



Clinical trial results:

A Phase 2, 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Evaluate Efficacy, Safety, Tolerability, and Pharmacokinetics of 3 Dose Levels of TAK-831 in Adjunctive Treatment of Adult Subjects With Negative Symptoms of Schizophrenia

Summary

EudraCT number	2017-003471-54
Trial protocol	ES CZ DE BG IT
Global end of trial date	12 January 2021

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-831-2002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03382639
WHO universal trial number (UTN)	U1111-1201-2722

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	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd
Sponsor organisation address	40 Landsdowne Street, Cambridge, United States, MA 02139
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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine whether add-on luvadaxistat (TAK-831) is superior to placebo on the Positive and Negative Syndrome Scale Negative Symptom Factor Score (PANSS NSFS).

Protection of trial subjects:

The study was conducted in accordance with Takeda and Neurocrine Biosciences, Inc. 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	22 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	Bulgaria: 54
Country: Number of subjects enrolled	Czechia: 14
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Serbia: 12
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Ukraine: 51
Country: Number of subjects enrolled	United States: 65
Worldwide total number of subjects	256
EEA total number of subjects	106

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)	256
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study assessed efficacy, safety, tolerability and pharmacokinetics (PK) of adjunctive treatment with luvadaxistat when given once daily (QD) in adult subjects with negative symptoms of schizophrenia. Effects of 3 dose levels of luvadaxistat (50 milligrams [mg], 125 mg and 500 mg) or placebo were assessed.

Pre-assignment

Screening details:

The study consisted of a screening period of up to 28 days, a 14-day single-blind placebo run-in period, a 12-week double-blind treatment period and a safety follow-up visit. Randomization was stratified by age at screening (<35 and ≥35 years). The allocation ratio was 2:2:2:3 to the 3 luvadaxistat groups and placebo group, respectively.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo (matching luvadaxistat) orally QD for 12 weeks (Days 1 to 84).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo QD, administered as 5 oral placebo (matching luvadaxistat) tablets.

Arm title	Luvadaxistat 50 mg
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Arm description:

Subjects received luvadaxistat 50 mg orally QD for 12 weeks (Days 1 to 84).

Arm type	Experimental
Investigational medicinal product name	Luvadaxistat
Investigational medicinal product code	TAK-831
Other name	NBI-1065844
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received luvadaxistat 50 mg QD, administered as 5 oral tablets of 10 mg each (T2 tablet formulation).

Arm title	Luvadaxistat 125 mg
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Arm description:

Subjects received luvadaxistat 125 mg orally QD for 12 weeks (Days 1 to 84).

Arm type	Experimental
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Investigational medicinal product name	Luvadaxistat
Investigational medicinal product code	TAK-831
Other name	NBI-1065844
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received luvadaxistat 125 mg QD, administered as 5 oral tablets of 25 mg each (T2 tablet formulation).

Arm title	Luvadaxistat 500 mg
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Arm description:

Subjects received luvadaxistat 500 mg orally QD for 12 weeks (Days 1 to 84).

Arm type	Experimental
Investigational medicinal product name	Luvadaxistat
Investigational medicinal product code	TAK-831
Other name	NBI-1065844
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received luvadaxistat 500 mg QD, administered as 5 oral tablets of 100 mg each (T2 tablet formulation).

Number of subjects in period 1	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg
Started	87	58	56
Completed	76	53	52
Not completed	11	5	4
Consent withdrawn by subject	4	3	2
Adverse event, non-fatal	2	-	1
Unsatisfactory therapeutic response	1	-	-
Noncompliance with study drug	1	2	1
Unspecified	2	-	-
Lost to follow-up	1	-	-

Number of subjects in period 1	Luvadaxistat 500 mg
Started	55
Completed	47
Not completed	8
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Unsatisfactory therapeutic response	-
Noncompliance with study drug	1
Unspecified	3
Lost to follow-up	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (matching luvadaxistat) orally QD for 12 weeks (Days 1 to 84).	
Reporting group title	Luvadaxistat 50 mg
Reporting group description:	
Subjects received luvadaxistat 50 mg orally QD for 12 weeks (Days 1 to 84).	
Reporting group title	Luvadaxistat 125 mg
Reporting group description:	
Subjects received luvadaxistat 125 mg orally QD for 12 weeks (Days 1 to 84).	
Reporting group title	Luvadaxistat 500 mg
Reporting group description:	
Subjects received luvadaxistat 500 mg orally QD for 12 weeks (Days 1 to 84).	

Reporting group values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg
Number of subjects	87	58	56
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)	87	58	56
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	39.9	39.9	40.1
standard deviation	± 11.11	± 10.96	± 9.80
Gender categorical Units: Subjects			
Female	24	20	22
Male	63	38	34
Race Units: Subjects			
American Indian or Alaska Native	2	0	1
Asian	2	0	3
Black or African American	10	9	9
Native Hawaiian or Other Pacific Islander	0	0	0
White	70	46	42
Multiracial	0	0	0
Not reported	3	3	1

Ethnicity			
Units: Subjects			
Hispanic or Latino	3	2	2
Not Hispanic and Latino	19	12	18
Not reported	65	44	36

Reporting group values	Luvadaxistat 500 mg	Total	
Number of subjects	55	256	
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)	55	256	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	40.1		
standard deviation	± 11.79	-	
Gender categorical			
Units: Subjects			
Female	22	88	
Male	33	168	
Race			
Units: Subjects			
American Indian or Alaska Native	0	3	
Asian	0	5	
Black or African American	5	33	
Native Hawaiian or Other Pacific Islander	0	0	
White	50	208	
Multiracial	0	0	
Not reported	0	7	
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	8	
Not Hispanic and Latino	8	57	
Not reported	46	191	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (matching luvadaxistat) orally QD for 12 weeks (Days 1 to 84).	
Reporting group title	Luvadaxistat 50 mg
Reporting group description:	
Subjects received luvadaxistat 50 mg orally QD for 12 weeks (Days 1 to 84).	
Reporting group title	Luvadaxistat 125 mg
Reporting group description:	
Subjects received luvadaxistat 125 mg orally QD for 12 weeks (Days 1 to 84).	
Reporting group title	Luvadaxistat 500 mg
Reporting group description:	
Subjects received luvadaxistat 500 mg orally QD for 12 weeks (Days 1 to 84).	

Primary: Change From Baseline on the PANSS NSFS at Week 12

End point title	Change From Baseline on the PANSS NSFS at Week 12
End point description:	
PANSS assesses the positive symptoms, negative symptoms and general psychopathology associated with schizophrenia. The scale consists of 30 items. Each item is rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). Here, the PANSS NSFS subscale consists of 7 items which assess the negative symptoms with subscale score ranging from 7 to 49, where a higher score indicates greater severity. Baseline was defined as the last observed value before the first dose of study treatment. Results are reported as least squares (LS) mean change from baseline at Week 12, determined using a mixed model for repeated measures (MMRM). A negative change from baseline indicates improvement. The full analysis set (FAS) included all randomized subjects who received at least 1 dose of double-blind study treatment.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	58	56	55
Units: scores on a scale				
least squares mean (standard error)	-3.1 (± 0.44)	-3.3 (± 0.52)	-3.4 (± 0.51)	-2.5 (± 0.55)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 12.	
Comparison groups	Luvadaxistat 50 mg v Placebo

Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.426
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.66

Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 12.	
Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.725 ^[1]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[1] - Adjusted p-value.

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 12.	
Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.808 ^[2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	0.68

Notes:

[2] - Adjusted p-value.

Secondary: Change from Baseline on the PANSS NSFS at Week 4 and Week 8

End point title	Change from Baseline on the PANSS NSFS at Week 4 and Week 8
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End point description:

PANSS assesses the positive symptoms, negative symptoms and general psychopathology associated with schizophrenia. The scale consists of 30 items. Each item is rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). Here, the PANSS NSFS subscale consists of 7 items which assess the negative symptoms with subscale score ranging from 7 to 49, where a higher score indicates greater severity. Baseline was defined as the last observed value before the first dose of study treatment. Results are reported as LS mean change from baseline at Weeks 4 and 8, determined using a MMRM. A negative change from baseline indicates improvement. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 4 and 8

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	58	56	55
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 4	-1.7 (± 0.32)	-1.6 (± 0.39)	-1.8 (± 0.38)	-1.4 (± 0.40)
Change at Week 8	-2.8 (± 0.39)	-2.2 (± 0.46)	-2.6 (± 0.45)	-2.3 (± 0.49)

Statistical analyses

Statistical analysis title	Week 4: Luvadaxistat 50 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the PANSS NSFS at Week 4.

Comparison groups	Luvadaxistat 50 mg v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.593
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.47

Statistical analysis title	Week 4: Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 4.	
Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.48

Statistical analysis title	Week 4: Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 4.	
Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.696
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.48

Statistical analysis title	Week 8: Luvadaxistat 50 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 8.	
Comparison groups	Luvadaxistat 50 mg v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.58

Statistical analysis title	Week 8: Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 8.	
Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.4
Variability estimate	Standard error of the mean
Dispersion value	0.58

Statistical analysis title	Week 8: Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS NSFS at Week 8.	
Comparison groups	Luvadaxistat 500 mg v Placebo

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.794
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.6

Secondary: Change from Baseline on the Brief Negative Symptom Scale (BNSS) Total Score (12-item) at Week 12

End point title	Change from Baseline on the Brief Negative Symptom Scale (BNSS) Total Score (12-item) at Week 12
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End point description:

The BNSS is a 13-item instrument that measures 5 domains of negative symptoms: blunted affect, alogia, asociality, anhedonia and avolition. All items in the BNSS are rated on a 7-point (0-6) scale, with anchor points generally ranging from symptoms being absent (0) to severe (6). Here, the BNSS total score (12-item, excluding item 4) was calculated by summing the 12 individual items; total score range of 0 to 72, where a higher score indicates higher severity of negative symptoms. Subjects required a BNSS total score ≥ 28 to be eligible for the study (excluding item 4). Baseline was defined as the last observed value before the first dose of study treatment. Results are reported as LS mean change from baseline at Week 12, determined using a MMRM. A negative change from baseline indicates improvement. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	58	56	55
Units: scores on a scale				
least squares mean (standard error)	-7.1 ($\pm$ 1.04)	-8.9 ($\pm$ 1.22)	-8.0 ($\pm$ 1.22)	-6.0 ($\pm$ 1.30)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the BNSS total score (12-item) at Week 12.

Comparison groups	Luvadaxistat 50 mg v Placebo
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Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.122
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	1.56

Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the BNSS total score (12-item) at Week 12.	
Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	2.1
Variability estimate	Standard error of the mean
Dispersion value	1.57

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the BNSS total score (12-item) at Week 12.	
Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	1.61

Secondary: Change from Baseline on the Brief Assessment of Cognition in Schizophrenia (BACS) Composite Score at Week 12

End point title	Change from Baseline on the Brief Assessment of Cognition in Schizophrenia (BACS) Composite Score at Week 12
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End point description:

BACS is a reliable and sensitive measure of cognitive function in schizophrenia. It is a cognition assessment battery that measures 6 domains of cognitive function found to be consistently impaired in schizophrenia: verbal memory, working memory, motor speed, attention, executive functions and verbal fluency. The primary measure from each test of the BACS 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 z-score is calculated by averaging the 6 standardized primary measures. 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 observed value before the first dose of study treatment. Results are reported as LS mean change from baseline at Week 12, determined using a MMRM. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	58	56	55
Units: z-score				
least squares mean (standard error)	2.3 (± 0.83)	4.6 (± 0.97)	3.5 (± 0.96)	2.3 (± 1.04)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the BACS composite score at Week 12.

Comparison groups	Luvadaxistat 50 mg v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	4.7
Variability estimate	Standard error of the mean
Dispersion value	1.22

Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the BACS composite score at Week 12.	
Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	3.6
Variability estimate	Standard error of the mean
Dispersion value	1.23

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the BACS composite score at Week 12.	
Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.519
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	1.26

Secondary: Change from Baseline on the Clinical Global Impression-Schizophrenia-Severity (CGI-SCH-S) Negative Symptoms Score at Week 12

End point title	Change from Baseline on the Clinical Global Impression-Schizophrenia-Severity (CGI-SCH-S) Negative Symptoms Score at Week 12
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End point description:

The CGI-SCH scale is an adapted version of the CGI scale that is designed to assess global illness status in patients with schizophrenia. CGI-SCH-S is a 7-point scale that requires the investigator to rate the severity of the subject's illness at the time of assessment. Here, CGI-SCH-S negative symptoms score assesses the severity of illness for negative symptoms on the following 7-point scale: 1. normal, not at all ill; 2. borderline mentally ill; 3. mildly ill; 4. moderately ill; 5. markedly ill; 6. severely ill; or 7. among the most extremely ill. Baseline was defined as the last observed value before the first dose of study treatment. The number of subjects with each CGI-SCH-S negative symptoms score at baseline and at Week 12 is reported. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	51	49	45
Units: subjects				
Baseline: Normal, not at all ill (1)	0	0	0	0
Baseline: Borderline mentally ill (2)	0	0	1	0
Baseline: Mildly ill (3)	3	3	1	3
Baseline: Moderately ill (4)	36	28	25	22
Baseline: Markedly ill (5)	26	18	20	18
Baseline: Severely ill (6)	6	2	2	2
Baseline: Among the most extremely ill (7)	0	0	0	0
Week 12: Normal, not at all ill (1)	0	0	0	0
Week 12: Borderline mentally ill (2)	1	3	2	3
Week 12: Mildly ill (3)	13	14	12	11
Week 12: Moderately ill (4)	34	22	21	18
Week 12: Markedly ill (5)	20	11	13	12
Week 12: Severely ill (6)	3	1	1	1
Week 12: Among the most extremely ill (7)	0	0	0	0

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the CGI-SCH-S negative symptoms score at Week 12.

Comparison groups	Luvadaxistat 50 mg v Placebo
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Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182 ^[3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - The 1-sided p-values were obtained using the Cochran-Mantel-Haenszel row mean score test for comparison of the shift from baseline to Week 12.

Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the CGI-SCH-S negative symptoms score at Week 12.

Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.255 ^[4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - The 1-sided p-values were obtained using the Cochran-Mantel-Haenszel row mean score test for comparison of the shift from baseline to Week 12.

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the CGI-SCH-S negative symptoms score at Week 12.

Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173 ^[5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - The 1-sided p-values were obtained using the Cochran-Mantel-Haenszel row mean score test for comparison of the shift from baseline to Week 12.

Secondary: Clinical Global Impression Schizophrenia Improvement (CGI-SCH-I) Negative Symptoms Score at Week 12

End point title	Clinical Global Impression Schizophrenia Improvement (CGI-SCH-I) Negative Symptoms Score at Week 12
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End point description:

The CGI-SCH-I assesses the subject's improvement (or worsening). CGI-SCH-I requires the investigator to assess the subject's condition relative to baseline on a 7-point scale. Here, CGI-SCH-I negative symptoms score assesses the improvement for negative symptoms on the following scale: very much improved; 2. much improved; 3. minimally improved; 4. no change; 5. minimally worse; 6. much worse; or 7. very much worse. Baseline was defined as the last observed value before the first dose of study treatment. The number of subjects with each CGI-SCH-I negative symptoms score at Week 12 is reported. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
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End point timeframe:

Baseline up to Week 12

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	51	49	45
Units: subjects				
1 - Very much improved	0	0	0	0
2 - Much improved	10	13	12	5
3 - Minimally improved	29	19	19	21
4 - No change	32	19	16	18
5 - Minimally worse	0	0	2	1
6 - Much worse	0	0	0	0
7 - Very much worse	0	0	0	0

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
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Statistical analysis description:

Analysis of CGI-SCH-I negative symptoms score at Week 12.

Comparison groups	Luvadaxistat 50 mg v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097 ^[6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - The 1-sided p-values were obtained using the Cochran-Mantel-Haenszel row mean score test.

Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
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Statistical analysis description:

Analysis of CGI-SCH-I negative symptoms score at Week 12.

Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179 ^[7]
Method	Cochran-Mantel-Haenszel

Notes:

[7] - The 1-sided p-values were obtained using the Cochran-Mantel-Haenszel row mean score test.

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
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Statistical analysis description:

Analysis of CGI-SCH-I negative symptoms score at Week 12.

Comparison groups	Luvadaxistat 500 mg v Placebo
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Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.623 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[8] - The 1-sided p-values were obtained using the Cochran-Mantel-Haenszel row mean score test.

Secondary: Change from Baseline on the Schizophrenia Cognition Rating Scale (SCoRS) Interviewer Total Score at Week 12

End point title	Change from Baseline on the Schizophrenia Cognition Rating Scale (SCoRS) Interviewer Total Score at Week 12
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End point description:

The SCoRS is an interview-based measure of cognitive functioning that is developed to specifically assess aspects of cognitive functioning in subjects with schizophrenia. The items assess the 7 cognitive domains of attention, memory, reasoning and problem solving, working memory, processing speed, language functions and social cognition. The SCoRS total score is the sum of the 20 items and varies from 20 to 80 with 20 being the best outcome and 80 being the worst. Baseline was defined as the last observed value before the first dose of study treatment. Results are reported as LS mean change from baseline at Week 12, determined using a MMRM. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	58	56	55
Units: scores on a scale				
least squares mean (standard error)	-1.6 (± 0.66)	-3.8 (± 0.77)	-2.3 (± 0.77)	-1.8 (± 0.83)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the SCoRS interviewer total score at Week 12.

Comparison groups	Luvadaxistat 50 mg v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-2.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.95

Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the SCoRS interviewer total score at Week 12.	
Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.257
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.96

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the SCoRS interviewer total score at Week 12.	
Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.436
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.98

Secondary: Change from Baseline on the PANSS Total Score at Week 12

End point title	Change from Baseline on the PANSS Total Score at Week 12
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End point description:

PANSS assesses the positive symptoms, negative symptoms and general psychopathology associated with schizophrenia. The scale consists of 30 items. Each item is rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). The sum of the 30 items is defined as the PANSS total score and ranges from 30 to 210, where a higher score indicates greater severity. Baseline was defined as the last observed value before the first dose of study treatment. Results are reported as LS mean change from baseline at Week 12, determined using a MMRM. A negative change from baseline indicates improvement. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	58	56	55
Units: scores on a scale				
least squares mean (standard error)	-6.2 (± 1.00)	-7.2 (± 1.19)	-6.8 (± 1.18)	-5.0 (± 1.26)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
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Statistical analysis description:

Change from baseline on the PANSS total score at Week 12.

Comparison groups	Luvadaxistat 50 mg v Placebo
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Number of subjects included in analysis	145
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.24
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Method	MMRM
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Parameter estimate	LS Mean Difference
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Point estimate	-1.1
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-4
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upper limit	1.9
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Variability estimate	Standard error of the mean
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Dispersion value	1.5
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Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS total score at Week 12.	
Comparison groups	Luvadaxistat 125 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.345
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	1.5

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS total score at Week 12.	
Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	1.54

Secondary: Change from Baseline on the PANSS Positive Symptom Factor Score (PSFS) at Week 12

End point title	Change from Baseline on the PANSS Positive Symptom Factor Score (PSFS) at Week 12
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End point description:

PANSS assesses the positive symptoms, negative symptoms and general psychopathology associated with schizophrenia. The scale consists of 30 items. Each item is rated on a scale from 1 (symptom not present) to 7 (symptoms extremely severe). Here, the PANSS PSFS subscale consists of 7 items which assess the positive symptoms with subscale score ranging from 7 to 49, where a higher score indicates greater severity. Baseline was defined as the last observed value before the first dose of study

treatment. Results are reported as LS mean change from baseline at Week 12, determined using a MMRM. A negative change from baseline indicates improvement. The FAS included all randomized subjects who received at least 1 dose of double-blind study treatment.

End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	58	56	55
Units: scores on a scale				
least squares mean (standard error)	-0.8 ($\pm$ 0.33)	-1.3 ($\pm$ 0.39)	-1.3 ($\pm$ 0.39)	-0.6 ($\pm$ 0.42)

Statistical analyses

Statistical analysis title	Luvadaxistat 50 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS PSFS at Week 12.	
Comparison groups	Luvadaxistat 50 mg v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.181
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.49

Statistical analysis title	Luvadaxistat 125 mg Compared to Placebo
Statistical analysis description:	
Change from baseline on the PANSS PSFS at Week 12.	
Comparison groups	Luvadaxistat 125 mg v Placebo

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.49

Statistical analysis title	Luvadaxistat 500 mg Compared to Placebo
Statistical analysis description: Change from baseline on the PANSS PSFS at Week 12.	
Comparison groups	Luvadaxistat 500 mg v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.639
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.5

Secondary: Luvadaxistat Plasma Concentrations

End point title	Luvadaxistat Plasma Concentrations ^[9]
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 double-blind study treatment and who had any available luvadaxistat plasma concentration data. Here 'n' refers to number of subjects analyzed at each time point. Note however that at Week 4, assessments were categorized as pre-dose or post-dose according to actual sampling time and due to this, some subjects may have had more than 1 record summarized for Week 4 pre-dose or Week 4 post-dose.	
End point type	Secondary
End point timeframe: Samples were collected pre-dose on Day 1 and Week 4 and post-dose on Weeks 4, 6, 8 and 12.	

Notes:

[9] - 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: Plasma concentrations of luvadaxistat were determined for the luvadaxistat treatment groups only and not for the placebo treatment group.

End point values	Luvadaxistat 50 mg	Luvadaxistat 125 mg	Luvadaxistat 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	56	55	
Units: nanograms / milliliter				
arithmetic mean (standard deviation)				
Day 1 - Pre-dose (n = 56, 55, 53)	0.0 (± 0.00)	0.0 (± 0.00)	0.0 (± 0.00)	
Week 4 - Pre-dose (n = 45, 31, 42)	22.5 (± 44.44)	106.5 (± 197.61)	345.2 (± 653.08)	
Week 4 - Post-dose (n = 64, 72, 53)	79.0 (± 115.75)	229.8 (± 368.27)	480.2 (± 717.15)	
Week 6 (n = 55, 53, 47)	83.6 (± 123.38)	183.6 (± 257.44)	409.3 (± 502.26)	
Week 8 (n = 54, 53, 46)	109.3 (± 144.76)	202.1 (± 294.60)	366.8 (± 473.74)	
Week 12 (n = 51, 48, 44)	61.5 (± 113.94)	185.62 (± 258.73)	356.0 (± 461.42)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12-week double-blind treatment period and up to 30 days follow-up: Day 1 up to Day 114.

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo (matching luvadaxistat) orally QD for 12 weeks (Days 1 to 84).

Reporting group title	Luvadaxistat 50 mg
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Reporting group description:

Subjects received luvadaxistat 50 mg orally QD for 12 weeks (Days 1 to 84).

Reporting group title	Luvadaxistat 125 mg
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Reporting group description:

Subjects received luvadaxistat 125 mg orally QD for 12 weeks (Days 1 to 84).

Reporting group title	Luvadaxistat 500 mg
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Reporting group description:

Subjects received luvadaxistat 500 mg orally QD for 12 weeks (Days 1 to 84).

Serious adverse events	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 87 (4.60%)	0 / 58 (0.00%)	1 / 56 (1.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 58 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 58 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 58 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 87 (1.15%)	0 / 58 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 87 (1.15%)	0 / 58 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Luvadaxistat 500 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

COVID-19			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Luvadaxistat 50 mg	Luvadaxistat 125 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 87 (4.60%)	0 / 58 (0.00%)	5 / 56 (8.93%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 87 (4.60%)	0 / 58 (0.00%)	5 / 56 (8.93%)
occurrences (all)	6	0	7

Non-serious adverse events	Luvadaxistat 500 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 55 (3.64%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2018	• The primary reason for this amendment was to revise elements of the study design. • In addition, inclusion/exclusion criteria, randomization criteria, excluded medications, criteria for discontinuation or withdrawal of a subject to include deterioration of the underlying illness, companion medications, monitoring of plasma levels of antipsychotic medication, contraception procedures, poststudy care, clarification of study procedures, and updating acceptable contraception options were revised for clarification or optimization of the prior protocol content. The number of subjects and statistical methods were revised to optimize the study efficacy analysis based on re-evaluation of the relevant scientific contingencies.
13 March 2019	• The primary reason for this amendment was to revise the assessments to reduce subject and site burden, revise inclusion/exclusion criteria to provide appropriate flexibility to the subject and site, revise concomitant medication requirements, and update recommendations for the management of pregnancy and lactation based on the relevant luvadaxistat nonclinical studies. • Additional clarifications were provided in study design, inclusion/exclusion criteria, randomization criteria, excluded medications, criteria for discontinuation or withdrawal of a subject, video monitoring for assessments, monitoring of plasma levels of antipsychotic medication, and rater monitoring.
08 June 2020	• The primary reason for this amendment was to describe management of study procedures (eg, alternative strategies for collecting data, conducting study visits, and distributing investigational product) during unexpected, unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) such as the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported