



Clinical trial results:

A randomized, double-blind, parallel-group study of the safety and efficacy of RO4917523 versus placebo, as adjunctive therapy in patients with major depressive disorder with inadequate response to ongoing antidepressant treatment.

Summary

EudraCT number	2011-001436-33
Trial protocol	DE
Global end of trial date	27 September 2013

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	08 August 2015

Trial information

Trial identification

Sponsor protocol code	NP25620
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01437657
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-LaRoche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F.Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F.Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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	27 September 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of two fixed doses of RO4917523 (basimglurant) compared to placebo in a confirmatory manner over 6 weeks as adjunctive therapy in patients with major depressive disorder (MDD) with inadequate response to ongoing antidepressant treatment. The change will be measured based on the mean change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy:

Ongoing treatment with a single antidepressant of the SSRI or SNRI class was continued for the duration of the double-blind treatment period without modification of the dosing schedule.

Evidence for comparator: -

Actual start date of recruitment	05 October 2011
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	Poland: 86
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Chile: 25
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	United States: 106
Country: Number of subjects enrolled	Romania: 16
Worldwide total number of subjects	333
EEA total number of subjects	127

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)	321
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened over a period of 2 weeks.

Period 1

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

Blinding implementation details:

Matching placebo capsules

Arms

Are arms mutually exclusive?	Yes
Arm title	RO4917523 0.5 mg

Arm description:

Subjects received 0.5 mg of RO4917523 once daily for 6 weeks, then were followed for 3 weeks.

Arm type	Experimental
Investigational medicinal product name	RO4917523
Investigational medicinal product code	
Other name	basimglurant
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One basimglurant 0.5 mg capsule was administered by the patient once a day in the morning immediately after breakfast. On visit days, treatment was taken after pre-dose assessments.

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

Dosage and administration details:

One placebo capsule was administered by the patient once a day in the morning immediately after breakfast. On visit days, treatment was taken after pre-dose assessments.

Arm title	RO4917523 1.5 mg
------------------	------------------

Arm description:

Subjects received 1.5 mg of RO4917523 once daily for 6 weeks, then were followed for 3 weeks.

Arm type	Experimental
Investigational medicinal product name	RO4917523
Investigational medicinal product code	
Other name	basimglurant
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One basimglurant 0.5 mg capsule and 1 basimglurant 1.0 mg capsule were administered by the patient once a day in the morning immediately after breakfast. On visit days, treatment was taken after pre-

Arm title	Placebo
Arm description: Subjects received placebo once daily for 6 weeks, then were followed for 3 weeks.	
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:

Two placebo capsules were administered by the patient once a day in the morning immediately after breakfast. On visit days, treatment was taken after pre-dose assessments.

Number of subjects in period 1	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo
Started	112	111	110
Completed treatment	97 ^[1]	96 ^[2]	99 ^[3]
Completed follow-up	103	105	106
Completed	103	105	106
Not completed	9	6	4
Not specified	9	6	3
Did not receive study drug	-	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects who discontinued treatment could enter the follow-up period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects who discontinued treatment could enter the follow-up period.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects who discontinued treatment could enter the follow-up period.

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
-----------------------	---------------

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	333	333	
Age categorical			
Units: Subjects			
Age =< 65 years	326	326	
Age > 65 years	7	7	
Age continuous			
Units: years			
arithmetic mean	46.6		
standard deviation	± 11.2	-	
Gender categorical			
Units: Subjects			
Female	217	217	
Male	116	116	

End points

End points reporting groups

Reporting group title	RO4917523 0.5 mg
Reporting group description: Subjects received 0.5 mg of RO4917523 once daily for 6 weeks, then were followed for 3 weeks.	
Reporting group title	RO4917523 1.5 mg
Reporting group description: Subjects received 1.5 mg of RO4917523 once daily for 6 weeks, then were followed for 3 weeks.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo once daily for 6 weeks, then were followed for 3 weeks.	

Primary: Change From Baseline in The Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change From Baseline in The Montgomery Asberg Depression Rating Scale (MADRS) Total Score
End point description: The clinician-rated MADRS is a 10-item instrument designed to assess the overall severity of depressive symptoms on a scale of 0 to 6, with 0 being the least amount of symptoms and 6 being the most amount of symptoms. The total score ranges from 0 to 60 and is equal to the sum of all items. A negative change from baseline indicates that symptoms improved.	
End point type	Primary
End point timeframe: From Baseline to Day 42	

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: scores on a scale				
least squares mean (standard error)	-14.1 (± 0.9)	-16.1 (± 0.9)	-14.6 (± 0.9)	

Statistical analyses

Statistical analysis title	Analysis of MADRS total score for RO4917523 0.5 mg
Comparison groups	Placebo v RO4917523 0.5 mg
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742
Method	mixed-effect model repeat measures

Statistical analysis title	Analysis of MADRS total score for RO4917523 1.5 mg
Comparison groups	RO4917523 1.5 mg v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.416
Method	mixed-effect model repeat measures

Secondary: Change From Baseline in The Quick Inventory of Depressive Symptomatology-Self Report 16-Item Version (QIDS-SR16) Total Score

End point title	Change From Baseline in The Quick Inventory of Depressive Symptomatology-Self Report 16-Item Version (QIDS-SR16) Total Score
-----------------	--

End point description:

The QIDS-SR16 is a 16-item scale completed by patients to assess the severity of their depressive symptoms. The scale assesses all nine symptom domains selected by DSMIV to diagnose a major depressive episode. Each of the 16 items is scored on a 4-point anchored scale, representing least severe (0) to most severe (3). Specific instructions for calculating a total score are included in the scale. Total scores range from 0 to 27 with a higher score indicating greater severity. A negative change from baseline indicates that symptoms improved.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Day 42

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: scores on a scale				
least squares mean (standard error)	-6 (± 0.5)	-7.5 (± 0.5)	-5.8 (± 0.5)	

Statistical analyses

Statistical analysis title	Analysis of QIDS-SR16 for RO4917523 0.5 mg
Comparison groups	RO4917523 0.5 mg v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.362 ^[1]
Method	mixed-effect model repeat measures

Notes:

[1] - Unadjusted 1-sided lower p-value

Statistical analysis title	Analysis of QIDS-SR16 for RO4917523 1.5 mg
Comparison groups	RO4917523 1.5 mg v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[2]
Method	mixed-effect model repeat measures

Notes:

[2] - Unadjusted 1-sided lower p-value

Secondary: Change From Baseline in The Clinician Global Impression-Severity (CGI-S) Rating Score-LOCF

End point title	Change From Baseline in The Clinician Global Impression-Severity (CGI-S) Rating Score-LOCF
-----------------	--

End point description:

The CGI-S was used to evaluate the overall clinical status (severity of illness). The CGI-S is rated on a scale of 1 to 7 with 1 referring to "normal" and 7 referring to "most severely ill." A negative change from baseline indicates that symptoms have improved. The analysis was applied to the last observation carried forward (LOCF) values.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Day 42

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: scores on a scale				
arithmetic mean (standard error)	-1.25 (± 0.11)	-1.49 (± 0.12)	-1.39 (± 0.11)	

Statistical analyses

Statistical analysis title	Analysis of CGI-S for RO4917523 0.5 mg
Comparison groups	RO4917523 0.5 mg v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775 ^[3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Unadjusted 1-sided lower p-value

Statistical analysis title	Analysis of CGI-S for RO4917523 1.5 mg
-----------------------------------	--

Comparison groups	Placebo v RO4917523 1.5 mg
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.268 ^[4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Unadjusted 1-sided lower p-value

Secondary: Distribution of Rating Scores For The Clinician Global Impression-Improvement (CGI-I) Scale-LOCF

End point title	Distribution of Rating Scores For The Clinician Global Impression-Improvement (CGI-I) Scale-LOCF
-----------------	--

End point description:

The CGI-I was used to evaluate the change from baseline in clinical status. The CGI-I is rated on a scale of 1 to 7 with 1 referring to "very much improved" and 7 referring to "very much worse." The analysis was applied to the last observation carried forward (LOCF) values.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Day 42

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: scores on a scale				
arithmetic mean (standard error)	2.58 (± 0.11)	2.21 (± 0.1)	2.41 (± 0.1)	

Statistical analyses

Statistical analysis title	Analysis of CGI-I for RO4917523 0.5 mg
Comparison groups	RO4917523 0.5 mg v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.851 ^[5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Unadjusted 1-sided lower p-value

Statistical analysis title	Analysis of CGI-I for RO4917523 1.5 mg
Comparison groups	RO4917523 1.5 mg v Placebo

Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 ^[6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Unadjusted 1-sided lower p-value

Secondary: Distribution of Rating Scores For The Patient Global Impression-Improvement (PGI-I) Scale

End point title	Distribution of Rating Scores For The Patient Global Impression-Improvement (PGI-I) Scale
-----------------	---

End point description:

The PGI-I is a self-reported instrument to record the patient's own assessment of improvement since baseline. The patient is asked to rate their condition now, as compared to how it was before they began study medication, using a 7-point scale ranging from very much better (1) to very much worse (7). The PGI-I is essentially a patient-reported version of the CGI-I.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Day 42

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: scores on a scale				
arithmetic mean (standard error)	2.7 (± 0.11)	2.41 (± 0.12)	2.63 (± 0.1)	

Statistical analyses

Statistical analysis title	Analysis of PGI-I for RO4917523 0.5 mg
Comparison groups	RO4917523 0.5 mg v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.534 ^[7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Unadjusted 1-sided lower p-value

Statistical analysis title	Analysis of PGI-I for RO4917523 1.5 mg
Comparison groups	Placebo v RO4917523 1.5 mg

Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045 ^[8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Unadjusted 1-sided lower p-value

Secondary: Percent of Subjects Exhibiting Response After 6 Weeks of Treatment

End point title	Percent of Subjects Exhibiting Response After 6 Weeks of Treatment
-----------------	--

End point description:

Response was defined as a $\geq 50\%$ improvement in the total score of the clinician-rated Montgomery Asberg Depression Rating Scale (MADRS) from Baseline to Day 42.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Day 42

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: percent of subjects				
number (not applicable)	41.96	50.45	46.79	

Statistical analyses

Statistical analysis title	Analysis of response for RO4917523 0.5 mg
Comparison groups	RO4917523 0.5 mg v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.804 ^[9]
Method	Fisher exact

Notes:

[9] - Unadjusted 1-sided upper p-value

Statistical analysis title	Analysis of response for RO4917523 1.5 mg
Comparison groups	Placebo v RO4917523 1.5 mg
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.342 ^[10]
Method	Fisher exact

Notes:

[10] - Unadjusted 1-sided upper p-value

Secondary: Percent of Subjects With Remission After 6 Weeks of Treatment

End point title	Percent of Subjects With Remission After 6 Weeks of Treatment
-----------------	---

End point description:

Remission was defined as having a clinician-rated Montgomery Asberg Depression Rating Scale (MADRS) total score of ≤ 10 at Day 42

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Day 42

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: percent of subjects				
number (not applicable)	26.79	36.04	30.28	

Statistical analyses

Statistical analysis title	Analysis of remission for RO4917523 0.5 mg
Comparison groups	RO4917523 0.5 mg v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765 ^[11]
Method	Fisher exact

Notes:

[11] - Unadjusted 1-sided upper p-value

Statistical analysis title	Analysis of remission for RO4917523 1.5 mg
Comparison groups	Placebo v RO4917523 1.5 mg
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222 ^[12]
Method	Fisher exact

Notes:

[12] - Unadjusted 1-sided upper p-value

Post-hoc: Change From Baseline in The Patient-Rated Montgomery Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change From Baseline in The Patient-Rated Montgomery Asberg Depression Rating Scale (MADRS) Total Score
-----------------	---

End point description:

Following the assessment of the MADRS by the rater, the patient then completed the MADRS as a self-assessment using the same laptop computer (the "patient-rated MADRS"; Sachs et al., 2011). The assessment of the patient-rated MADRS was made at all visits where the clinician-rated MADRS was assessed (excluding follow up). It was administered as a computerized, interactive interview, involving a series of probe and follow-up questions with multiple choice response options. A negative change from baseline indicates that symptoms improved.

End point type	Post-hoc
----------------	----------

End point timeframe:

From Baseline to Day 42

End point values	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	111	109	
Units: scores on a scale				
least squares mean (standard error)	-13.1 (\pm 1)	-16.2 (\pm 1)	-13.3 (\pm 1)	

Statistical analyses

Statistical analysis title	Analysis of MADRS total score for RO4917523 0.5 mg
Comparison groups	RO4917523 0.5 mg v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.547 ^[13]
Method	mixed-effect model repeat measures

Notes:

[13] - Unadjusted 1-sided lower p-value

Statistical analysis title	Analysis of MADRS total score for RO4917523 1.5 mg
Comparison groups	RO4917523 1.5 mg v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 ^[14]
Method	mixed-effect model repeat measures

Notes:

[14] - Unadjusted 1-sided lower p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

9 weeks after start of treatment

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.0
--------------------	------

Reporting groups

Reporting group title	RO4917523 0.5 mg
-----------------------	------------------

Reporting group description:

Subjects received 0.5 mg of RO4917523 once daily for 6 weeks, then were followed for 3 weeks.

Reporting group title	RO4917523 1.5 mg
-----------------------	------------------

Reporting group description:

Subjects received 1.5 mg of RO4917523 once daily for 6 weeks, then were followed for 3 weeks.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Subjects received placebo once daily for 6 weeks, then were followed for 3 weeks.

Serious adverse events	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 112 (2.68%)	1 / 111 (0.90%)	2 / 109 (1.83%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Tibia Fracture			
subjects affected / exposed	0 / 112 (0.00%)	1 / 111 (0.90%)	0 / 109 (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			
Abdominal Pain			
subjects affected / exposed	1 / 112 (0.89%)	0 / 111 (0.00%)	0 / 109 (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
Psychiatric disorders			
Major Depression			

subjects affected / exposed	0 / 112 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 111 (0.00%)	0 / 109 (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
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	1 / 112 (0.89%)	0 / 111 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 112 (0.00%)	0 / 111 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	RO4917523 0.5 mg	RO4917523 1.5 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 112 (30.36%)	44 / 111 (39.64%)	39 / 109 (35.78%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 112 (4.46%)	26 / 111 (23.42%)	6 / 109 (5.50%)
occurrences (all)	7	32	8
Headache			
subjects affected / exposed	12 / 112 (10.71%)	8 / 111 (7.21%)	8 / 109 (7.34%)
occurrences (all)	14	8	10
Somnolence			
subjects affected / exposed	13 / 112 (11.61%)	7 / 111 (6.31%)	10 / 109 (9.17%)
occurrences (all)	15	7	10
Gastrointestinal disorders			

Dry Mouth subjects affected / exposed occurrences (all)	4 / 112 (3.57%) 4	6 / 111 (5.41%) 6	4 / 109 (3.67%) 6
Nausea subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 6	8 / 111 (7.21%) 8	13 / 109 (11.93%) 14
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	7 / 112 (6.25%) 7	6 / 111 (5.41%) 6	2 / 109 (1.83%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1	0 / 111 (0.00%) 0	8 / 109 (7.34%) 9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2011	This amendment introduced the following key changes: -Blood sampling for the purpose of clinical genotyping was added to the collection of specimens from patients during the study (3 mL blood sample on Day 1). -An electrocardiogram (ECG) measurement on Day 14 was added to the schedule of assessments. -Individuals whose occupation is to drive or operate mass transportation (i.e., buses, trains), large vehicles (i.e., trucks), or heavy machinery were added to the exclusion criteria. -Fluvoxamine, pregabalin and gabapentin were added to the list of prohibited concomitant medications.
02 April 2012	This amendment introduced the following key changes: -The inclusion criteria were amended to enable enrollment of patients up to 70 years of age, and patients with a body mass index (BMI) between 18 and 38 kg/m ² inclusive. -By health authority request, patients with a positive finding on the Columbia-Suicide Severity Rating Scale (C-SSRS) or with liver function test abnormalities that met Hy's law were required to be withdrawn. -Assumptions for sample size calculation were clarified, and the description of handling of missing data was updated. -The option for the Drug Safety Monitoring Board (DSMB) to review efficacy data during safety reviews was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported