Clinical trial results:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate Pharmacodynamic Effects, Safety, Tolerability, and Pharmacokinetics of Multiple Oral Doses of TAK-831 in Adult Subjects With Schizophrenia

Summary

EudraCT number	2017-001739-38
Trial protocol	GB
Global end of trial date	21 December 2020

Results information

Result version number	v1 (current)
This version publication date	25 May 2022
First version publication date	25 May 2022

Trial information

Trial identification

Sponsor protocol code	TAK-831-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03359785
WHO universal trial number (UTN)	U1111-1197-9766
Other trial identifiers	NRES number: 17/YH/0196

Notes:

Sponsors

Sponsor organisation name	Neurocrine Biosciences, Inc.
Sponsor organisation address	12780 El Camino Real, San Diego, United States, CA 92130
Public contact	Neurocrine Medical Information, Neurocrine Biosciences, Inc., medinfo@neurocrine.com
Scientific contact	Neurocrine Medical Information, Neurocrine Biosciences, Inc., medinfo@neurocrine.com
Sponsor organisation name	Takeda Development Centre Europe Ltd
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	For contact information, see Neurocrine Biosciences, Inc., medinfo@neurocrine.com
Scientific contact	For contact information, see Neurocrine Biosciences, Inc., medinfo@neurocrine.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether luvadaxistat (TAK-831) is superior to placebo in improving cerebellar function as measured with the average percentage of conditioned responses during the eyeblink conditioning (EBC) test.

Protection of trial subjects:

The study was conducted in accordance with Takeda standards that meet regulations relating to Good Clinical Practice (GCP). The study was conducted in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use GCP guidelines and with the laws and regulations of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 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	United States: 31
Worldwide total number of subjects	31
EEA total number of subjects	0

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)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This 2-period cross-over study assessed the pharmacodynamic (PD) effects, safety, tolerability and pharmacokinetics (PK) of multiple oral doses of luvadaxistat given once daily (QD) in adult subjects with schizophrenia. Effects of 2 dose levels of luvadaxistat (500 milligrams [mg] and 50 mg) or placebo were assessed.

Pre-assignment

Screening details:

The study consisted of a screening period (30 days), treatment period 1 (8 days), washout (14 to 21 days), treatment period 2 (8 days) and a safety follow-up visit. 17 subjects were randomized to 1 of 2 sequences comparing luvadaxistat 500 mg to placebo and 14 subjects were randomized to 1 of 2 sequences comparing luvadaxistat 50 mg to placebo.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Luvadaxistat 500 mg, then Placebo

Arm description:

Subjects first received luvadaxistat 500 mg orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received matching placebo orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 1.

Arm type	Cross-over (experimental & placebo)
Investigational medicinal product name	Luvadaxistat
Investigational medicinal product code	TAK-831
Other name	NBI-1065844
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In treatment period 1, subjects received luvadaxistat QD, administered as 5 oral tablets of 100 mg each.

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

Dosage and administration details:

In treatment period 2, subjects received placebo QD, administered as 5 oral placebo (matching luvadaxistat) tablets.

Arm title	Placebo, then Luvadaxistat 500 mg

Arm description:

Subjects first received matching placebo orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received luvadaxistat 500 mg orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 2.

Arm type	Cross-over (experimental & placebo)

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

Dosage and administration details:

In treatment period 1, subjects received placebo QD, administered as 5 oral placebo (matching luvadaxistat) tablets.

Investigational medicinal product name	Luvadaxistat
Investigational medicinal product code	TAK-831
Other name	NBI-1065844
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In treatment period 2, subjects received luvadaxistat QD, administered as 5 oral tablets of 100 mg each.

Arm title	Luvadaxistat 50 mg, then Placebo

Arm description:

Subjects first received luvadaxistat 50 mg orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received matching placebo orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 3.

Arm type	Cross-over (experimental & placebo)
Investigational medicinal product name	Luvadaxistat
Investigational medicinal product code	TAK-831
Other name	NBI-1065844
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In treatment period 1, subjects received luvadaxistat QD, administered as 5 oral tablets of 10 mg each.

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

Dosage and administration details:

In treatment period 2, subjects received placebo QD, administered as 5 oral placebo (matching luvadaxistat) tablets.

Arm title	Placebo, then Luvadaxistat 50 mg

Arm description:

Subjects first received matching placebo orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received luvadaxistat 50 mg orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 4.

Arm type	Cross-over (experimental & placebo)
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In treatment period 1, subjects received placebo QD, administered as 5 oral placebo (matching luvadaxistat) tablets.

Investigational medicinal product name	Luvadaxistat
Investigational medicinal product code	TAK-831
Other name	NBI-1065844

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In treatment period 2, subjects received luvadaxistat QD, administered as 5 oral tablets of 10 mg each.

Number of subjects in period 1	Luvadaxistat 500 mg, then Placebo	Placebo, then Luvadaxistat 500 mg	Luvadaxistat 50 mg, then Placebo
Started	8	9	7
Completed	6	6	5
Not completed	2	3	2
Consent withdrawn by subject	2	2	-
Early study termination due to study pause	-	-	2
Protocol deviation	-	1	-

Number of subjects in period 1	Placebo, then Luvadaxistat 50 mg
Started	7
Completed	7
Not completed	0
Consent withdrawn by subject	-
Early study termination due to study pause	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Luvadaxistat 500 mg, then Placebo
Reporting group description:	
Subjects first received luvadaxistat 500 mg orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received matching placebo orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 1.	
Reporting group title	Placebo, then Luvadaxistat 500 mg
Reporting group description:	
Subjects first received matching placebo orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received luvadaxistat 500 mg orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 2.	
Reporting group title	Luvadaxistat 50 mg, then Placebo
Reporting group description:	
Subjects first received luvadaxistat 50 mg orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received matching placebo orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 3.	
Reporting group title	Placebo, then Luvadaxistat 50 mg
Reporting group description:	
Subjects first received matching placebo orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received luvadaxistat 50 mg orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 4.	

Reporting group values	Luvadaxistat 500 mg, then Placebo	Placebo, then Luvadaxistat 500 mg	Luvadaxistat 50 mg, then Placebo
Number of subjects	8	9	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	9	7
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.3	36.0	41.6
standard deviation	± 6.41	± 7.30	± 12.08
Gender categorical Units: Subjects			
Female	0	2	1
Male	8	7	6
Race Units: Subjects			
Asian	0	0	0
Black or African American	8	8	6
White	0	1	0

Unknown	0	0	1
Ethnicity Units: Subjects			
Not Hispanic or Latino	8	9	6
Hispanic or Latino	0	0	1

Reporting group values	Placebo, then Luvadaxistat 50 mg	Total	
Number of subjects	7	31	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	31	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.3		
standard deviation	± 10.24	-	
Gender categorical Units: Subjects			
Female	2	5	
Male	5	26	
Race Units: Subjects			
Asian	1	1	
Black or African American	4	26	
White	2	3	
Unknown	0	1	
Ethnicity Units: Subjects			
Not Hispanic or Latino	7	30	
Hispanic or Latino	0	1	

End points

End points reporting groups

Reporting group title	Luvadaxistat 500 mg, then Placebo

Reporting group description:

Subjects first received luvadaxistat 500 mg orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received matching placebo orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 1.

Reporting group title	Placebo, then Luvadaxistat 500 mg

Reporting group description:

Subjects first received matching placebo orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received luvadaxistat 500 mg orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 2.

Reporting group title	Luvadaxistat 50 mg, then Placebo

Reporting group description:

Subjects first received luvadaxistat 50 mg orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received matching placebo orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 3.

Reporting group title	Placebo, then Luvadaxistat 50 mg

Reporting group description:

Subjects first received matching placebo orally QD for 8 days during treatment period 1. After a washout of 14 to 21 days, subjects then received luvadaxistat 50 mg orally QD for 8 days during treatment period 2. Also referred to as treatment sequence 4.

Subject analysis set title	Luvadaxistat 50 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received luvadaxistat 50 mg orally QD for 8 days during either treatment periods 1 or 2 of the study.

Subject analysis set title	Placebo (reference for luvadaxistat 50 mg)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received matching placebo orally QD for 8 days during either treatment periods 1 or 2 of the study. Placebo treatment in this arm corresponds to subjects who received 50 mg luvadaxistat in the alternative treatment period (ie, subjects receiving 50 mg and 500 mg luvadaxistat were analyzed separately and placebo treatment was not pooled).

Subject analysis set title	Luvadaxistat 500 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received luvadaxistat 500 mg orally QD for 8 days during either treatment periods 1 or 2 of the study.

Subject analysis set title	Placebo (reference for luvadaxistat 500 mg)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received matching placebo orally QD for 8 days during either treatment periods 1 or 2 of the study. Placebo treatment in this arm corresponds to subjects who received 500 mg luvadaxistat in the alternative treatment period (ie, subjects receiving 50 mg and 500 mg luvadaxistat were analyzed separately and placebo treatment was not pooled).

Primary: Change From Baseline in Average Percent of Conditioned Responses During the EBC Test at Day 8

End point title	Change From Baseline in Average Percent of Conditioned Responses During the EBC Test at Day 8

End point description:

EBC is a method used to investigate cerebellar-dependent learning. In EBC, a conditioned stimulus, a tone precedes but co-terminates with an unconditioned stimulus, an airpuff to the eyelid. Learning is

demonstrated when an eyeblink (the conditioned response) occurs prior to the onset of the unconditioned stimulus. The percentage can range from 0% (no conditioned learning has occurred) to 100% (all responses are conditioned). Baseline was defined as the last observation prior to the dose of study treatment in the corresponding period. Results are reported as least squares (LS) mean change from baseline at Day 8, determined using an analysis of variance (ANOVA). The PD set consisted of all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-dose PD result.

End point type	Primary

End point timeframe:

Baseline and Day 8 of each treatment period

End point values	Luvadaxistat 50 mg	Placebo (reference for luvadaxistat 50 mg)	Luvadaxistat 500 mg	Placebo (reference for luvadaxistat 500 mg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	12	11	11
Units: percent change				
least squares mean (standard error)	0.597 (± 0.459)	0.319 (± 0.432)	0.578 (± 0.444)	1.344 (± 0.428)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo

Statistical analysis description:

Change from baseline in percent of conditioned responses during the EBC test at Day 8.

Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2401
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.278
Confidence interval	
level	90 %
sides	1-sided
lower limit	-0.246
Variability estimate	Standard error of the mean
Dispersion value	0.376

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo

Statistical analysis description:

Change from baseline in percent of conditioned responses during the EBC test at Day 8.

Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9053
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.766
Confidence interval	
level	90 %
sides	1-sided
lower limit	-1.513
Variability estimate	Standard error of the mean
Dispersion value	0.547

Secondary: Change From Baseline in the Mean Mismatch Negativity (MMN) at Day 8

End point title	Change From Baseline in the Mean Mismatch Negativity (MMN) at Day 8

End point description:

MMN is an event related potential (ERP) evoked in response to unattended changes in background stimulation. MMN reflects an automatic process of detecting a mismatch between a deviant stimulus and a sensory-memory trace. Smaller amplitudes of MMN have been consistently identified in schizophrenia subjects. MMN amplitude was measured at midline frontal electrode (Fz) of electroencephalogram (EEG). Baseline was defined as the last observation prior to the dose of study treatment in the corresponding period. Results are reported as LS mean change from baseline at Day 8, determined using an ANOVA. The PD set consisted of all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-dose PD result.

End point type	Secondary

End point timeframe:

Baseline and Day 8 of each treatment period

End point values	Luvadaxistat 50 mg	Placebo (reference for luvadaxistat 50 mg)	Luvadaxistat 500 mg	Placebo (reference for luvadaxistat 500 mg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	12	15	15
Units: normalized arbitrary unit				
least squares mean (standard error)	-0.239 (± 0.363)	0.669 (± 0.382)	0.594 (± 0.492)	-0.154 (± 0.501)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo

Statistical analysis description:

Change from baseline in MMN amplitude at Day 8.

Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0497
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.908
Confidence interval	
level	90 %
sides	1-sided
upper limit	-0.211
Variability estimate	Standard error of the mean
Dispersion value	0.527

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo
Statistical analysis description:	
Change from baseline in MMN amplitude at Day 8.	
Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8517
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.748
Confidence interval	
level	90 %
sides	1-sided
upper limit	1.67
Variability estimate	Standard error of the mean
Dispersion value	0.702

Secondary: Change From Baseline in the Mean P300 Amplitude at Day 8

End point title	Change From Baseline in the Mean P300 Amplitude at Day 8

End point description:

The P300 wave is an ERP component that is elicited by the presentation of a novel, behaviorally relevant target stimulus embedded among irrelevant stimuli in a manner similar to MMN but requiring active listening and responding from subjects. Auditory stimuli are presented in an oddball paradigm consisting of 1 standard tone and 1 target tone. Subjects are instructed to push a button as quickly as possible when they hear the target tone but not when they hear the standard tone. P300 reflects allocation of attention and activation of immediate memory. P300 amplitude was measured at midline parietal electrode (Pz) of EEG. Baseline was defined as the last observation prior to the dose of study treatment in the corresponding period. Results are reported as LS mean change from baseline at Day 8, determined using an ANOVA. The PD set consisted of all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-dose PD result.

End point type	Secondary

End point timeframe:

Baseline and Day 8 of each treatment period

End point values	Luvadaxistat 50 mg	Placebo (reference for luvadaxistat 50 mg)	Luvadaxistat 500 mg	Placebo (reference for luvadaxistat 500 mg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	14	14
Units: normalized arbitrary unit				
least squares mean (standard error)	-2.019 (± 1.68)	0.608 (± 1.68)	1.102 (± 1.77)	2.595 (± 1.86)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo
Statistical analysis description: Change from baseline in P300 target amplitude at Day 8.	
Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9185
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.627
Confidence interval	
level	90 %
sides	1-sided
lower limit	-5.02
Variability estimate	Standard error of the mean
Dispersion value	1.74

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo
Statistical analysis description: Change from baseline in P300 target amplitude at Day 8.	
Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7193
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.493

Confidence interval	
level	90 %
sides	1-sided
lower limit	-4.878
Variability estimate	Standard error of the mean
Dispersion value	2.5

Secondary: Change From Baseline in the Mean Auditory Steady State Response (ASSR) at Day 8

End point title	Change From Baseline in the Mean Auditory Steady State Response (ASSR) at Day 8

End point description:

ASSRs are evoked oscillatory responses that are entrained to the frequency and phase of temporally modulated stimuli. Individuals with schizophrenia experience subjective sensory anomalies and objective deficits on assessment of sensory function. These deficits can be produced by abnormal signaling in the sensory pathways and sensory cortex or by later-stage disturbances in the cognitive processing of such inputs. ASSR can be used to assess the integrity of sensory pathways including cortical processing. The ASSR applied a frequency stimulus of 40 hertz (Hz) and was measured at midline central electrode (Cz) of EEG. Baseline was defined as the last observation prior to the dose of study treatment in the corresponding period. Results are reported as LS mean change from baseline at Day 8, determined using an ANOVA. The PD set consisted of all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-dose PD result.

End point type	Secondary

End point timeframe:

Baseline and Day 8 of each treatment period

End point values	Luvadaxistat 50 mg	Placebo (reference for luvadaxistat 50 mg)	Luvadaxistat 500 mg	Placebo (reference for luvadaxistat 500 mg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	12	15	14
Units: normalized arbitrary unit				
least squares mean (standard error)	2.135 (± 8.83)	-16.282 (± 9.31)	9.411 (± 20.4)	9.203 (± 20.9)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo

Statistical analysis description:

Change from baseline in ASSR at 40 Hz stimulation at Day 8.

Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0561
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	18.417
Confidence interval	
level	90 %
sides	1-sided
lower limit	3.87
Variability estimate	Standard error of the mean
Dispersion value	10.7

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo
Statistical analysis description:	
Change from baseline in ASSR at 40 Hz stimulation at Day 8.	
Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4954
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.208
Confidence interval	
level	90 %
sides	1-sided
lower limit	-24.409
Variability estimate	Standard error of the mean
Dispersion value	17.6

Secondary: Change from Baseline on the Brief Assessment of Cognition in Schizophrenia (BACS) Composite Score at Day 7

End point title	Change from Baseline on the Brief Assessment of Cognition in Schizophrenia (BACS) Composite Score at Day 7

End point description:

BACS is a cognition assessment battery and includes brief assessments of reasoning and problem solving, verbal fluency, attention, verbal memory, working memory and motor speed. The primary measure from each test is standardized by creating z-scores whereby the mean of the test session of a healthy person is set to 0 and the standard deviation set to 1. A composite score was calculated by averaging the 4 measures from the BACS used in the study and then calculating a z-score of the composite. The composite z-score indicates how much higher or lower the subject's cognition is compared to a healthy person. Baseline was defined as the last observation prior to the dose of study treatment in the corresponding period. Results are reported as LS mean change from baseline at Day 7, determined using an ANOVA. The PD set consisted of all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-dose PD result.

End point type	Secondary

End point timeframe:

Baseline and Day 7 of each treatment period

End point values	Luvadaxistat 50 mg	Placebo (reference for luvadaxistat 50 mg)	Luvadaxistat 500 mg	Placebo (reference for luvadaxistat 500 mg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	15	15
Units: z-score				
least squares mean (standard error)	2.574 (± 2.51)	5.070 (± 2.55)	5.696 (± 1.41)	-0.075 (± 1.43)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo
Statistical analysis description:	
Change from baseline on the BACS composite score at Day 7.	
Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.799
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.495
Confidence interval	
level	90 %
sides	1-sided
lower limit	-6.426
Variability estimate	Standard error of the mean
Dispersion value	2.83

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo
Statistical analysis description:	
Change from baseline on the BACS composite score at Day 7.	
Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	5.771

Confidence interval	
level	90 %
sides	1-sided
lower limit	3.132
Variability estimate	Standard error of the mean
Dispersion value	2.01

Secondary: Change From Baseline in the Mean Plasma Concentrations of D-serine and L-serine at Day 8

End point title	Change From Baseline in the Mean Plasma Concentrations of D-serine and L-serine at Day 8

End point description:

Blood samples were collected at pre-specified timepoints and plasma concentrations of D-serine and L-serine were measured. Results are reported as LS mean change from baseline at Day 8, determined using a mixed model for repeated measures (MMRM). The PK analysis set included all randomized subjects who received at least 1 dose of study treatment and who had any available plasma concentration data.

End point type	Secondary

End point timeframe:

Samples were collected on Day 1 (pre-dose and 3 to 6 hours post-dose), Day 7 (pre-dose and 3 to 6 hours post-dose) and Day 8 (pre-dose).

End point values	Luvadaxistat 50 mg	Placebo (reference for luvadaxistat 50 mg)	Luvadaxistat 500 mg	Placebo (reference for luvadaxistat 500 mg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	15	15
Units: mg / liter				
least squares mean (standard error)				
D-serine	0.0402 (± 0.00632)	-0.000892 (± 0.00637)	0.0398 (± 0.00710)	0.00212 (± 0.00712)
L-serine	0.669 (± 0.479)	-0.543 (± 0.483)	-1.09 (± 0.514)	-0.304 (± 0.516)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo

Statistical analysis description:

Change from baseline in plasma concentrations of D-serine at Day 8.

Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.0411
Confidence interval	
level	90 %
sides	1-sided
lower limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.00836

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo

Statistical analysis description:

Change from baseline in plasma concentrations of D-serine at Day 8.

Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.0377
Confidence interval	
level	90 %
sides	1-sided
lower limit	0.0264
Variability estimate	Standard error of the mean
Dispersion value	0.00861

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo

Statistical analysis description:

Change from baseline in plasma concentrations of L-serine at Day 8.

Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0219
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.21

Confidence interval	
level	90 %
sides	1-sided
lower limit	0.466
Variability estimate	Standard error of the mean
Dispersion value	0.562

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo

Statistical analysis description:

Change from baseline in plasma concentrations of L-serine at Day 8.

Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8782
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.784
Confidence interval	
level	90 %
sides	1-sided
lower limit	-1.65
Variability estimate	Standard error of the mean
Dispersion value	0.658

Secondary: Change From Baseline in the Mean Plasma D-serine to Total Serine Ratio at Day 8

End point title	Change From Baseline in the Mean Plasma D-serine to Total Serine Ratio at Day 8

End point description:

Blood samples were collected at pre-specified timepoints and plasma concentrations of D-serine and total serine were measured. Plasma D-serine to total serine ratios were then calculated. Results are reported as LS mean change from baseline at Day 8, determined using a MMRM. The PK analysis set included all randomized subjects who received at least 1 dose of study treatment and who had any available plasma concentration data.

End point type	Secondary

End point timeframe:

Baseline and Day 8 of each treatment period

End point values	Luvadaxistat 50 mg	Placebo (reference for luvadaxistat 50 mg)	Luvadaxistat 500 mg	Placebo (reference for luvadaxistat 500 mg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	15	15
Units: ratio				
least squares mean (standard error)	0.00293 (± 0.000855)	0.000590 (± 0.000863)	0.00561 (± 0.000994)	0.000620 (± 0.000997)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared with Placebo

Statistical analysis description:

Change from baseline in plasma D-serine to total serine ratio at Day 8.

Comparison groups	Luvadaxistat 50 mg v Placebo (reference for luvadaxistat 50 mg)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0206
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.00234
Confidence interval	
level	90 %
sides	1-sided
lower limit	0.000925
Variability estimate	Standard error of the mean
Dispersion value	0.00107

Statistical analysis title	Luvadaxistat 500 mg Compared with Placebo

Statistical analysis description:

Change from baseline in plasma D-serine to total serine ratio at Day 8.

Comparison groups	Luvadaxistat 500 mg v Placebo (reference for luvadaxistat 500 mg)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.00499

Confidence interval	
level	90 %
sides	1-sided
lower limit	0.00321
Variability estimate	Standard error of the mean
Dispersion value	0.00135

Secondary: Mean Plasma Concentration of Luvadaxistat

End point title	Mean Plasma Concentration of Luvadaxistat

End point description:

Blood samples were collected at pre-specified timepoints and plasma concentrations of luvadaxistat were measured. The PK analysis set included all randomized subjects who received at least 1 dose of study treatment and who had any available luvadaxistat plasma concentration data. Here 'n' refers to number of subjects analyzed at each timepoint.

End point type	Secondary

End point timeframe:

Samples were collected on Day 1 (pre-dose and at 0.25 to 2 hours and 3 to 6 hours post-dose), Day 7 (pre-dose and at 0.25 to 2 hours and 3 to 6 hours post-dose) and Day 8 (pre-dose).

End point values	Luvadaxistat 50 mg	Luvadaxistat 500 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	15		
Units: nanograms / milliliter				
arithmetic mean (standard deviation)				
Day 1 - Post-dose (0.25 to 2 hours) (n = 14, 15)	253.4 (± 199.3)	700.4 (± 783.0)		
Day 1 - Post-dose (3 to 6 hours) (n = 14, 15)	47.66 (± 35.64)	671.1 (± 473.1)		
Day 7 - Pre-dose (n = 14, 15)	8.749 (± 19.212)	78.92 (± 229.90)		
Day 7 - Post-dose (0.25 to 2 hours) (n = 13, 15)	203.5 (± 199.6)	1184 (± 482)		
Day 7 - Post-dose (3 to 6 hours) (n = 13, 15)	38.94 (± 26.23)	301.5 (± 177.2)		
Day 8 - Pre-dose (n = 12, 15)	3.366 (± 2.726)	21.61 (± 14.65)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

8-day treatment period for each of treatment periods 1 and 2 (separated by washout of up to 21 days) and up to 30 days follow-up after last dose of study treatment. Up to a maximum of 67 days for overall timeframe.

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as adverse events that occurred after the first dose of study treatment and up to 30 days after the last dose or early termination. The safety analysis set included all randomized subjects who received at least 1 dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects who received matching placebo orally QD for 8 days during either treatment periods 1 or 2 of the study. Placebo treatment was pooled for subjects receiving 50 mg and 500 mg luvadaxistat.

Reporting group title	Luvadaxistat 500 mg

Reporting group description:

Subjects who received luvadaxistat 500 mg orally QD for 8 days during either treatment periods 1 or 2 of the study.

Reporting group title	Luvadaxistat 50 mg

Reporting group description:

Subjects who received luvadaxistat 50 mg orally QD for 8 days during either treatment periods 1 or 2 of the study.

Serious adverse events	Placebo	Luvadaxistat 500 mg	Luvadaxistat 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Luvadaxistat 500 mg	Luvadaxistat 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
Gastrointestinal disorders			
Dyspepsia			

subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 15 (0.00%) 0	1 / 14 (7.14%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2017	• The primary reason for this amendment was to revise pregnancy avoidance and contraception requirements.
11 October 2017	• The primary reason for this amendment was to revise luvadaxistat doses to be administered (from 400 mg and 40 mg to 500 mg and 50 mg) and procedures, dose justification and update clinical experience.
30 May 2018	• The primary reason for this amendment was to eliminate the functional magnetic resonance imaging blood oxygen level-dependent imaging component. In addition to the change in study design, inclusion/exclusion criteria were modified, study treatment distribution, including subject randomization process was modified to include interactive response technology and changes were made in the schedule of assessments. The clinical site in the UK where the study was initiated (Amendment 11 October 2017) was chosen based on its imaging capabilities. Since imaging was no longer to be conducted, a new study site (in the US) with an appropriate subject population and expertise for the modified study protocol was chosen to conduct the study. The study was initiated (Amendment 11 October 2017) at the previous site and 1 subject was enrolled and completed all assessments. The data from this subject was excluded from the current analysis as only those subjects participating in this study at the site in the US under Amendment 30 May 2018 were included.
17 December 2018	• The primary reason for this amendment was to modify exclusion criterion 17 to separate the prespecified exclusion criteria from those based on investigator opinion. Those exclusion which were subject to investigator opinion remained in exclusion criterion 17, while those that were measurable were moved to exclusion criteria 18 through 23. • In addition, an exploratory objective that did not have a corresponding endpoint was removed, revised the exclusion duration for any investigational drug to be consistent with the relevant exclusion criterion, clarified study design and added guidance for rescreening subjects, corrected inconsistency in randomization description and updated time of 12-lead electrocardiogram collection for ease of collection.
19 September 2019	• The primary reasons for this amendment were to modify inclusion criterion 10 to revise the maximum dose of quetiapine as add-on hypnotic from 100 mg to 300 mg as this increased dose was not expected to interfere with the primary and secondary endpoints and modify exclusion criterion 6 to allow rescreening of marijuana positive subjects at screening and to allow for increasing subject recruitment. • In addition, exclusion criteria were updated to capture corrections in Amendment 17 December 2018 informed to the sites via administrative letters and statistical procedure gave precedence to the statistical analysis plan over protocol to correct the inconsistencies.
09 January 2020	• The primary reason for this amendment was to modify inclusion criterion 3 to revise the maximum subject age from 50 to 60 years of age, to allow for increasing subject recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 March 2020	This study was paused in March 2020 due to Coronavirus Disease 2019 (COVID-19) site restrictions, but was able to restart in September 2020 and complete enrollment of 31 subjects. Due to this pause, there was a higher number of early terminations than planned; however, the integrity of the study, the ability to achieve the objectives, and the outcome of the study results were not impacted by COVID-19.	01 September 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

One subject was excluded from the study entirely (enrolled at a site in the UK), due to a new version of the protocol being used (Amendment 30 May 2018). Thus, only data from the site in the US were included in the current analysis.

Notes: