Clinical trial results:
A Prospective, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Safety and Efficacy Study of Oral ELND005 as an Adjunctive Maintenance Treatment in Patients with Bipolar I Disorder

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

Summary

EudraCT number	2012-001935-30
Trial protocol	CZ ES LT BG
Global end of trial date	09 June 2014

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	ELND005-BPD201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01674010
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Transition Therapeutics Ireland Limited
Sponsor organisation address	Earlsfort Centre, Earlsfort Terrace, Arthur Cox Building, Dublin 2, Ireland,
Public contact	Aleksandra Pastrak,MD, PhD, VP of Clinical Development and Medical Office, Transition Therapeutics Ireland Limited, +1 416 263 1227, apastrak@transitiontherapeutics.com
Scientific contact	Aleksandra Pastrak,MD, PhD, VP of Clinical Development and Medical Office, Transition Therapeutics Ireland Limited, +1 416 263 1227, apastrak@transitiontherapeutics.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	09 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of ELND005 compared to placebo as adjunctive maintenance therapy in patients with Bipolar I Disorder (BPD I), as evidenced by a delay in the time to recurrence of any type of mood episode in the randomized phase of the study

Protection of trial subjects:

400 patients planned for Phase 1

Background therapy:

lamotrigine (LTG) or valproic acid (VPA)

Evidence for comparator:

NA

Actual start date of recruitment	20 August 2012
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	Poland: 8
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Bulgaria: 43
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	United States: 210
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Turkey: 13
Worldwide total number of subjects	309
EEA total number of subjects	86

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)	308
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Stable BPD I patients (off study drug) treated for an index episode with Standard of Care Maintenance treatment (Screening up to 2 weeks)

Period 1

Period 1 title	Phase 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open Treatment Phase

Arm description:

ELND005 500 mg BID

Arm type	Experimental
Investigational medicinal product name	ELND005 500 mg
Investigational medicinal product code	ELND005 500 mg
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ELND005 500 mg BID

Number of subjects in period 1	Open Treatment Phase
Started	309
Completed	129
Not completed	180
Adverse event, serious fatal	1
Sponsor's decision	79
Consent withdrawn by subject	25
Physician decision	9
Did not remain in a stable remission	30
Adverse event, non-fatal	10
Lost to follow-up	19
Protocol deviation	7

Period 2	
Period 2 title	Phase 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo matching ELND005 500 mg BID
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo matching ELND005 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Placebo delivered as 2x 250 mg tablet matching the IP ELND005	
Arm title	ELND005 500 mg BID
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	ELND005
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 500 mg equivalent of 2 tablets of 250 mg BID	

Number of subjects in period 2	Placebo matching ELND005 500 mg BID	ELND005 500 mg BID
Started	65	64
Completed	3	3
Not completed	62	61
Sponsor's decision	-	45
Consent withdrawn by subject	8	7
Physician decision	-	2
Adverse event, non-fatal	1	1
Pregnancy	1	1
Mood Episode recurrence	8	2
Sponsor Decision	42	-
Lost to follow-up	1	2
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Open Treatment Phase
Reporting group description:	
ELND005 500 mg BID	

Reporting group values	Open Treatment Phase	Total	
Number of subjects	309	309	
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	44.3		
standard deviation	± 11.09	-	
Gender categorical			
Units: Subjects			
Female	163	163	
Male	146	146	

End points

End points reporting groups

Reporting group title	Open Treatment Phase
Reporting group description: ELND005 500 mg BID	
Reporting group title	Placebo matching ELND005 500 mg BID
Reporting group description: -	
Reporting group title	ELND005 500 mg BID
Reporting group description: -	

Primary: Time to recurrence of any mood episode

End point title	Time to recurrence of any mood episode[1]
End point description:	
End point type	Primary
End point timeframe: Time to recurrence of any mood episode (depressive, manic/hypomanic, or mixed episode), whichever occurs first, during the randomized phase of the study	

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: Justification: The trial was prematurely ended and no analysis was done on the primary endpoint

End point values	Placebo matching ELND005 500 mg BID	ELND005 500 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: days				

Notes:

[2] - The trial was prematurely ended and no analysis was done on the primary endpoint

[3] - The trial was prematurely ended and no analysis was done on the primary endpoint

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded for each patient starting from the time the consent form was signed until the
completion of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Phase 1 ELND005 500 mg BID
Reporting group description: -	
Reporting group title	Phase 2 Placebo
Reporting group description: -	
Reporting group title	Phase 2 ELND005 500 mg BID
Reporting group description: -	

Serious adverse events	Phase 1 ELND005 500 mg BID	Phase 2 Placebo	Phase 2 ELND005 500 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 309 (3.88%)	3 / 65 (4.62%)	2 / 64 (3.13%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Diplopia			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impulsive behaviour			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Phase 1 ELND005 500 mg BID	Phase 2 Placebo	Phase 2 ELND005 500 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	153 / 309 (49.51%)	29 / 65 (44.62%)	30 / 64 (46.88%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Hypertension			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Thrombosis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 309 (1.29%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Crying			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Eye complication associated with device			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Fatigue			
subjects affected / exposed	5 / 309 (1.62%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Influenza like illness			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Immune system disorders			
Allergy to animal			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Seasonal allergy			
subjects affected / exposed	2 / 309 (0.65%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Food allergy			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Uterine spasm			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Cough			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Nasal congestion			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Nasal cyst			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Painful respiration			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Sinus congestion			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Sleep apnoea syndrome			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Agitation			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Alcohol abuse			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Anorgasmia			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Anxiety			
subjects affected / exposed	10 / 309 (3.24%)	3 / 65 (4.62%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Bipolar I disorder			
subjects affected / exposed	5 / 309 (1.62%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Bruxism			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Depersonalisation			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Depressed mood			
subjects affected / exposed	13 / 309 (4.21%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Depression			
subjects affected / exposed	7 / 309 (2.27%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Depressive symptom			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Drug dependence			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Emotional poverty			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Impulsive behaviour			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Initial insomnia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Insomnia			

subjects affected / exposed	12 / 309 (3.88%)	2 / 65 (3.08%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Intentional self-injury			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Irritability			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Libido decreased			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Mania			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Nicotine dependence			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Nightmare			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Psychotic disorder			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Restlessness			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Stress			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Suicide attempt			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Alcoholism			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Investigations			

Blood glucose increased			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Blood insulin increased			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Hepatic enzyme increased			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Liver function test abnormal			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Weight decreased			
subjects affected / exposed	4 / 309 (1.29%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Weight increased			
subjects affected / exposed	7 / 309 (2.27%)	1 / 65 (1.54%)	3 / 64 (4.69%)
occurrences (all)	153	29	30
Blood pressure increased			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	6 / 309 (1.94%)	3 / 65 (4.62%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Animal bite			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Arthropod bite			
subjects affected / exposed	0 / 309 (0.00%)	2 / 65 (3.08%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Concussion			

subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Contusion			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Excoriation			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Fall			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Foot fracture			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Humerus fracture			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Joint dislocation			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Joint injury			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Ligament sprain			
subjects affected / exposed	5 / 309 (1.62%)	0 / 65 (0.00%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Meniscus injury			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Road traffic accident			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Superficial injury of eye			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Tendon rupture			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Tooth fracture			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Wrist fracture			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Bite			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Palpitations			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Tachyarrhythmia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Tachycardia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Disturbance in attention			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Dizziness			
subjects affected / exposed	11 / 309 (3.56%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Dysarthria			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Embolic stroke			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Essential tremor			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Headache			
subjects affected / exposed	14 / 309 (4.53%)	2 / 65 (3.08%)	4 / 64 (6.25%)
occurrences (all)	153	29	30
Hypersomnia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Hypoaesthesia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Hypogeusia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Memory impairment			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Migraine			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Paraesthesia			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Sciatica			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Sedation			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Somnolence			

subjects affected / exposed	5 / 309 (1.62%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Tardive dyskinesia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Tremor			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Ear and labyrinth disorders			
Ear deformity acquired			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Ear pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Vertigo			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Dry eye			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Photophobia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Vision blurred			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Abdominal pain			
subjects affected / exposed	0 / 309 (0.00%)	2 / 65 (3.08%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Abdominal pain upper			
subjects affected / exposed	4 / 309 (1.29%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Colitis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Constipation			
subjects affected / exposed	5 / 309 (1.62%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Dental caries			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Diarrhoea			
subjects affected / exposed	3 / 309 (0.97%)	2 / 65 (3.08%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Dry mouth			
subjects affected / exposed	4 / 309 (1.29%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Dyspepsia			
subjects affected / exposed	2 / 309 (0.65%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Food poisoning			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Haematochezia			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Nausea			
subjects affected / exposed	7 / 309 (2.27%)	0 / 65 (0.00%)	3 / 64 (4.69%)
occurrences (all)	153	29	30

Toothache			
subjects affected / exposed	6 / 309 (1.94%)	0 / 65 (0.00%)	3 / 64 (4.69%)
occurrences (all)	153	29	30
Vomiting			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Alopecia			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Dermal cyst			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Dermatitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Eczema			
subjects affected / exposed	2 / 309 (0.65%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Miliaria			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Pruritus			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Pruritus generalised			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Rash			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Rash erythematous			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Pyuria			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	30	153	29
Urinary incontinence			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 309 (0.65%)	1 / 65 (1.54%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Back pain			
subjects affected / exposed	3 / 309 (0.97%)	2 / 65 (3.08%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Flank pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Intervertebral disc degeneration			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Intervertebral disc protrusion			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Joint range of motion decreased			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Muscle spasms			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Musculoskeletal chest pain			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Musculoskeletal pain			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Myalgia			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Neck pain			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Pain in extremity			
subjects affected / exposed	2 / 309 (0.65%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Spinal pain			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Bronchitis			
subjects affected / exposed	2 / 309 (0.65%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Conjunctivitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30

Cystitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Ear infection			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Furuncle			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Gastroenteritis			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Gastroenteritis viral			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Influenza			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	3 / 64 (4.69%)
occurrences (all)	153	29	30
Kidney infection			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Laryngitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Lower respiratory tract infection			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Nasopharyngitis			
subjects affected / exposed	19 / 309 (6.15%)	2 / 65 (3.08%)	4 / 64 (6.25%)
occurrences (all)	153	29	30
Otitis media			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Paronychia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30

Pharyngitis			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Pharyngitis streptococcal			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Pneumonia			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Sinusitis			
subjects affected / exposed	4 / 309 (1.29%)	0 / 65 (0.00%)	3 / 64 (4.69%)
occurrences (all)	153	29	30
Subcutaneous abscess			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Tooth abscess			
subjects affected / exposed	1 / 309 (0.32%)	1 / 65 (1.54%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Tooth infection			
subjects affected / exposed	3 / 309 (0.97%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Upper respiratory tract infection			
subjects affected / exposed	2 / 309 (0.65%)	1 / 65 (1.54%)	2 / 64 (3.13%)
occurrences (all)	153	29	30
Urinary tract infection			
subjects affected / exposed	2 / 309 (0.65%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Gout			

subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Hypercholesterolaemia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Hypokalaemia			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Hyponatraemia			
subjects affected / exposed	0 / 309 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	153	29	30
Increased appetite			
subjects affected / exposed	4 / 309 (1.29%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Obesity			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 309 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	153	29	30
Vitamin D deficiency			
subjects affected / exposed	1 / 309 (0.32%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	153	29	30

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2012	Study Drug Supply: 100 count bottles replaced with 50 count bottles. Upper limit of MADRS and Y-MRS scores increased from ≤15 to ≤16. An inclusion criterion was updated to indicate that patients who experienced a mood episode of any polarity within 4 months (instead of 90 days in the original protocol) prior to the Screening Visit and responded to StOC therapy would be eligible for enrollment in the study. The exclusion criterion for BPD I patients with rapid cycling was updated to the following: patients with ≥8 cycles within the last year, instead of those with ≥6 episodes per year in the original protocol, were excluded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported