Clinical trial results:
Long-term, Phase 3, Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Oral OPC-34712 as Adjunctive Therapy in Adults with Major Depressive Disorder, the Orion Trial

Summary

EudraCT number	2011-001351-37
Trial protocol	HU DE SK
Global end of trial date	18 May 2017

Results information

Result version number	v1 (current)
This version publication date	23 June 2018
First version publication date	23 June 2018

Trial information

Trial identification

Sponsor protocol code	331-10-238

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01360866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Mary Hobart, PhD Senior Director, Global Clinical Development Phone: (240) 683-3194 Fax: (240) 76, Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., 44 1628581161, gtrewartha@INCResearch.com
Scientific contact	Mary Hobart, PhD Senior Director, Global Clinical Development Phone: (240) 683-3194 Fax: (240) 76, Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inq, 44 1628581161, gtrewartha@INCResearch.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2017
Global end of trial reached?	Yes
Global end of trial date	18 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of oral brexpiprazole (OPC-34712) as adjunctive therapy in the treatment of adults with major depressive disorder (MDD).

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the Institutional Review Board or Independent Ethics Committee at each respective trial center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 October 2011
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	Canada: 50
Country: Number of subjects enrolled	France: 156
Country: Number of subjects enrolled	Germany: 160
Country: Number of subjects enrolled	Hungary: 36
Country: Number of subjects enrolled	Poland: 312
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Russian Federation: 351
Country: Number of subjects enrolled	Serbia: 86
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Ukraine: 67
Country: Number of subjects enrolled	United States: 1699
Worldwide total number of subjects	2944
EEA total number of subjects	691

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)	2932
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 2944 participants at 188 sites in the following 11 countries: Canada, France, Germany, Hungary, Poland, Romania, Russian Federation, Serbia, Slovakia, Ukraine, and United States (US).

Pre-assignment

Screening details:

Participants who completed the last schedule visit of one of the double-blind, phase 3 brexpiprazole MDD trials (Trials 331-10-227, 331-10-228, and 331-12-282) and who, in investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole. Participants signed a separate informed consent form for 331-10-238.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior Placebo

Arm description:

Participants who had received placebo with antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.

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

Dosage and administration details:

The first dose of open-label brexpiprazole was taken one day after the last dose was taken for the prior double-blind, phase 3 efficacy trial so that adjunctive treatment continued without interruption. Participants initiated open-label dosing with brexpiprazole 0.5 mg/day for 1 Week. Participants unable to tolerate brexpiprazole 0.5 mg/day were withdrawn from the trial. The dose of brexpiprazole was increased to 1 mg/day at the Week 1 visit. Participants unable to tolerate brexpiprazole 1 mg/day may have decreased to 0.5 mg/day at any time after the Week 1 visit. Investigators might have further increased the dose to brexpiprazole 2 mg/day and then to brexpiprazole 3 mg/day, with an interval of at least 5 days between dose increases. An interval of at least 5 days between dose adjustments was recommended for dose decrease. During the Treatment Phase of Trial 331-10-238, participants remained on the same assigned open-label ADT from the prior double-blind, phase 3 efficacy trial.

Arm title	Prior Brexpiprazole

Arm description:

Participants who had received Brexpiprazole with antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.

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

Dosage and administration details:

The first dose of open-label brexpiprazole was taken one day after the last dose was taken for the prior double-blind, phase 3 efficacy trial so that adjunctive treatment continued without interruption. Participants initiated open-label dosing with brexpiprazole 0.5 mg/day for 1 Week. Participants unable to tolerate brexpiprazole 0.5 mg/day were withdrawn from the trial. The dose of brexpiprazole was increased to 1 mg/day at the Week 1 visit. Participants unable to tolerate brexpiprazole 1 mg/day may have decreased to 0.5 mg/day at any time after the Week 1 visit. Investigators might have further increased the dose to brexpiprazole 2 mg/day and then to brexpiprazole 3 mg/day, with an interval of at least 5 days between dose increases. An interval of at least 5 days between dose adjustments was recommended for dose decrease. During the Treatment Phase of Trial 331-10-238, participants remained on the same assigned open-label ADT from the prior double-blind, phase 3 efficacy trial.

Arm title	Prior ADT

Arm description:

Participants who had received only antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.

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

Dosage and administration details:

The first dose of open-label brexpiprazole was taken one day after the last dose was taken for the prior double-blind, phase 3 efficacy trial so that adjunctive treatment continued without interruption. Participants initiated open-label dosing with brexpiprazole 0.5 mg/day for 1 Week. Participants unable to tolerate brexpiprazole 0.5 mg/day were withdrawn from the trial. The dose of brexpiprazole was increased to 1 mg/day at the Week 1 visit. Participants unable to tolerate brexpiprazole 1 mg/day may have decreased to 0.5 mg/day at any time after the Week 1 visit. Investigators might have further increased the dose to brexpiprazole 2 mg/day and then to brexpiprazole 3 mg/day, with an interval of at least 5 days between dose increases. An interval of at least 5 days between dose adjustments was recommended for dose decrease. During the Treatment Phase of Trial 331-10-238, participants remained on the same assigned open-label ADT from the prior double-blind, phase 3 efficacy trial.

Arm title	Prior Seroquel

Arm description:

Participants who had received Seroquel with ADT in previous double blind phase 3 studies. In this study, participants received brexpiprazole.

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

Dosage and administration details:

The first dose of open-label brexpiprazole was taken one day after the last dose was taken for the prior double-blind, phase 3 efficacy trial so that adjunctive treatment continued without interruption. Participants initiated open-label dosing with brexpiprazole 0.5 mg/day for 1 Week. Participants unable to tolerate brexpiprazole 0.5 mg/day were withdrawn from the trial. The dose of brexpiprazole was increased to 1 mg/day at the Week 1 visit. Participants unable to tolerate brexpiprazole 1 mg/day may have decreased to 0.5 mg/day at any time after the Week 1 visit. Investigators might have further increased the dose to brexpiprazole 2 mg/day and then to brexpiprazole 3 mg/day, with an interval of at least 5 days between dose increases. An interval of at least 5 days between dose adjustments was recommended for dose decrease. During the Treatment Phase of Trial 331-10-238, participants remained on the same assigned open-label ADT from the prior double-blind, phase 3 efficacy trial.

Number of subjects in period 1	Prior Placebo	Prior Brexpiprazole	Prior ADT
Started	516	707	1645
Completed	295	420	1126
Not completed	221	287	519
Withdrawn by Investigator	9	8	31
Lack of Efficacy	30	40	30
Adverse Event	56	61	134
Protocol Deviation	25	33	61
Withdrawal by participant	79	89	168
Lost to follow-up	11	28	41
Paticipant met withdrawal criteria	11	28	54

Number of subjects in period 1	Prior Seroquel
Started	76
Completed	54
Not completed	22
Withdrawn by Investigator	2
Lack of Efficacy	4
Adverse Event	6
Protocol Deviation	2
Withdrawal by participant	8
Lost to follow-up	-
Paticipant met withdrawal criteria	-

Baseline characteristics

Reporting groups	
Reporting group title	Prior Placebo
Reporting group description:	
Participants who had received placebo with antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	
Reporting group title	Prior Brexpiprazole
Reporting group description:	
Participants who had received Brexpiprazole with antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	
Reporting group title	Prior ADT
Reporting group description:	
Participants who had received only antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	
Reporting group title	Prior Seroquel
Reporting group description:	
Participants who had received Seroquel with ADT in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	

Reporting group values	Prior Placebo	Prior Brexpiprazole	Prior ADT
Number of subjects	516	707	1645
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	45.0	45.0	44.0
standard deviation	± 11.0	± 11.0	± 12.0
Gender categorical			
Units: Subjects			
Female	367	479	1108
Male	149	228	537

Reporting group values	Prior Seroquel	Total	
Number of subjects	76	2944	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	

Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	44.0		
standard deviation	± 11.0	-	
Gender categorical			
Units: Subjects			
Female	51	2005	
Male	25	939	

End points

End points reporting groups

Reporting group title	Prior Placebo
Reporting group description:	
Participants who had received placebo with antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	
Reporting group title	Prior Brexpiprazole
Reporting group description:	
Participants who had received Brexpiprazole with antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	
Reporting group title	Prior ADT
Reporting group description:	
Participants who had received only antidepressant therapy [ADT] in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	
Reporting group title	Prior Seroquel
Reporting group description:	
Participants who had received Seroquel with ADT in previous double blind phase 3 studies. In this study, participants received brexpiprazole.	

Primary: Adverse Events (AEs) - Number of participants with AEs

End point title	Adverse Events (AEs) - Number of participants with AEs[1]
End point description:	
The primary outcome variable was the safety and tolerability of brexpiprazole, which was assessed by examining the frequency and severity of adverse events (AEs).	
End point type	Primary
End point timeframe:	
From screening to week 52/early termination	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistical analysis was done.

End point values	Prior Placebo	Prior Brexpiprazole	Prior ADT	Prior Seroquel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	516	706	1640	76
Units: Participants				
Participants with adverse events	400	511	1165	51
Participants with treatment emergent AE (TEAE)	399	510	1163	51
Participants with serious TEAE	14	23	33	1
Participants with severe TEAE	48	64	99	4
Partcipants discontinued due to AE	55	58	134	6

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Clinical Global Impression - Severity (CGI-S) of Illness scale Score

End point title	Mean Change From Baseline in Clinical Global Impression - Severity (CGI-S) of Illness scale Score

End point description:

The severity of illness for each participant was rated using the CGI-S .The investigator was answered the following question: "Considering your total clinical experience with this particular population, how mentally ill was the participant at that time?" Response choices included: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants.

End point type	Secondary

End point timeframe:

From screening to week 52/early termination

End point values	Prior Placebo	Prior Brexpiprazole	Prior ADT	Prior Seroquel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	512	698	1630	76
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.77 (± 1.11)	-0.63 (± 1.16)	-0.48 (± 1.04)	-0.93 (± 0.85)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Clinical Global Impression - Improvement (CGI-I) Score

End point title	Change From Baseline in Mean Clinical Global Impression - Improvement (CGI-I) Score

End point description:

The efficacy of trial treatment was rated for each participant using the CGI-I. The investigator rated the participant's total improvement whether or not it was due entirely to drug treatment. All responses were compared to the participant's condition at screening/Baseline (i.e., last scheduled visit of the prior double-blind phase 3 trial). Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse and 7 = very much worse.

End point type	Secondary

End point timeframe:

From screening to week 52/early termination

End point values	Prior Placebo	Prior Brexpiprazole	Prior ADT	Prior Seroquel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	505	693	1606	75
Units: Units on a scale				
arithmetic mean (standard deviation)	2.60 (± 1.30)	2.63 (± 1.34)	2.63 (± 1.39)	2.40 (± 1.17)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline in Sheehan Disability Scale (SDS) Mean Score

End point title	Summary of Mean Change From Baseline in Sheehan Disability Scale (SDS) Mean Score

End point description:

The SDS was a self-rated instrument used to measure the effect of the participant's symptoms on regular life responsibilities. The SDS was a visual analogue scale that used spatio-visual, numeric, and verbal descriptive anchors simultaneously to assess disability across the 3 domains with 0 = not at all, to 10 = extremely. Scores of 5 and above were associated with significant functional impairment.

End point type	Secondary

End point timeframe:

From screening to week 52/early termination

End point values	Prior Placebo	Prior Brexpiprazole	Prior ADT	Prior Seroquel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	346	457	1165	53
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.80 (± 2.80)	-0.70 (± 2.60)	-0.40 (± 2.30)	-1.00 (± 1.70)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Inventory of Depressive Symptomatology (Self-report) Total Score

End point title	Change From Baseline in the Inventory of Depressive Symptomatology (Self-report) Total Score

End point description:

The inventory of depressive symptomatology - self report (IDS-SR) was a 30-item self-report measure used to assess core diagnostic depressive symptoms as well as atypical and melancholic symptom features of MDD.

End point type	Secondary

End point timeframe:

From screening to week 52/early termination

End point values	Prior Placebo	Prior Brexpiprazole	Prior ADT	Prior Seroquel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	491	664	1556	75
Units: Units on a scale				
arithmetic mean (standard deviation)	-5.25 (± 12.21)	-4.76 (± 11.79)	-3.94 (± 10.57)	-7.44 (± 8.89)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From screening to 30 (+ 2) days following the 52 weeks treatment period or early termination.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Prior Placebo
Reporting group description: Participants who received placebo with antidepressant therapy [ADT] in previous double blind phase 3 studies.	
Reporting group title	Prior Brexpiprazole
Reporting group description: Participants who received Brexpiprazole with antidepressant therapy [ADT] in previous double blind phase 3 studies.	
Reporting group title	Prior ADT
Reporting group description: Participants who received only antidepressant therapy [ADT] in previous double blind phase 3 studies.	
Reporting group title	Prior Seroquel
Reporting group description: Participants who received Seroquel with antidepressant therapy [ADT] in previous double blind phase 3 studies.	

Serious adverse events	Prior Placebo	Prior Brexpiprazole	Prior ADT
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 516 (2.71%)	23 / 706 (3.26%)	33 / 1640 (2.01%)
number of deaths (all causes)	2	2	0
number of deaths resulting from adverse events	2	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Ovarian Cancer			

subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic Neuroendocrine Tumour			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Adenocarcinoma			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	0 / 1640 (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 Cell Carcinoma			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	2 / 1640 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Withdrawal Syndrome			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic Adhesions			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	2 / 516 (0.39%)	1 / 706 (0.14%)	0 / 1640 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Completed Suicide			
subjects affected / exposed	0 / 516 (0.00%)	2 / 706 (0.28%)	0 / 1640 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Depression			
subjects affected / exposed	2 / 516 (0.39%)	3 / 706 (0.42%)	3 / 1640 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive Symptom			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Self-Injury			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			

subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
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	0 / 516 (0.00%)	1 / 706 (0.14%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	2 / 516 (0.39%)	1 / 706 (0.14%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram Qt Prolonged			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella Fracture			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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

Cardiac disorders			
Aortic Valve Incompetence			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Congestive			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Ventricular Dysfunction			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Dizziness			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	2 / 1640 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal Disorder			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Radiculopathy			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	0 / 1640 (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

Ruptured Cerebral Aneurysm			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	0 / 1640 (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
Sciatica			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Vein Thrombosis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's Disease			

subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Gastric Ulcer Perforation			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	0 / 1640 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	2 / 1640 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis Acute			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Renal and urinary disorders			
Renal Disorder			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	0 / 1640 (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
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	0 / 1640 (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
Spinal Osteoarthritis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	0 / 1640 (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

Spondylolisthesis			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	0 / 1640 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Cellulitis			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Gastroenteritis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Herpes Zoster			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney Infection			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Peritonitis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 706 (0.00%)	0 / 1640 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (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
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 516 (0.00%)	1 / 706 (0.14%)	0 / 1640 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 516 (0.00%)	0 / 706 (0.00%)	1 / 1640 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Prior Seroquel		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 76 (1.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian Cancer			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic Neuroendocrine Tumour			

subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal Adenocarcinoma				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal Cell Carcinoma				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest Pain				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug Withdrawal Syndrome				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Pelvic Adhesions				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic Obstructive Pulmonary Disease				

subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Completed Suicide				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressive Symptom				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional Self-Injury				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Major Depression				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicidal Ideation				

subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicide Attempt				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Electrocardiogram Qt Prolonged				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Contusion				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional Overdose				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Patella Fracture				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Aortic Valve Incompetence				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac Failure Congestive				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular Dysfunction				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular Accident				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyskinesia				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Extrapyramidal Disorder				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar Radiculopathy				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ruptured Cerebral Aneurysm				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				

subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal Vein Thrombosis			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Crohn's Disease			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric Ulcer Perforation			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis Acute			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Disorder			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar Spinal Stenosis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Osteoarthritis			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Kidney Infection				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Tract Infection				

subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 76 (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	Prior Placebo	Prior Brexpiprazole	Prior ADT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	296 / 516 (57.36%)	323 / 706 (45.75%)	787 / 1640 (47.99%)
Investigations			
Weight Increased			
subjects affected / exposed	118 / 516 (22.87%)	100 / 706 (14.16%)	296 / 1640 (18.05%)
occurrences (all)	126	103	312
Nervous system disorders			
Akathisia			
subjects affected / exposed	54 / 516 (10.47%)	37 / 706 (5.24%)	99 / 1640 (6.04%)
occurrences (all)	60	41	109
Headache			
subjects affected / exposed	42 / 516 (8.14%)	55 / 706 (7.79%)	105 / 1640 (6.40%)
occurrences (all)	52	74	126
Somnolence			
subjects affected / exposed	40 / 516 (7.75%)	60 / 706 (8.50%)	130 / 1640 (7.93%)
occurrences (all)	43	65	137
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	37 / 516 (7.17%)	50 / 706 (7.08%)	88 / 1640 (5.37%)
occurrences (all)	40	57	101
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	14 / 516 (2.71%)	15 / 706 (2.12%)	33 / 1640 (2.01%)
occurrences (all)	14	17	34
Nausea			
subjects affected / exposed	26 / 516 (5.04%)	32 / 706 (4.53%)	61 / 1640 (3.72%)
occurrences (all)	29	37	63
Psychiatric disorders			
Anxiety			
subjects affected / exposed	39 / 516 (7.56%)	37 / 706 (5.24%)	76 / 1640 (4.63%)
occurrences (all)	44	45	89
Insomnia			
subjects affected / exposed	30 / 516 (5.81%)	40 / 706 (5.67%)	108 / 1640 (6.59%)
occurrences (all)	30	45	125
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	25 / 516 (4.84%)	35 / 706 (4.96%)	98 / 1640 (5.98%)
occurrences (all)	26	40	105
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	37 / 516 (7.17%)	28 / 706 (3.97%)	117 / 1640 (7.13%)
occurrences (all)	37	29	123

Non-serious adverse events	Prior Seroquel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 76 (43.42%)		
Investigations			
Weight Increased			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Nervous system disorders			
Akathisia			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	9		
Somnolence			

subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	5		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	6		
Infections and infestations			
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2011	Amendment 1: Clarification of trial procedures, administrative changes, and correction of typographical errors.
16 November 2012	Amendment 2: Allow enrollment of eligible participants who completed the last scheduled visit of a double-blind phase 3 brexpiprazole MDD trial, to remove the definitions of incomplete response and response, to match the specifications for potential Hy's Law cases, to clarify that the contraceptive methods of vasectomy and tubal ligation apply to the subject and partner, to update trial duration and the estimated number of enrolled subjects, and to make administrative changes
11 April 2014	Amendment 3: The study duration was reduced from 52 weeks to 26 weeks and the number of assessments was decreased, as well as administrative clarifications were made
13 June 2014	Amendment 4: Include Columbia-Suicide Severity Rating Scale (C-SSRS) assessment at Week 8 and Week 20 (removed in error from amendment 3 issued on 11 Apr 2014) and updated sponsor contact details

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported