	2	0
Gastroenteritis		
subjects affected / exposed	6 / 113 (5.31%)	5 / 108 (4.63%)
occurrences (all)	6	5
Gastrointestinal viral infection		
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)
occurrences (all)	0	2
Influenza		
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)
occurrences (all)	1	1
Urinary tract infection		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)
occurrences (all)	3	1
Localised infection		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Conjunctivitis		
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)
occurrences (all)	3	0
Laryngitis		
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)
occurrences (all)	1	1
Nasopharyngitis		
subjects affected / exposed	30 / 113 (26.55%)	25 / 108 (23.15%)
occurrences (all)	53	30
Ear infection		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0

Onychomycosis		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Oral herpes		
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)
occurrences (all)	0	2
Periodontitis		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Paronychia		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)
occurrences (all)	1	1
Genital infection fungal		
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)
occurrences (all)	0	2
Gastrointestinal fungal infection		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Pneumonia		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0
Pulpitis dental		
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences (all)	0	1
Sinobronchitis		
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)
occurrences (all)	3	1
Sinusitis		
subjects affected / exposed	4 / 113 (3.54%)	2 / 108 (1.85%)
occurrences (all)	5	2
Tinea pedis		
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)
occurrences (all)	1	0

Tinea versicolour subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Tonsillitis subjects affected / exposed occurrences (all)	2 / 113 (1.77%) 3	3 / 108 (2.78%) 3	
Vaginal infection subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
viral infection subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	1 / 108 (0.93%) 1	
Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	0 / 108 (0.00%) 0	
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	5 / 113 (4.42%) 5	5 / 108 (4.63%) 5	
Root canal infection subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Metabolism and nutrition disorders Decreased appetite alternative dictionary used: MedDRA 21.1 subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	2 / 108 (1.85%) 2	
Gout subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 113 (0.00%) 0	1 / 108 (0.93%) 1	
Lipoedema			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2014	Inclusion of study centers
21 January 2015	Inclusion of study centers
13 April 2015	Inclusion of study centers
17 September 2015	Inclusion of study centers. Unsubscription of other study centers. Change of address of a study center. Change of exclusion criteria. Change of time between Visit 2 and Visit 3.
28 February 2016	Change of centers involved.
06 May 2016	Prolongation of study duration
05 October 2016	Inclusion of study centers
04 January 2017	Inclusion of study centers
19 September 2017	Inclusion of study centers
22 August 2018	Inclusion of study centers, Prolongation of study duration, Change of QPPV, outsourcing of the investigator list, Erratum Batch formula Placebo
30 November 2018	Shortening of follow-up phase duration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported