Clinical trial results:
Efficacy and safety of S 47445 versus placebo as adjunctive treatment of Major Depressive Disorder in patients with an inadequate response to antidepressant therapy. A randomised, double-blind, placebo controlled international, multicentre study.

Summary

EudraCT number	2015-003867-13
Trial protocol	HU FI SK CZ BG
Global end of trial date	06 April 2017

Results information

Result version number	v1 (current)
This version publication date	08 March 2018
First version publication date	08 March 2018

Trial information

Trial identification

Sponsor protocol code	CL2-47445-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02805439
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches internationales Servier, +33 155 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	06 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2017
Global end of trial reached?	Yes
Global end of trial date	06 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of the efficacy of the two doses of S 47445 (15mg/day and 50mg/day) compared to placebo in add on to serotonine selective reuptake inhibitor after two periods of 4-week treatment using the Hamilton Depression Rating Scale 17 items (HAM-D).

Protection of trial subjects:

This 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.

Background therapy:

S 47445 was compared to placebo in add on to an antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI). SSRIs taken by the patient concomitantly to S 47455 or placebo were managed as recommended in their Summary of Product Characterisitics for the treatment of a depressive episode. Fluvoxamine was contraindicated.

Evidence for comparator: -

Actual start date of recruitment	23 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 71
Country: Number of subjects enrolled	Bulgaria: 76
Country: Number of subjects enrolled	Czech Republic: 57
Country: Number of subjects enrolled	Finland: 25
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Ukraine: 93
Worldwide total number of subjects	414
EEA total number of subjects	271

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	414
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female patients aged from 18 to 65 years suffering from moderate to severe major depressive episode with an inadequate response to current SSRI after at least 6 weeks of treatment.

Period 1

Period 1 title	First 4-week treatment period (W0-W4)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	S 47445 15 mg (W0-W4)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S 47445 15 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of S47445 15 mg was administered once a day during breakfast with a glass of water.

Arm title	S 47445 50 mg (W0-W4)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S 47445 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of S47445 50 mg was administered once a day during breakfast with a glass of water.

Arm title	Placebo (W0-W4)

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:

1 tablet of placebo was administered once a day during breakfast with a glass of water.

Number of subjects in period 1	S 47445 15 mg (W0-W4)	S 47445 50 mg (W0-W4)	Placebo (W0-W4)
Started	70	66	278
Completed	68	64	267
Not completed	2	2	11
Consent withdrawn by subject	1	1	4
Patient left the city.	-	-	1
Adverse event, non-fatal	1	-	3
Lack of efficacy	-	1	2
Protocol deviation	-	-	1

Period 2

Period 2 title	Second 4-week treatment period (W4-W8)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	S 47445 15 mg (W4-W8)

Arm description:

These patients were in the placebo group during W0-W4 and not sufficiently improved at the end of the first 4-week treatment period (W0-W4). They were re-randomised at W4 to S 47445 15 mg before entering in the second 4-week treatment period (W4-W8).

Arm type	Experimental
Investigational medicinal product name	S 47445 15 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of S 47445 15 mg was administered once a day during breakfast with a glass of water.

Arm title	S 47445 50 mg (W4-W8)

Arm description:

These patients were in the placebo group during W0-W4 and not sufficiently improved at the end of the first 4-week treatment period (W0-W4). They were re-randomised at W4 to S 47445 50 mg before entering in the second 4-week treatment period (W4-W8).

Arm type	Experimental
Investigational medicinal product name	S 47445 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of S47445 50 mg was administered once a day during breakfast with a glass of water.

Arm title	Placebo (W4-W8)

Arm description:

These patients were in the placebo group during W0-W4 and not sufficiently improved at the end of the first 4-week treatment period (W0-W4). They were re-randomised at W4 to placebo before entering in the second 4-week treatment period (W4-W8).

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:

1 tablet of placebo was administered once a day during breakfast with a glass of water.

Number of subjects in period 2[1]	S 47445 15 mg (W4-W8)	S 47445 50 mg (W4-W8)	Placebo (W4-W8)
Started	74	77	76
Completed	73	77	76
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

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: A sequential parallel comparison design was used for the study. Patients starting the period 2 (W4-W8) have not been defined as all patients completing the period 1 (W0-W4) but as those of the placebo not sufficiently improved at the end the period 1.

Baseline characteristics

Reporting groups	
Reporting group title	S 47445 15 mg (W0-W4)
Reporting group description: -	
Reporting group title	S 47445 50 mg (W0-W4)
Reporting group description: -	
Reporting group title	Placebo (W0-W4)
Reporting group description: -	

Reporting group values	S 47445 15 mg (W0-W4)	S 47445 50 mg (W0-W4)	Placebo (W0-W4)
Number of subjects	70	66	278
Age categorical Units: Subjects			
Adults (18-64 years)	69	63	275
From 65-84 years	1	3	3
Age continuous Units: years			
arithmetic mean	47.5	45.8	46.7
standard deviation	± 11.6	± 12.2	± 11.6
Gender categorical Units: Subjects			
Female	49	41	198
Male	21	25	80

Reporting group values	Total		
Number of subjects	414		
Age categorical Units: Subjects			
Adults (18-64 years)	407		
From 65-84 years	7		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	288		
Male	126		

Subject analysis sets	
Subject analysis set title	Re-randomised Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Patients in placebo group not sufficiently improved at the end of the first 4-week treatment period (W4) were re-randomised either to placebo, S 47445 15 mg or S 47445 50 mg. Re-randomised Full Analysis Set (RFAS) were those re-randomised patients having taken at least one dose of IMP after W4 and having a value at W4 and at least one post W4 value during the second 4-week treatment period (W4-

W8) for the primary efficacy endpoint.

Reporting group values	Re-randomised Full Analysis Set		
Number of subjects	227		
Age categorical Units: Subjects			
Adults (18-64 years)	225		
From 65-84 years	2		
Age continuous Units: years			
arithmetic mean	46.8		
standard deviation	± 11.1		
Gender categorical Units: Subjects			
Female	157		
Male	70		

End points

End points reporting groups

Reporting group title	S 47445 15 mg (W0-W4)
Reporting group description: -	
Reporting group title	S 47445 50 mg (W0-W4)
Reporting group description: -	
Reporting group title	Placebo (W0-W4)
Reporting group description: -	
Reporting group title	S 47445 15 mg (W4-W8)
Reporting group description:	
These patients were in the placebo group during W0-W4 and not sufficiently improved at the end of the first 4-week treatment period (W0-W4). They were re-randomised at W4 to S 47445 15 mg before entering in the second 4-week treatment period (W4-W8).	
Reporting group title	S 47445 50 mg (W4-W8)
Reporting group description:	
These patients were in the placebo group during W0-W4 and not sufficiently improved at the end of the first 4-week treatment period (W0-W4). They were re-randomised at W4 to S 47445 50 mg before entering in the second 4-week treatment period (W4-W8).	
Reporting group title	Placebo (W4-W8)
Reporting group description:	
These patients were in the placebo group during W0-W4 and not sufficiently improved at the end of the first 4-week treatment period (W0-W4). They were re-randomised at W4 to placebo before entering in the second 4-week treatment period (W4-W8).	
Subject analysis set title	Re-randomised Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients in placebo group not sufficiently improved at the end of the first 4-week treatment period (W4) were re-randomised either to placebo, S 47445 15 mg or S 47445 50 mg. Re-randomised Full Analysis Set (RFAS) were those re-randomised patients having taken at least one dose of IMP after W4 and having a value at W4 and at least one post W4 value during the second 4-week treatment period (W4-W8) for the primary efficacy endpoint.	

Primary: Change in HAM-D total score (W0-W4 and W4-W8)

End point title	Change in HAM-D total score (W0-W4 and W4-W8)
End point description:	
During the treatment period W0-W4, expression of the endpoint was change in HAM-D total score between W0 (baseline for this period) and W4. During the treatment period W4-W8, expression of the endpoint was change in HAM-D total score between W4 (baseline for this period) and W8.	
End point type	Primary
End point timeframe:	
This endpoint was based on the weighted average of W0-W4 and W4-W8 treatment effects.	

End point values	S 47445 15 mg (W0-W4)	S 47445 15 mg (W4-W8)	S 47445 50 mg (W0-W4)	S 47445 50 mg (W4-W8)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	73	65	77
Units: no units				
arithmetic mean (standard deviation)	-5.6 (± 4.1)	-5.9 (± 4.0)	-4.9 (± 4.0)	-6.8 (± 4.5)

End point values	Placebo (W0-W4)	Placebo (W4-W8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	76		
Units: no units				
arithmetic mean (standard deviation)	-6.2 (± 4.6)	-6.7 (± 5.2)		

Statistical analyses

Statistical analysis title	Primary analysis (W0-W4)
Statistical analysis description:	
All the longitudinal observations at each post-baseline visit on the W0-W4 period of all patients in the FAS were considered.	
Comparison groups	S 47445 15 mg (W0-W4) v Placebo (W0-W4)
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	1.45
Variability estimate	Standard deviation
Dispersion value	0.57

Statistical analysis title	Primary analysis (W0-W4)
Statistical analysis description:	
All the longitudinal observations at each post-baseline visit on the W0-W4 period of all patients in the FAS were considered.	
Comparison groups	S 47445 50 mg (W0-W4) v Placebo (W0-W4)
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.44
Variability estimate	Standard deviation
Dispersion value	0.58

Statistical analysis title	Primary analysis (W4-W8)
Statistical analysis description: All the longitudinal observations at each post-baseline visit on the W4-W8 period of all patients in the RFAS were considered.	
Comparison groups	S 47445 15 mg (W4-W8) v Placebo (W4-W8)
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	2.36
Variability estimate	Standard deviation
Dispersion value	0.73

Statistical analysis title	Primary analysis (W4-W8)
Statistical analysis description: All the longitudinal observations at each post-baseline visit on the W4-W8 period of all patients in the RFAS were considered.	
Comparison groups	S 47445 50 mg (W4-W8) v Placebo (W4-W8)
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	1.44
Variability estimate	Standard deviation
Dispersion value	0.72

Statistical analysis title	Primary analysis (W0-W4 and W4-W8)
Statistical analysis description: The comparison of S47445 15 mg to placebo was based on the weighted average of period W0-W4 and period W4-W8 treatment effects, in the FAS and the RFAS respectively. A weight w=0.5 for each period was used. All the longitudinal observations at each post-baseline visit on the W0-W8 period of all patients in the FAS were considered. Note: the groups to be taken in account for the comparison are [S47445 15 mg (W0-W4) and S47445 15 mg (W4-W8)] versus [Placebo (W0-W4) and Placebo (W4-W8)].	
Comparison groups	S 47445 15 mg (W0-W4) v Placebo (W0-W4)

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [1]
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	1.53
Variability estimate	Standard deviation
Dispersion value	0.46

Notes:

[1] - One-sided adjusted p-value taking into account Holm procedure for multiplicity adjustment (to be compared to 0.025)

Statistical analysis title	Primary analysis (W0-W4 and W4-W8)

Statistical analysis description:

The comparison of S47445 15 mg to placebo was based on the weighted average of period W0-W4 and period W4-W8 treatment effects, in the FAS and the RFAS respectively. A weight w=0.5 for each period was used. All the longitudinal observations at each post-baseline visit on the W0-W8 period of all patients in the FAS were considered.
Note: the groups to be taken in account for the comparison are [S47445 50 mg (W0-W4) and S47445 50 mg (W4-W8)] versus [Placebo (W0-W4) and Placebo (W4-W8)].

Comparison groups	S 47445 50 mg (W0-W4) v Placebo (W0-W4)
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [2]
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	1.57
Variability estimate	Standard deviation
Dispersion value	0.46

Notes:

[2] - p-value to be compared to 0.025

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious between the first intake and last IMP intake + 15 days (both included), except those for patients in placebo during W0-W4 re-randomised in S 47445 groups between first and last IMP intakes.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	S 47445 15 mg - W0-W4
Reporting group description: -	
Reporting group title	S 47445 50 mg - W0-W4
Reporting group description: -	
Reporting group title	Placebo - W0-W4
Reporting group description: -	
Reporting group title	S 47445 15 mg - W4-W8
Reporting group description: -	
Reporting group title	S 47445 50 mg - W4-W8
Reporting group description: -	
Reporting group title	S 47445 15 mg - W0-W8
Reporting group description: -	
Reporting group title	Placebo - W4-W8
Reporting group description: -	
Reporting group title	S 47445 50 mg - W0-W8
Reporting group description: -	
Reporting group title	Placebo - W0-W8

Reporting group description: -

Serious adverse events	S 47445 15 mg - W0-W4	S 47445 50 mg - W0-W4	Placebo - W0-W4
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vision blurred			

subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	S 47445 15 mg - W4-W8	S 47445 50 mg - W4-W8	S 47445 15 mg - W0-W8
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Spinal pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (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

Serious adverse events	Placebo - W4-W8	S 47445 50 mg - W0-W8	Placebo - W0-W8
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	2 / 127 (1.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	S 47445 15 mg - W0-W4	S 47445 50 mg - W0-W4	Placebo - W0-W4
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 70 (20.00%)	11 / 66 (16.67%)	60 / 278 (21.58%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Hangover			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Premenstrual headache			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0

Rhinitis allergic			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Emotional poverty			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Nightmare			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	0 / 278 (0.00%)
occurrences (all)	0	1	0
Suicidal ideation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Tension			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	2
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	1 / 278 (0.36%)
occurrences (all)	0	1	1
Blood triglycerides increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
ECG signs of ventricular hypertrophy			

subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	1 / 278 (0.36%)
occurrences (all)	0	1	1
Electrocardiogram J wave abnormal			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	2
Weight increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Hand fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Sinus bradycardia			

subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	3 / 278 (1.08%)
occurrences (all)	0	1	4
Dizziness exertional			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	2
Dizziness postural			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	4 / 278 (1.44%)
occurrences (all)	0	0	4
Dysgeusia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	0 / 278 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	4 / 70 (5.71%)	4 / 66 (6.06%)	8 / 278 (2.88%)
occurrences (all)	4	4	8
Intercostal neuralgia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	1 / 278 (0.36%)
occurrences (all)	0	2	1
Restless legs syndrome			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 70 (0.00%)	2 / 66 (3.03%)	1 / 278 (0.36%)
occurrences (all)	0	2	1
Tension headache			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0

Tremor			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Chronic gastritis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	2
Dyspepsia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis eosinophilic			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	0 / 278 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Irritable bowel syndrome			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Nausea			

subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	6 / 278 (2.16%)
occurrences (all)	0	0	6
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Urethral prolapse			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Spinal pain			

subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 66 (1.52%)	0 / 278 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis viral			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	2 / 278 (0.72%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	2 / 70 (2.86%)	1 / 66 (1.52%)	1 / 278 (0.36%)
occurrences (all)	2	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	3 / 278 (1.08%)
occurrences (all)	0	0	3
Respiratory tract infection viral			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	0 / 278 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 70 (0.00%)	0 / 66 (0.00%)	1 / 278 (0.36%)
occurrences (all)	0	0	1

Non-serious adverse events	S 47445 15 mg - W4-W8	S 47445 50 mg - W4-W8	S 47445 15 mg - W0-W8

Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 74 (13.51%)	17 / 77 (22.08%)	14 / 70 (20.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Hangover			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Premenstrual headache			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			

subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Emotional poverty			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Tension			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
ECG signs of ventricular hypertrophy			

subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram J wave abnormal			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	1 / 74 (1.35%)	1 / 77 (1.30%)	1 / 70 (1.43%)
occurrences (all)	1	1	1
Hand fracture			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			

subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Dizziness exertional			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 74 (2.70%)	3 / 77 (3.90%)	4 / 70 (5.71%)
occurrences (all)	2	3	5
Intercostal neuralgia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Tension headache			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0

Tremor			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Chronic gastritis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 74 (1.35%)	2 / 77 (2.60%)	0 / 70 (0.00%)
occurrences (all)	1	2	0
Dry mouth			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Gastroenteritis eosinophilic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Nausea			

subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	2 / 70 (2.86%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Urethral prolapse			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Spinal pain			

subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Conjunctivitis viral			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	0 / 70 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 74 (1.35%)	2 / 77 (2.60%)	0 / 70 (0.00%)
occurrences (all)	1	2	0
Nasopharyngitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 77 (1.30%)	2 / 70 (2.86%)
occurrences (all)	0	1	2
Respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	2 / 70 (2.86%)
occurrences (all)	1	0	2
Tracheitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 74 (0.00%)	0 / 77 (0.00%)	0 / 70 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo - W4-W8	S 47445 50 mg - W0-W8	Placebo - W0-W8

Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 116 (14.66%)	15 / 66 (22.73%)	33 / 127 (25.98%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Hangover			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Premenstrual headache			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			

subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Emotional poverty			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
Suicidal ideation			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Tension			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 116 (0.00%)	2 / 66 (3.03%)	0 / 127 (0.00%)
occurrences (all)	0	2	0
Blood triglycerides increased			
subjects affected / exposed	2 / 116 (1.72%)	0 / 66 (0.00%)	2 / 127 (1.57%)
occurrences (all)	2	0	2
ECG signs of ventricular hypertrophy			

subjects affected / exposed	0 / 116 (0.00%)	2 / 66 (3.03%)	0 / 127 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram J wave abnormal			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Hand fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Sinus bradycardia			

subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	2 / 127 (1.57%)
occurrences (all)	0	1	2
Dizziness exertional			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Dizziness postural			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 116 (0.86%)	4 / 66 (6.06%)	5 / 127 (3.94%)
occurrences (all)	1	4	5
Intercostal neuralgia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	2	0
Restless legs syndrome			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 116 (0.00%)	2 / 66 (3.03%)	0 / 127 (0.00%)
occurrences (all)	0	2	0
Tension headache			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0

Tremor			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Chronic gastritis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis eosinophilic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Irritable bowel syndrome			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed	2 / 116 (1.72%)	0 / 66 (0.00%)	3 / 127 (2.36%)
occurrences (all)	2	0	3
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1
Urethral prolapse			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Spinal pain			

subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 66 (1.52%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis viral			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	2 / 127 (1.57%)
occurrences (all)	1	0	2
Nasopharyngitis			
subjects affected / exposed	2 / 116 (1.72%)	2 / 66 (3.03%)	3 / 127 (2.36%)
occurrences (all)	2	2	3
Respiratory tract infection			
subjects affected / exposed	2 / 116 (1.72%)	0 / 66 (0.00%)	4 / 127 (3.15%)
occurrences (all)	2	0	5
Respiratory tract infection viral			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	1	0	1
Increased appetite			
subjects affected / exposed	0 / 116 (0.00%)	0 / 66 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2016	Breast Cancer Resistance Protein substrate was forbidden as concomitant treatment except those prescribed at lower dosage and already described in the protocol. To ensure a more accurate follow-up and analysis of suicidal ideation, these symptoms when collected with Columbia Suicide Severity Rating Scale had to be reported as adverse event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported