Clinical trial results:
AN INTERNATIONAL, MULTICENTRE, DOUBLE-BLIND, RANDOMISED STUDY OF THE EFFECT OF DIACEREIN VS CELECOXIB ON SYMPTOMS AND STRUCTURAL CHANGES IN SYMPTOMATIC KNEE OSTEOARTHRITIS PATIENTS AS ASSESSED BY MAGNETIC RESONANCE IMAGING

Summary

EudraCT number	2015-002933-23
Trial protocol	CZ ES AT BE
Global end of trial date	26 June 2018

Results information

Result version number	v1 (current)
This version publication date	03 July 2019
First version publication date	03 July 2019

Trial information

Trial identification

Sponsor protocol code	DAR-INT-14-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02688400
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TRB Chemedica International SA
Sponsor organisation address	Michel-Servet 12, Geneva, Switzerland, CH-1211
Public contact	Marie-Claude Gravel, SPharm inc., 1 8198246869, mcgravel@spharm-inc.com
Scientific contact	Dr. Jean-Pierre Pelletier, Arthrolab inc., 1 5149924939, dr@jppelletier.ca

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 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2018
Global end of trial reached?	Yes
Global end of trial date	26 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to show that Diacerein is non-inferior to Celecoxib in terms of pain reduction (WOMAC A pain subscale) after 182 days of treatment in symptomatic knee OA patients.

Protection of trial subjects:

If the patient is experiencing pain, acetaminophen, dosed at 500 mg, is authorised up to 2 g per day, i.e., 4 tablets per day.

Other rescue analgesia with narcotics will be authorised for a maximum of 3 days a month for treatment of pain related to the target knee or any other painful condition for which it is the physician's judgement that such treatment is indicated.

Background therapy:

Acetaminophen is given as a rescue medication for this study.

Evidence for comparator:

Celecoxib is recognised as the current gold standard in the treatment of knee OA. The clinical effectiveness of Celecoxib in the treatment of OA of the knee and hip was demonstrated in several placebo- and active-controlled clinical studies. Celecoxib demonstrated significant reductions in joint pain and disease activity, and also improvement in patient functional activity and health-related quality of life compared to placebo. In OA patients, treatment with Celecoxib 100 mg twice a day or 200 mg once daily resulted in improvement in functional activity as demonstrated by an improvement in pain, stiffness, function and total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.

Actual start date of recruitment	16 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 122
Country: Number of subjects enrolled	Canada: 159
Worldwide total number of subjects	380
EEA total number of subjects	221

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)	203
From 65 to 84 years	177
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment between April 2016 to December 2017 in Canada, Spain, Austria, Czech and Belgium

Pre-assignment

Screening details:

screening period 30 days
wash-out 7 days

Overall (N=527)
Not Randomized patients: 147
Primary reason for non randomization
- Lack of efficacy: 0
- Adverse Event(s): 0
- Lost to Follow-Up: 0
- Protocol violation: 0
- Consent withdrawal: 10
- Other : 137

Period 1

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

Blinding implementation details:

The test products and placebo capsules will be presented as identical capsules concerning the colour, size and shape and weight. They will be packed in identical blisters and these blisters will be placed in identical plain, carton boxes. Patients in both groups will take the same number of capsules daily.

Arms

Are arms mutually exclusive?	Yes
Arm title	Diacerein

Arm description:

Diacerein 50 mg capsule and matching placebo (first month)

Arm type	Experimental
Investigational medicinal product name	Diacerein
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Diacerein: one placebo capsule once daily in the morning (breakfast) and one Diacerein 50 mg capsule once daily with meals (dinner) in the evening for the first month; then twice daily with meals in the morning (breakfast) and the evening (dinner)

Arm title	Celecoxib

Arm description:

Celecoxib 200 mg capsule and matching placebo

Arm type	Active comparator

Investigational medicinal product name	Celecoxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Celecoxib (Celebrex®): one Celecoxib 200 mg capsule once daily in the morning (breakfast) and one placebo capsule once daily in the evening (dinner)

Number of subjects in period 1	Diacerein	Celecoxib
Started	187	193
Completed	141	149
Not completed	46	44
Consent withdrawn by subject	15	13
Adverse event, non-fatal	21	12
no study medication intake	1	4
Lost to follow-up	-	3
Lack of efficacy	7	7
Protocol deviation	2	5

Baseline characteristics

Reporting groups	
Reporting group title	Diacerein
Reporting group description:	
Diacerein 50 mg capsule and matching placebo (first month)	
Reporting group title	Celecoxib
Reporting group description:	
Celecoxib 200 mg capsule and matching placebo	

Reporting group values	Diacerein	Celecoxib	Total
Number of subjects	187	193	380
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)	106	97	203
From 65-84 years	81	96	177
85 years and over	0	0	0
Age continuous			
Male or female aged more than 50 years old			
Units: years			
arithmetic mean	63.7	64.4	
standard deviation	± 6.3	± 7.0	-
Gender categorical Units: Subjects			
Female	137	146	283
Male	50	47	97
study knee Units: Subjects			
right	87	96	183
left	100	97	197

Subject analysis sets	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intention-To-Treat was composed of all randomized patients who received at least one dose of the study medication, had an efficacy measurement at inclusion and at least one corresponding post-inclusion efficacy measurement (for the primary efficacy variable).	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set (PPS) was a subset of the ITT and included all patients who did not present any major deviation of the protocol over the 6-month follow-up period. These deviations were detected during the blind review meeting.

Reporting group values	ITT population	Per Protocol Set	
Number of subjects	370	288	
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)	201	157	
From 65-84 years	169	131	
85 years and over			
Age continuous			
Male or female aged more than 50 years old			
Units: years			
arithmetic mean	64.1	63.9	
standard deviation	± 6.7	± 6.3	
Gender categorical Units: Subjects			
Female	274	213	
Male	96	75	
study knee Units: Subjects			
right	179	136	
left	191	152	

End points

End points reporting groups

Reporting group title	Diacerein
Reporting group description:	
Diacerein 50 mg capsule and matching placebo (first month)	
Reporting group title	Celecoxib
Reporting group description:	
Celecoxib 200 mg capsule and matching placebo	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intention-To-Treat was composed of all randomized patients who received at least one dose of the study medication, had an efficacy measurement at inclusion and at least one corresponding post-inclusion efficacy measurement (for the primary efficacy variable).	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) was a subset of the ITT and included all patients who did not present any major deviation of the protocol over the 6-month follow-up period. These deviations were detected during the blind review meeting.	

Primary: WOMAC Pain subscale

End point title	WOMAC Pain subscale
End point description:	
End point type	Primary
End point timeframe:	
182 days	

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	148		
Units: cm				
least squares mean (standard error)	-11.14 (± 0.91)	-11.82 (± 0.89)		

Statistical analyses

Statistical analysis title	Absolute change from Baseline
Comparison groups	Celecoxib v Diacerein

Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.67
Confidence interval	
level	95 %
sides	1-sided
upper limit	3.18

Secondary: WOMAC OA Scores

End point title	WOMAC OA Scores

End point description:

Absolute Changes from Baseline - Intention-To-Treat (N=370)

End point type	Secondary

End point timeframe:

Day 182 or early termination

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[1]	182		
Units: score				
arithmetic mean (standard deviation)				
Total Score	-41.0 (± 53.1)	-42.9 (± 55.0)		
Pain Score	-10.03 (± 11.95)	-9.60 (± 12.02)		
Stiffness Score	-3.56 (± 4.99)	-3.99 (± 5.32)		
Physical Function Score	-27.2 (± 39.0)	-29.3 (± 39.8)		

Notes:

[1] - For Pain Score and Stiffness Score the number of subjects is 178

Statistical analyses

Statistical analysis title	WOMAC OA Statistical Analysis
Comparison groups	Diacerein v Celecoxib
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %

Secondary: Pain Visual Analogue Scale

End point title	Pain Visual Analogue Scale
End point description:	
Absolute Changes from Baseline - Intention-To-Treat (N=370)	
End point type	Secondary
End point timeframe:	
Day 182 or early termination	

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	182		
Units: score				
arithmetic mean (standard deviation)	-2.34 (± 2.55)	-2.46 (± 2.61)		

Statistical analyses

Statistical analysis title	Pain Visual Analogue Scale
Comparison groups	Celecoxib v Diacerein
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Secondary: OARSI Responders

End point title	OARSI Responders
End point description:	
Absolute Changes from Baseline - Intention-To-Treat (N=370)	
End point type	Secondary
End point timeframe:	
Day 182 or early termination	

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	182		
Units: score				
number (not applicable)	99	97		

Statistical analyses

Statistical analysis title	OARSI Responder
Comparison groups	Diacerein v Celecoxib
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: Assessment of Joint Swelling, Effusion or Both

End point title	Assessment of Joint Swelling, Effusion or Both

End point description:

End point type	Secondary

End point timeframe:

Day 182 or early termination

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	184		
Units: subject				
number (not applicable)				
Joint Swelling	47	48		
Joint Effusion	37	37		
Joint Swelling and Effusion	19	23		

Statistical analyses

Statistical analysis title	Joint swelling, effusion or both Analysis
Comparison groups	Diacerein v Celecoxib

Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	between group comparison
Confidence interval	
level	95 %

Secondary: Consumption of Acetaminophen

End point title	Consumption of Acetaminophen
End point description:	
Overall Daily number of tablets taken during the 6 month study	
End point type	Secondary
End point timeframe:	
Day 182 or early termination	

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	185		
Units: tablets				
arithmetic mean (standard deviation)	1.06 (± 1.75)	0.91 (± 1.02)		

Statistical analyses

Statistical analysis title	Overall Consumption of Acetaminophen
Comparison groups	Diacerein v Celecoxib
Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Secondary: Global Assessment of Disease Activity

End point title	Global Assessment of Disease Activity
End point description:	
End point type	Secondary

End point timeframe:
Day 182 or early termination

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	179		
Units: score				
arithmetic mean (standard deviation)				
Patient's Global Assessment	-1.81 (± 2.79)	-1.97 (± 2.97)		
Investigator's Global Assessment	-2.02 (± 2.55)	-2.65 (± 2.55)		

Statistical analyses

Statistical analysis title	Global Assessment of Disease Activity
Comparison groups	Diacerein v Celecoxib
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Secondary: Global Assessment of Response to Therapy

End point title	Global Assessment of Response to Therapy
End point description:	
Absolute Changes from Baseline - Intention-To-Treat (N=370)	
End point type	Secondary
End point timeframe:	
Day 182 or early termination	

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[2]	182[3]		
Units: score				
arithmetic mean (standard deviation)				
Patient's Global Assessement	3.89 (± 2.57)	3.61 (± 2.52)		
Investigator's Global Assessment	3.85 (± 2.51)	3.35 (± 2.42)		

Notes:
[2] - 176 subjects evaluated for the Investigator's Global Assessment
[3] - 180 subjects evaluated for the Investigator's Global Assessment

Statistical analyses

Statistical analysis title	Global Assessment Response to Therapy
Comparison groups	Diacerein v Celecoxib
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Secondary: Quality of life SF-36

End point title	Quality of life SF-36
End point description:	
Absolute Changes from Baseline - Intention-To-Treat (N=370)	
End point type	Secondary
End point timeframe:	
Day 182 or early termination	

End point values	Diacerein	Celecoxib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: score				
arithmetic mean (standard deviation)				
Physical Component Summary	2.46 (± 6.74)	4.57 (± 8.08)		
Mental Component Summary	1.56 (± 8.34)	-0.14 (± 8.87)		

Statistical analyses

Statistical analysis title	Quality of life SF-36

Statistical analysis description:
Absolute Changes from Baseline by Visit and Comparisons Between Treatment Groups - Intention-To-Treat (N=370)

Comparison groups	Diacerein v Celecoxib

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each post-screening visit: Day 0, 60, 120 and 182

Adverse event reporting additional description:

Emergent Adverse Events Related to Study Treatment (non-serious adverse events only)

Serious adverse events (SAEs) were experienced in 3 (1.6%) patients in the Diacerein group versus 4 (2.1%) patients in the Celecoxib group (which were considered not related to Celecoxib).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Diacerein

Reporting group description:

Diacerein 50 mg capsule and matching placebo (first month)

Reporting group title	Celecoxib

Reporting group description:

Celecoxib 200 mg capsule and matching placebo

Serious adverse events	Diacerein	Celecoxib	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 186 (1.61%)	4 / 190 (2.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm prostate			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			

subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Temporal arteritis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Diacerein	Celecoxib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 186 (59.68%)	103 / 190 (54.21%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Hypertensive crisis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Psychiatric disorders			
Libido decreased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 186 (0.54%)	1 / 190 (0.53%)	
occurrences (all)	1	1	

Alanine aminotransferase increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 186 (0.54%)	3 / 190 (1.58%)	
occurrences (all)	1	4	
Dizziness			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 186 (10.22%)	7 / 190 (3.68%)	
occurrences (all)	21	7	
Dyspepsia			
subjects affected / exposed	5 / 186 (2.69%)	5 / 190 (2.63%)	
occurrences (all)	5	5	
Faeces soft			
subjects affected / exposed	3 / 186 (1.61%)	6 / 190 (3.16%)	
occurrences (all)	3	6	
Abdominal pain			
subjects affected / exposed	6 / 186 (3.23%)	2 / 190 (1.05%)	
occurrences (all)	7	2	
Abdominal pain upper			
subjects affected / exposed	4 / 186 (2.15%)	1 / 190 (0.53%)	
occurrences (all)	4	1	
Nausea			
subjects affected / exposed	2 / 186 (1.08%)	2 / 190 (1.05%)	
occurrences (all)	2	2	

Constipation			
subjects affected / exposed	2 / 186 (1.08%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Frequent bowel movements			
subjects affected / exposed	1 / 186 (0.54%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 186 (1.08%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 186 (0.54%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Abdominal tenderness			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia oral			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Paraesthesia oral			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Tongue geographic			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 186 (0.00%)	2 / 190 (1.05%)	
occurrences (all)	0	2	
Angioedema			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	5 / 186 (2.69%)	0 / 190 (0.00%)	
occurrences (all)	5	0	
Haematuria			
subjects affected / exposed	2 / 186 (1.08%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 186 (1.08%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 186 (0.54%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Labyrinthitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Cardiac disorder			

subjects affected / exposed	2 / 186 (1.08%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Palpitations			
subjects affected / exposed	2 / 186 (1.08%)	1 / 190 (0.53%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported