Clinical trial results:
A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of RO4995819 Versus Placebo, as Adjunctive Therapy in Patients with Major Depressive Disorder Having Inadequate Response to Ongoing Antidepressant Treatment

Summary

EudraCT number	2011-002160-24
Trial protocol	AT DE SK
Global end of trial date	04 June 2014

Results information

Result version number	v1 (current)
This version publication date	17 July 2016
First version publication date	17 July 2016

Trial information

Trial identification

Sponsor protocol code	BP25712

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01457677
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche Ltd
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	Trial Information Support Line-TISL, F.Hoffmann-La Roche Ltd., +41 61688 1111, global.rochegenentechtrials@roche.com
Scientific contact	Trial Information Support Line-TISL, F.Hoffmann-La Roche Ltd., +41 61688 1111, global.rochegenentechtrials@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	17 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 6 weeks treatment of RO4995819 versus placebo as adjunctive therapy in patients with MDD having inadequate response to ongoing antidepressant treatment based on mean change in Montgomery Asberg Depression Rating Scale (MADRS) scores from baseline to end of treatment.

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. The participants were provided an Emergency Medical Call Center Help Desk in the case of emergency during the study to ensure the safety . An Independent Data Monitoring Committee (IDMC) supervised the participants safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Ukraine: 34
Country: Number of subjects enrolled	United States: 191
Worldwide total number of subjects	357
EEA total number of subjects	42

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)	353
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 01 December 2011 to 04 June 2014 in 72 sites in 8 countries. The 30 mg RO4995819 arm was dropped after the interim analysis, and therefore contains a smaller number of patients compared with the other arms.

Pre-assignment

Screening details:

A total of 357 patients were enrolled in the study.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo oral once daily for 6 weeks.

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

Dosage and administration details:

Participants were to take matching placebo capsule orally once daily for 6 weeks.

Arm title	RO4995819 5mg

Arm description:

Participants received RO4995819 5 mg oral once daily for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	RO4995819
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were to take RO4995819 5 mg capsule orally once daily for 6 weeks.

Arm title	RO4995819 15mg

Arm description:

Participants received RO4995819 15 mg oral once daily for 6 weeks.

Arm type	Experimental

Investigational medicinal product name	RO4995819
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were to take RO4995819 15 mg capsule orally once daily for 6 weeks.

Arm title	RO4995819 30mg

Arm description:

Participants received RO4995819 30 mg oral once daily for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	RO4995819
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were to take RO4995819 30 mg capsule orally once daily for 6 weeks.

Number of subjects in period 1	Placebo	RO4995819 5mg	RO4995819 15mg
Started	99	101	102
Completed	87	85	84
Not completed	12	16	18
Consent withdrawn by subject	2	8	7
Failure to return	3	1	3
Adverse event, non-fatal	1	5	4
Violation of selection criteria at entry	1	-	1
Administrative/Other	4	2	3
Refused Treatment/Did Not Cooperate	1	-	-

Number of subjects in period 1	RO4995819 30mg
Started	55
Completed	45
Not completed	10
Consent withdrawn by subject	1
Failure to return	3
Adverse event, non-fatal	5
Violation of selection criteria at entry	1
Administrative/Other	-
Refused Treatment/Did Not Cooperate	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo oral once daily for 6 weeks.	
Reporting group title	RO4995819 5mg
Reporting group description:	
Participants received RO4995819 5 mg oral once daily for 6 weeks.	
Reporting group title	RO4995819 15mg
Reporting group description:	
Participants received RO4995819 15 mg oral once daily for 6 weeks.	
Reporting group title	RO4995819 30mg
Reporting group description:	
Participants received RO4995819 30 mg oral once daily for 6 weeks.	

Reporting group values	Placebo	RO4995819 5mg	RO4995819 15mg
Number of subjects	99	101	102
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	45.7	46.1	46.3
standard deviation	± 11.3	± 11.2	± 11.5
Gender categorical Units: Subjects			
Female	69	71	69
Male	30	30	33

Reporting group values	RO4995819 30mg	Total	
Number of subjects	55	357	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	44.6		
standard deviation	± 12.9	-	
Gender categorical Units: Subjects			
Female	38	247	
Male	17	110	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo oral once daily for 6 weeks.	
Reporting group title	RO4995819 5mg
Reporting group description:	
Participants received RO4995819 5 mg oral once daily for 6 weeks.	
Reporting group title	RO4995819 15mg
Reporting group description:	
Participants received RO4995819 15 mg oral once daily for 6 weeks.	
Reporting group title	RO4995819 30mg
Reporting group description:	
Participants received RO4995819 30 mg oral once daily for 6 weeks.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol population included all participants who were randomized, had a valid baseline assessment of the MADRS total score (centralized rating) and at "Day 42/Early Withdrawal" Visit.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of all participants who have received at least one dose of study medication and had at least one post-dose safety assessment, whether withdrawn prematurely or not.	

Primary: Mean Change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at Day 42

End point title	Mean Change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at Day 42
End point description:	
The MADRS is a 10-item scale designed to measure depression severity and detects changes due to antidepressant treatment. Each item is scored on a 7-point scale and the scores range from "0 = item not present or normal" to "6 = severe or continuous presence of the symptoms". Total score is calculated by adding the scores for all the 10 items and it will range from "0 to 60". The interpretation of the scores are: 0 to 6 – normal/symptom absent; 7 to 19 – mild depression; 20 to 34 – moderate depression; > 34 – severe depression. Higher scores represent a more severe condition. Per protocol population was used for this analysis.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) and Day 42	

End point values	Placebo	RO4995819 5mg	RO4995819 15mg	RO4995819 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86[1]	89[2]	88[3]	47[4]
Units: Units on scale				
least squares mean (confidence interval 95%)	-11.77 (-14.16 to -9.38)	-12.82 (-15.18 to -10.46)	-11.79 (-14.16 to -9.42)	-13.2 (-16.42 to -9.99)

Notes:
[1] - Only those participants available at the specified time points were analyzed
[2] - Only those participants available at the specified time points were analyzed
[3] - Only those participants available at the specified time points were analyzed
[4] - Only those participants available at the specified time points were analyzed

Statistical analyses

Statistical analysis title	Effect of 05 mg dose Vs Placebo
Comparison groups	Placebo v RO4995819 5mg
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.53
Method	Mixed models analysis
Parameter estimate	Effect
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.36
upper limit	2.26

Statistical analysis title	Effect of 15 mg dose Vs Placebo
Comparison groups	Placebo v RO4995819 15mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.99
Method	Mixed models analysis
Parameter estimate	Effect
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.34
upper limit	3.3

Statistical analysis title	Copy of Effect of 30 mg dose Vs Placebo
Comparison groups	RO4995819 30mg v Placebo

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.48
Method	Mixed models analysis
Parameter estimate	Effect
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.41
upper limit	2.54

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Safety population was used for this analysis.

End point type	Secondary

End point timeframe:

Up to Day 98

End point values	Placebo	RO4995819 5mg	RO4995819 15mg	RO4995819 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	101	102	55
Units: Participants				
Participants with AEs	74	76	79	47
Serious Adverse Events	1	3	2	0
AE leading to withdrawal	1	4	4	5

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Exhibiting Remission (a MADRS score of <=10)

End point title	Number of Participants Exhibiting Remission (a MADRS score of <=10)

End point description:

Number of participants in remission with one previous treatment failure and with total Montgomery Asberg Depression Rating Scale (MADRS) score <=10. The MADRS is a 10-item scale designed to measure depression severity and detects changes due to antidepressant treatment. Each item is scored on a 7-point scale and the scores range from "0 = item not present or normal" to "6 = severe or continuous presence of the symptoms". Total score is calculated by adding the scores for all the 10 items and it will range from "0 to 60". The interpretation of the scores are: 0 to 6 – normal/symptom

absent; 7 to 19 – mild depression; 20 to 34 – moderate depression; > 34 – severe depression. Higher scores represent a more severe condition. Per protocol population was used for this analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 42

End point values	Placebo	RO4995819 5mg	RO4995819 15mg	RO4995819 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	89	88	47
Units: Participants	25	31	25	13

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Exhibiting Response (reduction in MADRS score of >= 50% of the baseline score)

End point title	Number of Participants Exhibiting Response (reduction in MADRS score of >= 50% of the baseline score)

End point description:

Number of participants with reduction of >=50 percent (%) in MADRS total score (indicates response). The MADRS is a 10-item scale designed to measure depression severity and detects changes due to antidepressant treatment. Each item is scored on a 7-point scale and the scores range from "0 = item not present or normal" to "6 = severe or continuous presence of the symptoms". Total score is calculated by adding the scores for all the 10 items and it will range from "0 to 60". The interpretation of the scores are: 0 to 6 – normal/symptom absent; 7 to 19 – mild depression; 20 to 34 – moderate depression; > 34 – severe depression. Higher scores represent a more severe condition. Per protocol population was used for this analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 42

End point values	Placebo	RO4995819 5mg	RO4995819 15mg	RO4995819 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	89	88	47
Units: Participants	29	32	33	18

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormalities in Neurological Examination

End point title	Number of Participants with Abnormalities in Neurological Examination

End point description:

Number of participants with abnormalities in neurological examinations as determined by the investigators. Neurological examinations included assessment of general tone, power, sensation, deep reflexes, gait, balance, coordination, ocular movements and mental status. Safety population was used for this analysis.

End point type	Secondary

End point timeframe:

Up to 14 weeks

End point values	Placebo	RO4995819 5mg	RO4995819 15mg	RO4995819 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	101	102	55
Units: Participants	2	3	4	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Extrapyramidal Symptom Rating Scale (Abbreviated)

End point title	Change from Baseline in Extrapyramidal Symptom Rating Scale (Abbreviated)

End point description:

The ESRS is a 12-item clinician-rated scale designed to assess the severity of extrapyramidal symptoms. Dyskinesic movements are rated according to both frequency and amplitude. It measures the four types of drug-induced movement disorders (Parkinsonism, Dystonia, akathisia, and Dyskinesia). Items are rated on a "6 point scale ranging from 0 (normal) to 5 (extremely severe)". The higher the score, the more severely the symptoms affect function. Safety population was used for this analysis.

End point type	Secondary

End point timeframe:

Up to 14 weeks

End point values	Placebo	RO4995819 5mg	RO4995819 15mg	RO4995819 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	90	88	49
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.08 (± 0.46)	-0.1 (± 0.45)	-0.09 (± 0.4)	-0.02 (± 0.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS is a tool used to assess the lifetime suicidality of a patient (C-SSRS screening/baseline) as well as any new instances of suicidality (C-SSRS since last visit). The CSSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. Safety population was used for this analysis.

End point type	Secondary

End point timeframe:

Baseline to 14 Weeks

End point values	Placebo	RO4995819 5mg	RO4995819 15mg	RO4995819 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	101	102	55
Units: Participants				
Suicidal Ideation	23	18	22	12
Suicidal Behavior	0	1	1	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
14 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients who received placebo oral once daily for 6 weeks	
Reporting group title	RO4995819 5mg
Reporting group description:	
Particpants who received RO4995819 5 mg oral once daily for 6 weeks.	
Reporting group title	RO4995819 15mg
Reporting group description:	
Particpants who received RO4995819 15 mg oral once daily for 6 weeks.	
Reporting group title	RO4995819 30mg
Reporting group description:	
Particpants who received RO4995819 30 mg oral once daily for 6 weeks.	

Serious adverse events	Placebo	RO4995819 5mg	RO4995819 15mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 99 (1.01%)	3 / 101 (2.97%)	2 / 102 (1.96%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 99 (1.01%)	0 / 101 (0.00%)	0 / 102 (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			
Depression			

subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 102 (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
Suicidal ideation			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 102 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 102 (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

Serious adverse events	RO4995819 30mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	RO4995819 5mg	RO4995819 15mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 99 (74.75%)	76 / 101 (75.25%)	79 / 102 (77.45%)
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 99 (27.27%)	22 / 101 (21.78%)	31 / 102 (30.39%)
occurrences (all)	48	70	85
Dizziness			
subjects affected / exposed	12 / 99 (12.12%)	12 / 101 (11.88%)	21 / 102 (20.59%)
occurrences (all)	20	17	32
Somnolence			
subjects affected / exposed	1 / 99 (1.01%)	7 / 101 (6.93%)	4 / 102 (3.92%)
occurrences (all)	1	8	4
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	3 / 99 (3.03%)	4 / 101 (3.96%)	4 / 102 (3.92%)
occurrences (all)	4	4	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 99 (15.15%)	10 / 101 (9.90%)	25 / 102 (24.51%)
occurrences (all)	19	14	32
Diarrhoea			
subjects affected / exposed	10 / 99 (10.10%)	11 / 101 (10.89%)	6 / 102 (5.88%)
occurrences (all)	18	17	7
Vomiting			
subjects affected / exposed	5 / 99 (5.05%)	6 / 101 (5.94%)	10 / 102 (9.80%)
occurrences (all)	6	9	12
Abdominal pain upper			
subjects affected / exposed	6 / 99 (6.06%)	1 / 101 (0.99%)	1 / 102 (0.98%)
occurrences (all)	13	1	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 99 (6.06%)	10 / 101 (9.90%)	8 / 102 (7.84%)
occurrences (all)	8	12	10
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 99 (1.01%)	2 / 101 (1.98%)	5 / 102 (4.90%)
occurrences (all)	1	2	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 99 (7.07%)	3 / 101 (2.97%)	10 / 102 (9.80%)
occurrences (all)	7	3	12
Upper respiratory tract infection			
subjects affected / exposed	7 / 99 (7.07%)	7 / 101 (6.93%)	4 / 102 (3.92%)
occurrences (all)	8	8	4
Influenza			
subjects affected / exposed	4 / 99 (4.04%)	6 / 101 (5.94%)	4 / 102 (3.92%)
occurrences (all)	4	6	4
Ear infection			

subjects affected / exposed	0 / 99 (0.00%)	1 / 101 (0.99%)	0 / 102 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	RO4995819 30mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 55 (85.45%)		
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	27		
Dizziness			
subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	54		
Somnolence			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	17 / 55 (30.91%)		
occurrences (all)	27		
Diarrhoea			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	31		
Abdominal pain upper			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2011	Modifications to inclusion criteria re outpatient status & medications. Removal of AESIs. Modification of PK sampling.
28 November 2011	Addition of neurological & cognitive examinations. Removal of 'recurrent' from diagnostic criteria.
26 January 2012	Addition of updated toxicological Data. CZ country-specific change upper limit on the CGI-S.
10 May 2012	Clarification of suicidal risk assessment, change in version of CSSRS used at screening. Modification of prohibited medications. Addition of pepsinogen test, cotinine test. Update to SAE/pregnancy reporting. Consent requirement for pregnant partner. Additional potential exploratory post-hoc analyses. Admin changes (# study centres, clarifications, correction of typographical errors).
28 November 2012	Change to D1 post-dose monitoring and ePK schedule. Change to sample size & interim analysis. Inclusion of re-screening (for non-medical fails) and extension of screening period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported