Clinical trial results:
A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo controlled, 2 Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Summary

EudraCT number	2017-003940-19
Trial protocol	BG ES HU SK
Global end of trial date	01 June 2022

Results information

Result version number	v1 (current)
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification

Sponsor protocol code	331-14-213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03548584
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Blvd, Rockville, Maryland, 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	01 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study compares the efficacy of 2 doses of brexpiprazole with placebo in subjects with agitation associated with dementia of the Alzheimer's type.

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	16 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Serbia: 19
Country: Number of subjects enrolled	Ukraine: 107
Country: Number of subjects enrolled	United States: 152
Worldwide total number of subjects	345
EEA total number of subjects	67

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)	37
From 65 to 84 years	283
85 years and over	25

Subject disposition

Recruitment

Recruitment details:

A total of 345 subjects were randomised, and participated in the study from 16 May 2018 to 1 June 2022.

Pre-assignment

Screening details:

The enrolled subjects were randomised to, brexpiprazole or placebo group in a ratio of 2:1. Within the brexpiprazole arm group, subjects were further randomised in a 1:2 ratio to 2 milligrams per day (mg/day) or 3 mg/day.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole 2 mg

Arm description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 milligrams (mg), once daily until Week 12.

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

Dosage and administration details:

Brexpiprazole was administered orally in gradually increasing doses starting from 0.5 mg/day to 2 mg/day from Day 15. Brexpiprazole 2 mg was then given once daily until Week 12.

Arm title	Brexpiprazole 3 mg

Arm description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12.

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

Dosage and administration details:

Brexpiprazole was administered orally in gradually increasing doses starting from 0.5 mg/day in the starting to 3 mg/day from Day 29. Brexpiprazole 3 mg was then given, once daily until Week 12.

Arm title	Placebo

Arm description:

Subjects received matching placebo, once daily for 12 weeks.

Arm type	Placebo

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

Dosage and administration details:

Matching placebo, once daily for 12 weeks.

Number of subjects in period 1	Brexpiprazole 2 mg	Brexpiprazole 3 mg	Placebo
Started	75	153	117
Intent-to-treat Population	73	153	116
Completed	68	130	104
Not completed	7	23	13
Reason not specified (unrelated to COVID-19)	-	2	2
Site terminated by sponsor	1	3	2
Adverse event	1	11	5
Non-compliance with study drug	-	1	-
Lost to follow-up	-	-	1
Subject withdrew consent to participate	5	5	3
Lack of efficacy	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole 2 mg
Reporting group description:	
Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 milligrams (mg), once daily until Week 12.	
Reporting group title	Brexpiprazole 3 mg
Reporting group description:	
Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo, once daily for 12 weeks.	

Reporting group values	Brexpiprazole 2 mg	Brexpiprazole 3 mg	Placebo
Number of subjects	75	153	117
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	74.3	74.6	73.0
standard deviation	± 7.3	± 8.0	± 7.0
Gender categorical Units: Subjects			
Female	43	92	60
Male	32	61	57
Ethnicity Units: Subjects			
Hispanic or Latino	25	46	37
Not Hispanic or Latino	50	107	80
Race Units: Subjects			
Asian	0	3	1
Black or African American	5	6	1
White	70	144	115
Cohen-Mansfield Agitation Inventory (CMAI) Total Score			
The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour.			
Units: score on a scale			
arithmetic mean	78.6	81.2	79.4
standard deviation	± 15.5	± 17.2	± 17.6

Reporting group values	Total		
Number of subjects	345		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	195		
Male	150		
Ethnicity Units: Subjects			
Hispanic or Latino	108		
Not Hispanic or Latino	237		
Race Units: Subjects			
Asian	4		
Black or African American	12		
White	329		
Cohen-Mansfield Agitation Inventory (CMAI) Total Score			
The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour.			
Units: score on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Brexpiprazole 2 mg

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 milligrams (mg), once daily until Week 12.

Reporting group title	Brexpiprazole 3 mg

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo, once daily for 12 weeks.

Subject analysis set title	Brexpiprazole 2 and 3 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15 or from 0.5 mg/day in the starting to 3 mg/day from Day 29.
Subjects continued to receive brexpiprazole 2 or 3 mg, once daily until Week 12.

Primary: Change From Baseline to Week 12 in the CMAI Total Score

End point title	Change From Baseline to Week 12 in the CMAI Total Score[1]

End point description:

The CMAI score is used to assess the frequency of manifestations of agitated behaviours in subjects. The CMAI consists of 29 agitated behaviours, rated on a 7-point scale of frequency across four subscales of aggressive behaviour, physically nonaggressive behaviour, verbally agitated behaviour and hiding and hoarding ranging from 1=never to 7=several times an hour. The CMAI total score ranges from 29 to 203. Higher scores indicate worsening of the condition. A negative change from baseline indicates improvement. Mixed model repeated measures (MMRM) was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of investigational medical product (IMP) and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Primary

End point timeframe:

Baseline and Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: score on a scale				
least squares mean (standard error)	-17.3 (± 1.44)	-22.6 (± 1.08)		

Statistical analyses

Statistical analysis title	Change From Baseline in the CMAI Total Score
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0026 [3]
Method	MMRM
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-5.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.77
upper limit	-1.87

Notes:

[2] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[3] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Secondary: Change From Baseline to Week 12 in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Agitation

End point title	Change From Baseline to Week 12 in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Agitation[4]

End point description:

CGI-S was used to rate the severity of agitation. The score ranges from 0 to 7 with response choices as, 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. The higher the value, the more severe the agitation. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: score on a scale				
least squares mean (standard error)	-0.93 (± 0.08)	-1.20 (± 0.06)		

Statistical analyses

Statistical analysis title	Change From Baseline to Week 12 in the CGI-S Score
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0078 [6]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.07

Notes:

[5] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[6] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Secondary: Change From Baseline to Week 12 in CMAI Subscale Scores

End point title	Change From Baseline to Week 12 in CMAI Subscale Scores[7]

End point description:

The CMAI score is used to assess the frequency of manifestations of agitated behaviours in subjects. The CMAI consists of 29 agitated behaviours that are rated on a 7-point scale of frequency across four subscales of aggressive behaviour, physically nonaggressive behaviour, verbally agitated behaviour and hiding and hoarding as: 1=never; 2=less than once a week; 3=once or twice a week; 4=several times a week; 5=once or twice a day; 6=several times a day; 7=several times an hour. Higher scores indicate worsening of the condition. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: score on a scale				
least squares mean (standard error)				
Aggressive Behaviour	-7.13 (± 0.56)	-9.09 (± 0.42)		
Physically Nonaggressive Behaviour	-5.04 (± 0.53)	-6.45 (± 0.40)		
Verbally Agitated Behaviour	-3.14 (± 0.40)	-4.39 (± 0.31)		
Hiding and Hoarding	-1.14 (± 0.23)	-1.50 (± 0.17)		

Statistical analyses

Statistical analysis title	Change From Baseline in CMAI Subscale Scores
Statistical analysis description:	
Aggressive Behaviour	
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.004 [9]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	-0.63

Notes:

[8] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[9] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Subscale Scores
Statistical analysis description:	
Physically Nonaggressive Behaviour	
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0296 [11]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	-0.14

Notes:

[10] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[11] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Subscale Scores
Statistical analysis description:	
Verbally Agitated Behaviour	
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.0113 [13]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.21
upper limit	-0.28

Notes:

[12] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[13] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Subscale Scores

Statistical analysis description:

Hiding and Hoarding

Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.1941 [15]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.18

Notes:

[14] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[15] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Secondary: Change From Baseline in CMAI Total Score for Each Trial Visit During the Double-blind Treatment Period

End point title	Change From Baseline in CMAI Total Score for Each Trial Visit During the Double-blind Treatment Period[16]

End point description:

The CMAI score is used to assess the frequency of manifestations of agitated behaviours in subjects. The CMAI consists of 29 agitated behaviours, rated on a 7-point scale of frequency across four subscales of aggressive behaviour, physically nonaggressive behaviour, verbally agitated behaviour and hiding and hoarding ranging from 1=never to 7=several times an hour. The CMAI total score ranges from 29 to 203. Higher scores indicate worsening of the condition. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the Statistical Analysis Plan (SAP), data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: score on a scale				
least squares mean (standard error)				
Change From Baseline at Week 2	-6.61 (± 0.90)	-5.76 (± 0.71)		
Change From Baseline at Week 4	-11.0 (± 1.06)	-12.1 (± 0.82)		
Change From Baseline at Week 6	-13.9 (± 1.19)	-16.2 (± 0.91)		
Change From Baseline at Week 8	-14.4 (± 1.28)	-19.4 (± 0.96)		
Change From Baseline at Week 10	-15.7 (± 1.29)	-22.2 (± 0.97)		
Change From Baseline at Week 12	-17.3 (± 1.44)	-22.6 (± 1.08)		

Statistical analyses

Statistical analysis title	Change From Baseline in CMAI Total Score - Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.4242 [18]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	2.93

Notes:

[17] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[18] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Total Score - Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.3665 [20]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.63
upper limit	1.34

Notes:

[19] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[20] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Total Score - Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.1065 [22]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.15
upper limit	0.5

Notes:

[21] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[22] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Total Score - Week 8
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.0011 [24]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-5.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.12
upper limit	-2.05

Notes:

[23] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[24] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Total Score - Week 10
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.0001 [26]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-6.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.54
upper limit	-3.4

Notes:

[25] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[26] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CMAI Total Score - Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.0026 [28]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-5.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.77
upper limit	-1.87

Notes:

[27] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[28] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Secondary: Change From Baseline in CGI-S for Each Trial Visit During the Double-Blind Treatment Period

End point title	Change From Baseline in CGI-S for Each Trial Visit During the Double-Blind Treatment Period[29]

End point description:

CGI-S was used to rate the severity of agitation. The score ranges from 0 to 7 with response choices as, 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. The higher the value, the more severe the agitation. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score.

Number of subjects analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: score on a scale				
least squares mean (standard error)				
Change From Baseline at Week 2	-0.27 (± 0.04)	-0.21 (± 0.03)		
Change From Baseline at Week 4	-0.50 (± 0.06)	-0.53 (± 0.05)		
Change From Baseline at Week 6	-0.68 (± 0.07)	-0.74 (± 0.05)		
Change From Baseline at Week 8	-0.70 (± 0.08)	-0.97 (± 0.06)		
Change From Baseline at Week 10	-0.86 (± 0.08)	-1.14 (± 0.06)		
Change From Baseline at Week 12	-0.93 (± 0.08)	-1.20 (± 0.06)		

Statistical analyses

Statistical analysis title	Change From Baseline in CGI-S Score at Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.3048 [31]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.16

Notes:

[30] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[31] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CGI-S Score at Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.7058 [33]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.12

Notes:

[32] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[33] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CGI-S Score at Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.4516 [35]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.1

Notes:

[34] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[35] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CGI-S Score at Week 8
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.0052 [37]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.08

Notes:

[36] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[37] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CGI-S Score at Week 10
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.006 [39]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.08

Notes:

[38] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[39] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Statistical analysis title	Change From Baseline in CGI-S Score at Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.0078 [41]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.07

Notes:

[40] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[41] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

Secondary: Clinical Global Impressions-Improvement (CGI-I) Score at Each Trial Visit During the Double-Blind Treatment Period

End point title	Clinical Global Impressions-Improvement (CGI-I) Score at Each Trial Visit During the Double-Blind Treatment Period[42]

End point description:

CGI-I is a 7-point scale that requires the clinician to assess whether a subject's condition has improved or worsened relative to a baseline state at the beginning of the intervention. This was rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; or 7=very much worse. Higher scores indicate worse condition. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the

number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=114, 221)	3.57 (± 0.69)	3.70 (± 0.75)		
Week 4 (n=116, 225)	3.39 (± 0.87)	3.19 (± 0.85)		
Week 6 (n=116, 225)	3.19 (± 0.95)	2.92 (± 0.94)		
Week 8 (n=116, 225)	3.16 (± 1.01)	2.80 (± 1.00)		
Week 10 (n=116, 225)	2.97 (± 1.00)	2.62 (± 0.99)		
Week 12 (n=116, 225)	2.97 (± 1.12)	2.66 (± 1.09)		

Statistical analyses

Statistical analysis title	CGI-I Score at Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.1975
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.26

Notes:

[43] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Score at Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.0084
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.06

Notes:

[44] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Score at Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.0101
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.06

Notes:

[45] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Score at Week 8
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.0008
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.15

Notes:

[46] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Score at Week 10

Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.0023
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	-0.12

Notes:

[47] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Score at Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	-0.09

Notes:

[48] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Secondary: CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period

End point title	CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period[49]

End point description:

The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 6, 8, 10, and 12

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: percentage of subjects				
number (not applicable)				
>/= 20%: Week 2 (n=114, 221)	13.2	11.3		
>/= 20%: Week 4 (n=116, 225)	27.6	29.3		
>/= 20%: Week 6 (n=116, 225)	37.9	43.1		
>/= 20%: Week 8 (n=116, 225)	38.8	59.6		
>/= 20%: Week 10 (n=116, 225)	45.7	65.8		
>/= 20%: Week 12 (n=116, 225)	47.4	68.4		
>/= 30%: Week 2 (n=114, 221)	3.51	3.62		
>/= 30%: Week 4 (n=116, 225)	10.3	10.7		
>/= 30%: Week 6 (n=116, 225)	20.7	22.7		
>/= 30%: Week 8 (n=116, 225)	19.0	32.9		
>/= 30%: Week 10 (n=116, 225)	24.1	38.2		
>/= 30%: Week 12 (n=116, 225)	25.9	42.7		
>/= 40%: Week 2 (n=114, 221)	1.75	1.81		
>/= 40%: Week 4 (n=116, 225)	5.17	4.89		
>/= 40%: Week 6 (n=116, 225)	8.62	10.7		
>/= 40%: Week 8 (n=116, 225)	8.62	16.9		
>/= 40%: Week 10 (n=116, 225)	11.2	20.9		
>/= 40%: Week 12 (n=116, 225)	14.7	23.1		

Statistical analyses

Statistical analysis title	CMAI Response Rate- >/= 20%: Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.729
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.91

Notes:

[50] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 20%: Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.6196
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.52

Notes:

[51] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 20%: Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.2718
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.53

Notes:

[52] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 20%: Week 8
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.93

Notes:

[53] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 20%: Week 10
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.0006
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.76

Notes:

[54] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 20%: Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.72

Notes:

[55] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 30%: Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.7211
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	3.85

Notes:

[56] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 30%: Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.7606
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	2.14

Notes:

[57] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 30%: Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.5902
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.68

Notes:

[58] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 30%: Week 8

Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.0054
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	2.54

Notes:

[59] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 30%: Week 10
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.0066
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	2.26

Notes:

[60] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 30%: Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.0017
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	2.23

Notes:

[61] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 40%: Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	= 0.9074
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	5.97

Notes:

[62] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 40%: Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[63]
P-value	= 0.9625
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	2.64

Notes:

[63] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 40%: Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.512
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.53

Notes:

[64] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 40%: Week 8
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[65]
P-value	= 0.0244
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	3.79

Notes:

[65] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 40%: Week 10
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.0161
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	3.18

Notes:

[66] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate- >/= 40%: Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.0347
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.61

Notes:

[67] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Secondary: CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response Based on Improvement From Baseline in Agitation Status at Every Scheduled Trial Visit in the Double-Blind Treatment Period

End point title	CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response Based on Improvement From Baseline in Agitation Status at Every Scheduled Trial Visit in the Double-Blind Treatment Period[68]

End point description:

The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: percentage of subjects				
number (not applicable)				
Week 2 (n=114, 221)	14.0	8.14		
Week 4 (n=116, 225)	19.0	20.4		
Week 6 (n=116, 225)	26.7	33.8		
Week 8 (n=116, 225)	31.0	44.0		
Week 10 (n=116, 225)	34.5	50.2		
Week 12 (n=116, 225)	37.1	52.4		

Statistical analyses

Statistical analysis title	CMAI Response Rate at Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.1503
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.16

Notes:

[69] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate at Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.7559
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.67

Notes:

[70] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate at Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	= 0.2246
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.72

Notes:

[71] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate at Week 8

Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.0276
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.87

Notes:

[72] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate at Week 10
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[73]
P-value	= 0.0031
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	1.89

Notes:

[73] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CMAI Response Rate at Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	= 0.0017
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	1.89

Notes:

[74] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Secondary: CGI-I Response Rate Assessed as Percentage of Subjects With CGI-I Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period

End point title	CGI-I Response Rate Assessed as Percentage of Subjects With CGI-I Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period[75]

End point description:

CGI-I is a 7-point scale that requires the clinician to assess whether a subject's condition has improved or worsened relative to a baseline state at the beginning of the intervention. This was rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; or 7=very much worse. Higher scores indicate worse condition. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

End point values	Placebo	Brexpiprazole 2 and 3 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	116	225		
Units: percentage of subjects				
number (not applicable)				
Week 2 (n=114, 221)	5.26	4.98		
Week 4 (n=116, 225)	12.1	21.8		
Week 6 (n=116, 225)	23.3	35.1		
Week 8 (n=116, 225)	24.1	44.4		
Week 10 (n=116, 225)	33.6	52.4		
Week 12 (n=116, 225)	40.5	52.4		

Statistical analyses

Statistical analysis title	CGI-I Response Rate at Week 2
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 0.8549
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.03

Notes:

[76] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Response Rate at Week 4
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[77]
P-value	= 0.0093
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	3.32

Notes:

[77] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Response Rate at Week 6
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	= 0.0083
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.22

Notes:

[78] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Response Rate at Week 8
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[79]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	2.58

Notes:

[79] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Response Rate at Week 10
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	= 0.0005
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	2.09

Notes:

[80] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Statistical analysis title	CGI-I Response Rate at Week 12
Comparison groups	Placebo v Brexpiprazole 2 and 3 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	= 0.016
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response Rate
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.69

Notes:

[81] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent up to end of study (Week 16)

Adverse event reporting additional description:

Randomised Sample was used to assess all-cause deaths. It consisted of all subjects who were randomised into this trial. Safety Sample was used to assess serious adverse events (SAEs) and non-serious adverse events (NSAEs) and consisted of all subjects who were administered at least one dose of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Brexpiprazole 2 mg

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 mg, once daily until Week 12.

Reporting group title	Brexpiprazole 3 mg

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo, once daily for 12 weeks.

Serious adverse events	Brexpiprazole 2 mg	Brexpiprazole 3 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 73 (0.00%)	6 / 153 (3.92%)	3 / 116 (2.59%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 73 (0.00%)	0 / 153 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hip fracture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (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
Psychotic disorder			
subjects affected / exposed	0 / 73 (0.00%)	0 / 153 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 73 (0.00%)	2 / 153 (1.31%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 153 (0.65%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Brexpiprazole 2 mg	Brexpiprazole 3 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 73 (6.85%)	10 / 153 (6.54%)	8 / 116 (6.90%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 73 (6.85%)	10 / 153 (6.54%)	8 / 116 (6.90%)
occurrences (all)	5	12	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2019	The following changes were implemented as per Amendment 1: 1. Sample size was increased from 225 subjects to 255 subjects. 2. The number of trial sites was increased from 60 to 80 sites.
06 August 2020	The following change was implemented as per Amendment 2: A Coronavirus disease 2019 (COVID-19) addendum was introduced for any protocol specified activities that were not able to be performed or could not be performed due to COVID-19 considerations.
14 September 2020	The following changes were implemented as per Amendment 3: 1. Sample size was increased from approximately 255 subjects to approximately 330 subjects. 2. References to German sites were removed. 3. Trial duration was increased. 4. Details were added regarding the interim analysis and possible rollover of subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported