Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole as Adjunctive Therapy in the Maintenance Treatment of Adults With Major Depressive Disorder

Summary

EudraCT number	2018-000601-22
Trial protocol	DE PL
Global end of trial date	29 July 2022

Results information

Result version number	v1 (current)
This version publication date	01 November 2023
First version publication date	01 November 2023

Trial information

Trial identification

Sponsor protocol code	331-201-00079

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03538691
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524-6788, clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development , Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524-6788, clinicaltransparency@otsuka-us.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	29 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to compare the efficacy of brexpiprazole (2 to 3 milligrams per day [mg/day]) to placebo as adjunctive therapy to antidepressant therapy (ADT) for the maintenance treatment in subjects with major depressive disorder (MDD).

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2018
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: 251
Country: Number of subjects enrolled	Germany: 88
Country: Number of subjects enrolled	United States: 810
Worldwide total number of subjects	1149
EEA total number of subjects	339

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)	1141
From 65 to 84 years	8

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1149 subjects with MDD participated in the study from 13 July 2018 to 29 July 2022.

Pre-assignment

Screening details:

Of the 1149 subjects enrolled in Phase A(Acute Treatment) of the trial,766 eligible subjects continued to Phase B (Stabilisation).Eligible subjects completing Phase B were randomised into Phase C(Double-blind Randomised Withdrawal) to receive brexpiprazole or placebo along with open-label antidepressant therapy (ADT) in 1:1 ratio for upto 26 weeks.

Period 1

Period 1 title	Phase A: Acute Treatment (up to 8 Weeks)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Phase A: Brexpiprazole + ADT

Arm description:

Subjects received brexpiprazole 2 or 3 milligrams per day (mg/day) along with protocol-specified antidepressant therapy (ADT), orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related adverse events (AEs), and had not achieved the maximum dose of medication had their dose increased up to 3 mg.

Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	
Other name	OPC-34712, Rexulti
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole tablets 2 or 3 mg/day.

Investigational medicinal product name	Antidepressant therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets, sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

Number of subjects in period 1	Phase A: Brexpiprazole + ADT
Started	1149
Phase A Safety Sample	1136
Completed	766
Not completed	383
Physician decision	1
Adverse Event	82
Subject Withdrew Consent	54
Death	1
Not Specified:Not due to COVID-19 Restriction	15
Non-Compliance With Study Drug	9
Lost to follow-up	24
Lack of efficacy	185
Protocol deviation	12

Period 2

Period 2 title	Phase B: Stabilisation (12 Weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Phase B: Brexpiprazole + ADT

Arm description:

Eligible subjects completing Phase A were enrolled in Phase B to receive brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	
Other name	OPC-34712, Rexulti
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole tablets 2 or 3 mg/day.

Investigational medicinal product name	Antidepressant therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets,

sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

Number of subjects in period 2	Phase B: Brexpiprazole + ADT
Started	766
Phase B Safety Sample	765
Completed	489
Not completed	277
Physician decision	6
Adverse Event	52
Subject Withdrew Consent	47
Due to COVID-19 Restriction	1
Not Specified:Not due to COVID-19 Restriction	11
Non-Compliance With Study Drug	9
Pregnancy	1
Lost to follow-up	5
Lack of efficacy	136
Protocol deviation	9

Period 3	
Period 3 title	Phase C:Randomised Withdrawal (26 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Phase C: Brexpiprazole + ADT

Arm description:

Eligible subjects completing Phase B received brexpiprazole 2 or 3 mg/day (dose of brexpiprazole that they were receiving at Week 20 of the Stabilisation Phase) along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

Arm type	Experimental

Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	
Other name	OPC-34712, Rexulti
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole tablets 2 or 3 mg/day.

Investigational medicinal product name	Antidepressant therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets, sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

Arm title	Phase C: Placebo + ADT

Arm description:

Eligible subjects completing Phase B received brexpiprazole-matching placebo along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

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

Dosage and administration details:

Brexpiprazole-matching placebo tablets.

Investigational medicinal product name	Antidepressant therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets, sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

Number of subjects in period 3	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT
Started	240	249
Phase C Safety Sample	240	248
Completed	120	131
Not completed	120	118
Physician decision	-	1
Adverse Event	6	6
Subject Withdrew Consent	6	19

Lack of Efficacy (Phase C MDD Relapse)	54	52
Not Specified:Not due to COVID-19 Restriction	4	6
Non-Compliance With Study Drug	1	2
Non-compliant Subjects	32	28
Pregnancy	1	-
Lost to follow-up	16	4

Baseline characteristics

Reporting groups	
Reporting group title	Phase A: Brexpiprazole + ADT
Reporting group description:	
Subjects received brexpiprazole 2 or 3 milligrams per day (mg/day) along with protocol-specified antidepressant therapy (ADT), orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related adverse events (AEs), and had not achieved the maximum dose of medication had their dose increased up to 3 mg.	

Reporting group values	Phase A: Brexpiprazole + ADT	Total	
Number of subjects	1149	1149	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	42.3		
standard deviation	± 13.1	-	
Gender categorical Units: Subjects			
Female	734	734	
Male	415	415	
Ethnicity Units: Subjects			
Hispanic or Latino	110	110	
Not Hispanic or Latino	968	968	
Unknown or Not Reported	71	71	
Race Units: Subjects			
American Indian or Alaska Native	5	5	
Asian	22	22	
Native Hawaiian or Other Pacific Islander	5	5	
Black or African American	159	159	
White	868	868	
More than one race	0	0	
Unknown or Not Reported	90	90	

End points

End points reporting groups

Reporting group title	Phase A: Brexpiprazole + ADT

Reporting group description:

Subjects received brexpiprazole 2 or 3 milligrams per day (mg/day) along with protocol-specified antidepressant therapy (ADT), orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related adverse events (AEs), and had not achieved the maximum dose of medication had their dose increased up to 3 mg.

Reporting group title	Phase B: Brexpiprazole + ADT

Reporting group description:

Eligible subjects completing Phase A were enrolled in Phase B to receive brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 12 weeks.

Reporting group title	Phase C: Brexpiprazole + ADT

Reporting group description:

Eligible subjects completing Phase B received brexpiprazole 2 or 3 mg/day (dose of brexpiprazole that they were receiving at Week 20 of the Stabilisation Phase) along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

Reporting group title	Phase C: Placebo + ADT

Reporting group description:

Eligible subjects completing Phase B received brexpiprazole-matching placebo along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

Primary: Phase C: Time-to-Relapse by Any Criteria as Defined in Blinded Addendum

End point title	Phase C: Time-to-Relapse by Any Criteria as Defined in Blinded Addendum

End point description:

Relapse criteria:At same visit,increase in MADRS total score(10items,0=no symptoms to 6=severe symptoms)of 50% from randomisation and CGI-S(0=not assessed to 7=most extremely ill)score≥4,hospitalisation for depression,discontinuation for lack of efficacy/worsening of depression,active suicidality(score≥4 on MADRS item10 of suicidality)or 'yes' on question 4/5 of C-SSRS(Suicidal Ideation[SI] has 5 questions:wish to be dead,non-specific active suicidal thoughts,active SI with any methods[not plan]without intent to act,active SI with some intent to act without specific plan,active SI with specific plan,intent)or 'yes' to any question in suicidal behaviour(preparatory acts/behaviour,aborted attempt,interrupted attempt,actual attempt[non-fatal],completed suicide).PhaseC Efficacy Sample=all subjects randomised to double-blind treatment who had taken atleast 1dose of investigational medicinal product(IMP).Number of subjects analysed for median time to

End point type	Primary

End point timeframe:

Up to 14 days post last dose in Phase C (up to 28 weeks)

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: days				
median (full range (min-max))	63.0 (8 to 185)	63.0 (8 to 190)		

Statistical analyses

Statistical analysis title	Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.51
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.138
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.776
upper limit	1.669

Notes:

[1] - The hazard ratio and 95% confidence interval (CI) were derived from the Cox proportional hazard model with treatment as fixed effect.

Secondary: Phase C: Change From Baseline for Randomisation Phase in Sheehan Disability Scale (SDS) Mean Total Score at Week 46

End point title	Phase C: Change From Baseline for Randomisation Phase in Sheehan Disability Scale (SDS) Mean Total Score at Week 46

End point description:

The SDS is a self-rated instrument used to measure the effect of the participant's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0=not at all, to 10=extremely. The SDS total score is the mean of the 3 item responses. The SDS total score ranges from 0 to 10, with higher scores indicating greater functional impairment. Baseline was defined as the last available assessment value between Week 14 and Week 20 in Phase B for this outcome measure. Analysis of covariance (ANCOVA) model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 46

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	242		
Units: score on a scale				
least squares mean (standard error)	0.72 (± 0.18)	0.48 (± 0.18)		

Statistical analyses

Statistical analysis title	Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2393 [2]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.62

Notes:

[2] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Secondary: Phase C: Time-to-functional Relapse Based on SDS Criteria

End point title	Phase C: Time-to-functional Relapse Based on SDS Criteria

End point description:

Time-to-functional relapse was based on a 30% increase in the SDS mean total score from Phase C Baseline, at least one SDS sub-score at 4 or greater, and an SDS total score ≥7 when all 3 sub-scores were available. The SDS is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0=not at all, to 10=extremely. Higher scores of 5 and above are associated with significant functional impairment. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed for median time to functional relapse is the number of subjects with impending functional relapse.

End point type	Secondary

End point timeframe:

Up to 14 days post last dose in Phase C (up to 28 weeks)

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	73		
Units: days				
median (full range (min-max))	36.0 (6 to 185)	35.0 (8 to 176)		

Statistical analyses

Statistical analysis title	Brexpiprazole + ADT vs Placebo + ADT

Statistical analysis description:

The hazard ratio and 95% CI were derived from the Cox proportional hazard model with treatment as fixed effect.

Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3086
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.857
upper limit	1.615

Secondary: Phase C: Percentage of Subjects Meeting Any Relapse Criteria

End point title	Phase C: Percentage of Subjects Meeting Any Relapse Criteria

End point description:

Relapse criteria:50% increase in MADRS total score(10 items,7-point scale,0=no symptoms to 6=severe symptoms,total score=0-60) from randomisation and CGI-S(8-point scale,0=not assessed to 7=most extremely ill)score≥4, hospitalisation for depression,discontinuation for lack of efficacy/worsening of depression,active suicidality(score≥4 on MADRS item 10 of suicidality)or answer 'yes' on question 4/5 of C-SSRS(SI=5 questions:wish to be dead,non-specific active suicidal thoughts,active SI with any methods[not plan]without intent to act,active SI with some intent to act without specific plan,active SI with specific plan,intent)or answer 'yes' to any question in suicidal behaviour section(5 questions:preparatory acts/behaviour,aborted attempt,interrupted attempt,actual attempt[non-fatal],completed suicide).Percentage of subjects were rounded off to single decimal point.Phase C Efficacy Sample=all subjects randomised to double-blind treatment who had taken at least one IMP dose

End point type	Secondary

End point timeframe:

Up to 26 weeks in Phase C

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	248		
Units: percentage of subjects				
number (not applicable)	22.5	20.6		

Statistical analyses

Statistical analysis title	Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.603
Method	Chi-squared

Secondary: Phase C: Percentage of Subjects Maintaining Remission

End point title	Phase C: Percentage of Subjects Maintaining Remission

End point description:

Subjects maintaining remission was defined as MADRS total score ≤10. The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Subjects were rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses. 'n' is the number of subjects with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Weeks 21, 23, 25, 29, 33, 37, 41, 45, and 46

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	242		
Units: percentage of subjects				
number (not applicable)				
Week 21 (n=238, 242)	90.34	91.3		
Week 23 (n=230, 237)	85.22	82.7		
Week 25 (n=217, 224)	84.79	82.6		
Week 29 (n=189, 200)	79.89	85.5		
Week 33 (n=166, 181)	88.55	88.4		
Week 37 (n=149, 164)	87.92	89.0		

Week 41 (n=138, 151)	84.78	89.4		
Week 45 (n=118, 127)	88.14	89.0		
Week 46 (n=121, 132)	90.91	91.7		

Statistical analyses

Statistical analysis title	Week 21: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7081
Method	Chi-squared

Statistical analysis title	Week 23: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4589
Method	Chi-squared

Statistical analysis title	Week 25: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5314
Method	Chi-squared

Statistical analysis title	Week 29: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1433
Method	Chi-squared

Statistical analysis title	Week 33: Brexpiprazole + ADT vs Placebo + ADT

Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9636
Method	Chi-squared

Statistical analysis title	Week 37: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7596
Method	Chi-squared

Statistical analysis title	Week 41: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2402
Method	Chi-squared

Statistical analysis title	Week 45: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8363
Method	Chi-squared

Statistical analysis title	Week 46: Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8308
Method	Chi-squared

Secondary: Phase C: Change From Baseline for Randomisation Phase in MADRS Total Score at Week 46

End point title	Phase C: Change From Baseline for Randomisation Phase in MADRS Total Score at Week 46

End point description:

The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Subjects were rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. A positive change from Baseline indicates worsening of symptoms. Baseline was defined as the last available assessment value in Phase B for this outcome measure. ANCOVA model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 46

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	247		
Units: score on a scale				
least squares mean (standard error)	4.09 (± 0.75)	4.21 (± 0.73)		

Statistical analyses

Statistical analysis title	Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8806 [3]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	1.49

Notes:

[3] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Secondary: Phase C: Change From Baseline for Randomisation Phase in CGI-S Score at Week 46

End point title	Phase C: Change From Baseline for Randomisation Phase in CGI-S Score at Week 46

End point description:

The CGI -S was used to rate the severity of illness for each subject on an 8-point scale ranging from 0 to 7 where 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 subjects. A positive change from Baseline indicates worsening of illness. Baseline was defined as the last available assessment value in Phase B for this outcome measure. ANCOVA model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 46

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	247		
Units: score on a scale				
least squares mean (standard error)	0.56 (± 0.10)	0.53 (± 0.09)		

Statistical analyses

Statistical analysis title	Brexpiprazole + ADT vs Placebo + ADT
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7956 [4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.24

Notes:

[4] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Secondary: Phase C: Change From Baseline for Randomisation Phase in Each of the SDS Individual Item Scores at Week 46

End point title	Phase C: Change From Baseline for Randomisation Phase in Each of the SDS Individual Item Scores at Week 46

End point description:

The SDS is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0=not at all, to 10=extremely. Higher scores of 5 and above are associated with significant functional impairment. A positive change from Baseline indicates worsening of symptoms

impacting each area. Baseline was defined as the last available assessment value between Week 14 and Week 20 in Phase B for this outcome measure. ANCOVA model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses. 'n' is the number of subjects with data available for analysis for the specified category.

End point type	Secondary

End point timeframe:

Baseline and Week 46

End point values	Phase C: Brexpiprazole + ADT	Phase C: Placebo + ADT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	244		
Units: score on a scale				
least squares mean (standard error)				
Work/School (n=195, 197)	0.46 (± 0.22)	0.31 (± 0.23)		
Social Life (n=239, 244)	0.91 (± 0.19)	0.56 (± 0.19)		
Family Life (n=239, 242)	0.78 (± 0.19)	0.52 (± 0.19)		

Statistical analyses

Statistical analysis title	SDS Individual Item: Work/School
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5223 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.61

Notes:

[5] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Statistical analysis title	SDS Individual Item: Social Life
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0904 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.77

Notes:

[6] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Statistical analysis title	SDS Individual Item: Family Life
Comparison groups	Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2289 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.67

Notes:

[7] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 21 days after the last dose (Up to 49 weeks)

Adverse event reporting additional description:

All-cause Mortality: Enrolled Sample=all subjects who signed ICF; entered PhaseA.
Serious; Other AEs: Phase A and B Safety Sample=all subjects who received at least 1 dose of brexpiprazole in Phase A and B respectively. Phase C Safety Sample=all subjects who were randomised to double-blind treatment and received at least one 1 IMP dose in Phase C.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Phase A: Brexpiprazole + ADT

Reporting group description:

Subjects received brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related AEs, and had not achieved the maximum dose of medication had their dose increased up to 3 mg.

Reporting group title	Phase B: Brexpiprazole + ADT

Reporting group description:

Eligible subjects completing Phase A were enrolled in Phase B to receive brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 12 weeks.

Reporting group title	Phase C: Brexpiprazole + ADT

Reporting group description:

Eligible subjects completing Phase B received brexpiprazole 2 or 3 mg/day (dose of brexpiprazole that they were receiving at Week 20 of the Stabilisation Phase) along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

Reporting group title	Phase C: Placebo + ADT

Reporting group description:

Eligible subjects completing Phase B received brexpiprazole-matching placebo along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

Serious adverse events	Phase A: Brexpiprazole + ADT	Phase B: Brexpiprazole + ADT	Phase C: Brexpiprazole + ADT
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 1136 (0.88%)	12 / 765 (1.57%)	1 / 240 (0.42%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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

Prostate cancer			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	0 / 1136 (0.00%)	0 / 765 (0.00%)	1 / 240 (0.42%)
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			
Pulmonary embolism			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (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
Suicidal ideation			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Suicide attempt			

subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Injury, poisoning and procedural complications			
Dislocation of vertebra			
subjects affected / exposed	0 / 1136 (0.00%)	0 / 765 (0.00%)	0 / 240 (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
Epicondylitis			
subjects affected / exposed	0 / 1136 (0.00%)	0 / 765 (0.00%)	0 / 240 (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
Fall			
subjects affected / exposed	0 / 1136 (0.00%)	0 / 765 (0.00%)	0 / 240 (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
Hand fracture			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (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
Tibia fracture			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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			
Cardiac arrest			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (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

Myocardial infarction			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Cervicobrachial syndrome			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 1136 (0.00%)	0 / 765 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Haematemesis			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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
Cholecystitis			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (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
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 1136 (0.00%)	0 / 765 (0.00%)	0 / 240 (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 pain			
subjects affected / exposed	1 / 1136 (0.09%)	0 / 765 (0.00%)	0 / 240 (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
Infections and infestations			
Upper respiratory tract infection			

subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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			
Electrolyte imbalance			
subjects affected / exposed	0 / 1136 (0.00%)	1 / 765 (0.13%)	0 / 240 (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

Serious adverse events	Phase C: Placebo + ADT		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 248 (1.21%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaphylactic shock			

subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 248 (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 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Dislocation of vertebra			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epicondylitis			

subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Akathisia				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carpal tunnel syndrome				
subjects affected / exposed	0 / 248 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervicobrachial syndrome			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 248 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 248 (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	Phase A: Brexpiprazole + ADT	Phase B: Brexpiprazole + ADT	Phase C: Brexpiprazole + ADT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	423 / 1136 (37.24%)	232 / 765 (30.33%)	40 / 240 (16.67%)
Investigations			
Weight increased			
subjects affected / exposed	48 / 1136 (4.23%)	122 / 765 (15.95%)	25 / 240 (10.42%)
occurrences (all)	51	161	45
Nervous system disorders			

Akathisia			
subjects affected / exposed	109 / 1136 (9.60%)	33 / 765 (4.31%)	4 / 240 (1.67%)
occurrences (all)	109	34	4
Headache			
subjects affected / exposed	113 / 1136 (9.95%)	41 / 765 (5.36%)	5 / 240 (2.08%)
occurrences (all)	158	55	6
Somnolence			
subjects affected / exposed	90 / 1136 (7.92%)	37 / 765 (4.84%)	6 / 240 (2.50%)
occurrences (all)	94	38	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	64 / 1136 (5.63%)	18 / 765 (2.35%)	1 / 240 (0.42%)
occurrences (all)	78	20	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	72 / 1136 (6.34%)	8 / 765 (1.05%)	1 / 240 (0.42%)
occurrences (all)	74	8	1
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	60 / 1136 (5.28%)	18 / 765 (2.35%)	1 / 240 (0.42%)
occurrences (all)	61	20	1

Non-serious adverse events	Phase C: Placebo + ADT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 248 (14.92%)		
Investigations			
Weight increased			
subjects affected / exposed	13 / 248 (5.24%)		
occurrences (all)	14		
Nervous system disorders			
Akathisia			
subjects affected / exposed	3 / 248 (1.21%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	14 / 248 (5.65%)		
occurrences (all)	18		
Somnolence			

subjects affected / exposed occurrences (all)	3 / 248 (1.21%) 3		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 0 / 248 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 248 (0.81%) 2		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	 4 / 248 (1.61%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2018	The following major changes were implemented based on Amendment 1: 1) Corrected EudraCT number.2) Updated trial design schematic noting Phase A Baseline Visit and corrected number of subjects planned to be enrolled in Phase A. 3) Aligned exclusion criteria for clinical laboratory values with other brexpiprazole protocols.4) Collection of pharmacogenomic sample was moved from baseline visit to Week 20/Randomisation visit.
08 July 2020	The following major changes were implemented based on Amendment 2: 1) Updated the names and contact information of Sponsor representatives. 2) Added trial conduct information after the title page to introduce the coronavirus disease (COVID-19) Addendum. 3) Incorporated the following items from the protocol clarification memo: a. Revised the following text: A QT Interval Corrected Using Fridericia's Formula (QTcF) ≥450 milliseconds (msec) for males and ≥470 msec for females at screening is exclusionary. b. Revised the following text: Based on the QTcF corrections reported by the central service, a subject will be excluded if the correction equals or exceeds 450 msec for males and 470 msec for females for 2 or more of the 3 time points of the electrocardiogram (ECGs) conducted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported