Clinical trial results:
Efficacy and safety of 2 doses of agomelatine (10 mg/day or 25 mg/day) versus placebo given orally for 12 weeks in non depressed out-patients with Generalized Anxiety Disorder.
A 12-week randomised, double-blind, placebo-controlled, 3-arm parallel groups, international multicenter study.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-001666-15
Trial protocol	FI SK PL
Global end of trial date	21 January 2015

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	27 April 2016

Trial information

Trial identification

Sponsor protocol code	CL3-20098-087

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.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	21 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2015
Global end of trial reached?	Yes
Global end of trial date	21 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the short-term efficacy of at least one of the 2 dose regimens of agomelatine (versus placebo) using Hamilton Anxiety (HAM-A) scale after a 12-week treatment period in non-depressed out-patients suffering from Generalized Anxiety Disorder (GAD).

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Criteria for mandatory discontinuation of treatment were:
- Absence of written consent or consent withdrawal by the patient.
- Suicidal risk, according to investigator's judgment and or with a suicidal ideation of 4 or 5 on Columbia Suicide Severity Rating Scale (C-SSRS).
- Any suicide attempt during the study whatever its severity (could be checked with C-SSRS suicidal behavior part).
- Pregnancy.
- ALT or AST > 8 ULN , or ALT or AST > 5 ULN and sustained after two weeks of close monitoring.
- ALT or AST > 3 ULN and total bilirubin > 2 ULN.
- ALT or AST > 3 ULN with clinical signs of hepatitis.
- Symptoms or signs of potential liver injury: such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue.

Other criteria for premature discontinuation of treatment were:
- Any event or circumstance related or unrelated to treatment justifying the discontinuation of the treatment in the investigator's opinion.
- Treatment failure, i.e. lack of efficacy which in the opinion of the investigator required the patients to be withdrawn. All withdrawals for worsening of GAD were to be considered as lack of efficacy.
- Adverse event
- Any protocol deviation which jeopardized the patient’s safety.
- Lost to follow-up.

Background therapy: -

Evidence for comparator:

Placebo

Actual start date of recruitment	19 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ukraine: 100
Country: Number of subjects enrolled	Russian Federation: 75
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Slovakia: 71
Country: Number of subjects enrolled	Finland: 110
Worldwide total number of subjects	412
EEA total number of subjects	237

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)	376
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Investigators were psychiatrists

Pre-assignment

Screening details:

Non-depressed adult patients of both genders, fufilling DSM-IV criteria for GAD. At selection HAM-A total score was to be ≥ 22, HAD anxious score ≥ HAD depression score, and MADRS total score ≤ 16. At inclusion HAM-A total score was still to be ≥ 22 and no more than 20% of decrease in HAM-A total score between selection and inclusion.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Agomelatine 10mg

Arm description: -

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

Dosage and administration details:

From inclusion to W12, patients received one capsule per day of agomelatine 10 mg, to be taken orally at bedtime.

Arm title	Agomelatine 25mg

Arm description: -

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

Dosage and administration details:

From inclusion to W12, patients received one capsule per day of agomelatine 25 mg daily , to be taken orally at bedtime.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:
From inclusion to W12, patients received one capsule per day of placebo to be taken orally at bedtime.

Number of subjects in period 1	Agomelatine 10mg	Agomelatine 25mg	Placebo
Started	131	139	142
Completed	113	126	112
Not completed	18	13	30
Adverse event, non-fatal	1	3	1
Non-medical reason	8	8	8
Protocol deviation	1	1	1
Lack of efficacy	8	1	20

Baseline characteristics

Reporting groups	
Reporting group title	Agomelatine 10mg
Reporting group description: -	
Reporting group title	Agomelatine 25mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Agomelatine 10mg	Agomelatine 25mg	Placebo
Number of subjects	131	139	142
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)	120	125	131
From 65-84 years	11	14	11
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	43.6	44.1	44.1
standard deviation	± 13.4	± 15.2	± 13.1
Gender categorical Units: Subjects			
Female	89	100	90
Male	42	39	52

Reporting group values	Total		
Number of subjects	412		
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)	376		
From 65-84 years	36		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	279		
Male	133		

End points

End points reporting groups

Reporting group title	Agomelatine 10mg
Reporting group description: -	
Reporting group title	Agomelatine 25mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients of the RS having taken at least one dose of IMP and having a value at baseline (W0) and at least one post-baseline value for the primary efficacy criterion.	

Primary: HAM-A total score

End point title	HAM-A total score
End point description:	
The main analytical approach was the change from baseline to W12 (LOCF).	
End point type	Primary
End point timeframe:	
Evaluation at ASSE, W0, W2, W4, W8 and W12.	

End point values	Agomelatine 10mg	Agomelatine 25mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	130	138	140	
Units: score				
arithmetic mean (standard deviation)				
change from baseline to W12 (LOCF)	-13.7 (± 8.7)	-18 (± 7.7)	-6.9 (± 9.2)	

Statistical analyses

Statistical analysis title	primary analysis
Statistical analysis description:	
Analysis of covariance model on factor treatment with baseline HAM-A total score and centre (random effect) as covariates	
Comparison groups	Agomelatine 10mg v Placebo
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	primary analysis

Statistical analysis description:

Analysis of covariance model on factor treatment with baseline HAM-A total score and centre (random effect) as covariates

Comparison groups	Agomelatine 25mg v Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

all adverse events which occurred or worsen or became serious according to the investigator, or upgraded by the Sponsor, between the first IMP intake date (included) and the last IMP intake date + 1 day (included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Agomelatine 10mg
Reporting group description: -	
Reporting group title	Agomelatine 25mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Agomelatine 10mg	Agomelatine 25mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 131 (3.05%)	3 / 139 (2.16%)	2 / 140 (1.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 131 (0.00%)	2 / 139 (1.44%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 131 (0.76%)	2 / 139 (1.44%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (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			

Flushing			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
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			
Presyncope			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (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
Somnolence			
subjects affected / exposed	2 / 131 (1.53%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (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
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depressed mood			

subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised anxiety disorder			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (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
Infections and infestations			
Diarrhoea infectious			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (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
Hepatitis A			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (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
Hyperglycaemia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (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

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	Agomelatine 10mg	Agomelatine 25mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 131 (28.24%)	47 / 139 (33.81%)	35 / 140 (25.00%)
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 131 (2.29%)	2 / 139 (1.44%)	2 / 140 (1.43%)
occurrences (all)	3	2	2
Local swelling			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Sensitivity to weather change			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Sluggishness			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 131 (0.00%)	2 / 139 (1.44%)	0 / 140 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Anorgasmia			

subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Fear of injection			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	2 / 131 (1.53%)	2 / 139 (1.44%)	2 / 140 (1.43%)
occurrences (all)	2	2	2
Irritability			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	2	0
Nightmare			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	2 / 140 (1.43%)
occurrences (all)	0	0	2
Sleep disorder			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Blood potassium increased			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Low density lipoprotein increased			

subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Wrist fracture			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 131 (0.76%)	3 / 139 (2.16%)	3 / 140 (2.14%)
occurrences (all)	1	5	3
Headache			
subjects affected / exposed	6 / 131 (4.58%)	9 / 139 (6.47%)	9 / 140 (6.43%)
occurrences (all)	6	13	12
Paraesthesia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 131 (0.00%)	4 / 139 (2.88%)	1 / 140 (0.71%)
occurrences (all)	0	5	1
Speech disorder			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Tension headache			

subjects affected / exposed	2 / 131 (1.53%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 131 (0.00%)	2 / 139 (1.44%)	0 / 140 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	2	0	0
Abdominal pain			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	1 / 140 (0.71%)
occurrences (all)	0	1	1
Colitis microscopic			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 131 (0.76%)	1 / 139 (0.72%)	1 / 140 (0.71%)
occurrences (all)	1	1	1
Dry mouth			

subjects affected / exposed	1 / 131 (0.76%)	3 / 139 (2.16%)	1 / 140 (0.71%)
occurrences (all)	2	3	1
Dyspepsia			
subjects affected / exposed	1 / 131 (0.76%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	1	1	0
Flatulence			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Gastritis erosive			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 131 (0.76%)	4 / 139 (2.88%)	2 / 140 (1.43%)
occurrences (all)	1	4	2
Oesophageal pain			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Paraesthesia oral			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	1	0	1
Hyperhidrosis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	1 / 140 (0.71%)
occurrences (all)	0	1	1
Urticaria contact			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1

Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 131 (0.00%)	3 / 139 (2.16%)	0 / 140 (0.00%)
occurrences (all)	0	3	0
Back pain			
subjects affected / exposed	0 / 131 (0.00%)	6 / 139 (4.32%)	1 / 140 (0.71%)
occurrences (all)	0	6	2
Bursitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Muscle tightness			
subjects affected / exposed	1 / 131 (0.76%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal pain			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	2 / 140 (1.43%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	1 / 131 (0.76%)	1 / 139 (0.72%)	1 / 140 (0.71%)
occurrences (all)	1	2	1
Plantar fascial fibromatosis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0

Bronchopneumonia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	3 / 131 (2.29%)	0 / 139 (0.00%)	2 / 140 (1.43%)
occurrences (all)	3	0	2
Nasopharyngitis			
subjects affected / exposed	7 / 131 (5.34%)	1 / 139 (0.72%)	1 / 140 (0.71%)
occurrences (all)	7	1	1
Pharyngitis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	1	0	1
Respiratory tract infection			
subjects affected / exposed	1 / 131 (0.76%)	1 / 139 (0.72%)	2 / 140 (1.43%)
occurrences (all)	1	1	2
Sialoadenitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	1 / 131 (0.76%)	2 / 139 (1.44%)	4 / 140 (2.86%)
occurrences (all)	1	2	4
Upper respiratory tract infection			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	1 / 140 (0.71%)
occurrences (all)	0	1	1

Urinary tract infection			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	1 / 140 (0.71%)
occurrences (all)	0	1	1
Urinary tract infection bacterial			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 131 (0.00%)	0 / 139 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 139 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported