



Clinical trial results:

A Phase 2, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Two Fixed Doses (10 mg and 30 mg QD) of CVL-231 (Emraclidine) in Participants With Schizophrenia Experiencing an Acute Exacerbation of Psychosis Summary

EudraCT number	2022-000580-52
Trial protocol	BG
Global end of trial date	26 August 2024

Results information

Result version number	v1 (current)
This version publication date	29 August 2025
First version publication date	29 August 2025

Trial information

Trial identification

Sponsor protocol code	CVL-231-2001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05227690
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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	26 August 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 6-week trial to evaluate the efficacy, safety, and tolerability of 2 fixed doses of CVL-231 (Emraclidine) (10 mg QD and 30 mg QD) in male and female participants who have schizophrenia and are experiencing an acute exacerbation of psychosis.

Protection of trial subjects:

The investigator or his/her representative will explain the nature of the trial to the participant and answer all questions regarding the trial.

Participants must be informed that their participation is voluntary. Participants will be required to agree to (eg, provide electronic agreement or written signature) a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or trial center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2022
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: 29
Country: Number of subjects enrolled	United States: 356
Worldwide total number of subjects	385
EEA total number of subjects	29

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)	385
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants will enter a Screening Period up to 15 days (up to a maximum of 21 days allowed with approval of the medical monitor) to assess eligibility criteria and washout from prior antipsychotic medications and other prohibited medications.

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	Placebo

Arm description:

Participants received placebo tablets orally once daily (QD) through Day 45 of Week 6.

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

Dosage and administration details:

Matching placebo, oral (tablet), once per day for 6 weeks

Arm title	Emraclidine 10 mg, Once Daily (QD)
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Arm description:

Participants received emraclidine 10 mg tablets orally once daily (QD) through Day 45 of Week 6.

Arm type	Experimental
Investigational medicinal product name	Emraclidine 10 mg
Investigational medicinal product code	
Other name	CVL-231, ABBV-1231
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Emraclidine 10 mg, oral (tablet), once per day for 6 weeks

Arm title	Emraclidine 30 mg, Once Daily (QD)
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Arm description:

Participants received emraclidine 30 mg tablets orally once daily (QD) through Day 45 of Week 6.

Arm type	Experimental
Investigational medicinal product name	Emraclidine 30 mg
Investigational medicinal product code	
Other name	CVL-231, ABBV-1231
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Emraclidine 30 mg, oral (tablet), once per day for 6 weeks

Number of subjects in period 1	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)
Started	128	128	129
Completed	85	89	92
Not completed	43	39	37
Physician decision	6	-	4
Adverse event, non-fatal	5	6	10
Other, not specified	2	2	1
Withdrawal of consent	28	27	21
Lack of efficacy	2	4	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo tablets orally once daily (QD) through Day 45 of Week 6.	
Reporting group title	Emraclidine 10 mg, Once Daily (QD)
Reporting group description:	
Participants received emraclidine 10 mg tablets orally once daily (QD) through Day 45 of Week 6.	
Reporting group title	Emraclidine 30 mg, Once Daily (QD)
Reporting group description:	
Participants received emraclidine 30 mg tablets orally once daily (QD) through Day 45 of Week 6.	

Reporting group values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)
Number of subjects	128	128	129
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	42.9	40.6	42.5
standard deviation	± 11.46	± 11.28	± 12.23
Gender categorical			
Units: Subjects			
Female	31	31	27
Male	97	97	102
Ethnicity			
Units: Subjects			
Hispanic or Latino	21	20	9
Not Hispanic or Latino	107	105	118
Unknown or Not Reported	0	3	2
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	3
Asian	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	89	88	87
White	37	39	33
More than one race	2	1	3
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	385		
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	89		
Male	296		
Ethnicity Units: Subjects			
Hispanic or Latino	50		
Not Hispanic or Latino	330		
Unknown or Not Reported	5		
Race Units: Subjects			
American Indian or Alaska Native	3		
Asian	2		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	264		
White	109		
More than one race	6		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo tablets orally once daily (QD) through Day 45 of Week 6.	
Reporting group title	Emraclidine 10 mg, Once Daily (QD)
Reporting group description:	
Participants received emraclidine 10 mg tablets orally once daily (QD) through Day 45 of Week 6.	
Reporting group title	Emraclidine 30 mg, Once Daily (QD)
Reporting group description:	
Participants received emraclidine 30 mg tablets orally once daily (QD) through Day 45 of Week 6.	

Primary: Change From Baseline at Week 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score

End point title	Change From Baseline at Week 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score
End point description:	
The PANSS measures symptom severity of participants with schizophrenia and contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Participants are rated from 1 to 7 on each symptom scale with a total minimum score of 30 and a maximum score of 210. A decrease in PANSS total score correlates with an improvement in schizophrenia symptoms.	
Analysis population: Modified Intent-to-Treat population (mITT): All randomized participants who received at least 1 dose of investigational medicinal product (IMP) and have both a Baseline and at least 1 post-Baseline PANSS assessment; participants with available data	
End point type	Primary
End point timeframe:	
Baseline through Week 6	

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87	90	93	
Units: units on a scale				
least squares mean (confidence interval 95%)	-13.5 (-17.0 to -10.0)	-14.7 (-18.1 to -11.2)	-16.5 (-20.0 to -13.1)	

Statistical analyses

Statistical analysis title	Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1765 ^[1]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	1.4
Variability estimate	Standard error of the mean
Dispersion value	2.24

Notes:

[1] - Emraclidine 30 mg - Placebo

Statistical analysis title	Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Emraclidine 10 mg, Once Daily (QD) v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6007 ^[2]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	2.26

Notes:

[2] - Emraclidine 10 mg - Placebo

Secondary: Change From Baseline at Week 6 in the Clinical Global Impression - Severity (CGI-S) Score

End point title	Change From Baseline at Week 6 in the Clinical Global Impression - Severity (CGI-S) Score
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End point description:

The CGI-S captures clinician's response to: "Considering your total clinical experience, how mentally ill is the participant at this time?" The clinician's answer was based on the following scale: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill participants. Negative changes from Baseline indicate less mental illness.

Analysis population: Modified Intent-to-Treat population (mITT): All randomized participants who received at least 1 dose of investigational medicinal product (IMP) and have both a Baseline and at least 1 post-Baseline PANSS assessment; participants with available data

End point type	Secondary
End point timeframe:	
Baseline through Week 6	

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87	90	93	
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.70 (-0.89 to -0.51)	-0.75 (-0.94 to -0.56)	-0.84 (-1.03 to -0.65)	

Statistical analyses

Statistical analysis title	Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2534 ^[3]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.124

Notes:

[3] - Emraclidine 30 mg - Placebo

Statistical analysis title	Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
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Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6774 ^[4]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.125

Notes:

[4] - Emraclidine 10 mg - Placebo

Secondary: Change From Baseline at All Time Points in Positive and Negative Syndrome Scale (PANSS) Total Score

End point title	Change From Baseline at All Time Points in Positive and Negative Syndrome Scale (PANSS) Total Score
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End point description:

The PANSS measures symptom severity of participants with schizophrenia and contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Participants are rated from 1 to 7 on each symptom scale with a total minimum score of 30 and a maximum score of 210. A decrease in PANSS total score correlates with an improvement in schizophrenia symptoms.

Analysis population: Modified Intent-to-Treat population (mITT): All randomized participants who received at least 1 dose of investigational medicinal product (IMP) and have both a Baseline and at least 1 post-Baseline PANSS assessment; participants with available data

End point type	Secondary
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End point timeframe:

Baseline; Weeks 1, 2, 3, 4, 5, and 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	124	127	
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 1 (n=127, 124, 127)	-5.2 (-7.3 to -3.0)	-5.7 (-7.8 to -3.6)	-6.2 (-8.3 to -4.1)	
Week 2 (n=113, 114, 118)	-8.7 (-11.3 to -6.1)	-8.8 (-11.4 to -6.3)	-9.0 (-11.6 to -6.5)	
Week 3 (n=108, 106, 110)	-10.3 (-13.1 to -7.5)	-10.0 (-12.8 to -7.2)	-11.3 (-14.1 to -8.6)	
Week 4 (n=99, 102, 104)	-12.1 (-15.3 to -9.0)	-12.8 (-15.9 to -9.6)	-13.3 (-16.4 to -10.2)	
Week 5 (n=93, 96, 97)	-13.2 (-16.5 to -9.9)	-14.0 (-17.3 to -10.7)	-14.7 (-18.0 to -11.4)	

Week 6 (n=87, 90, 93)	-13.5 (-17.0 to -10.0)	-14.7 (-18.1 to -11.2)	-16.5 (-20.0 to -13.1)	
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Statistical analyses

Statistical analysis title	Week 1-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3596 ^[5]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	1.1

Notes:

[5] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 1-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6053 ^[6]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	1.6

Variability estimate	Standard error of the mean
Dispersion value	1.1

Notes:

[6] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 2-- Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8149 ^[7]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	1.54

Notes:

[7] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 2-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Emraclidine 10 mg, Once Daily (QD) v Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9058 ^[8]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	1.55

Notes:

[8] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 3-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5419 ^[9]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	1.71
Notes:	
[9] - Emraclidine 30 mg - Placebo	

Statistical analysis title	Week 3-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8585 ^[10]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	1.72
Notes:	
[10] - Emraclidine 10 mg - Placebo	

Statistical analysis title	Week 4-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5521 ^[11]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	1.99
Notes:	
[11] - Emraclidine 30 mg - Placebo	

Statistical analysis title	Week 4-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.754 ^[12]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	2
Notes:	
[12] - Emraclidine 10 mg - Placebo	

Statistical analysis title	Week 5-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit	

interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4842 ^[13]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[13] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 5-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6999 ^[14]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	3.4
Variability estimate	Standard error of the mean
Dispersion value	2.13

Notes:

[14] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
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Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1765 ^[15]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	1.4
Variability estimate	Standard error of the mean
Dispersion value	2.24

Notes:

[15] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6007 ^[16]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	2.26

Notes:

[16] - Emraclidine 10 mg - Placebo

Secondary: Change From Baseline at All Time Points in the Clinical Global Impression - Severity (CGI-S) Score

End point title	Change From Baseline at All Time Points in the Clinical Global Impression - Severity (CGI-S) Score
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End point description:

The CGI-S captures clinician's response to: "Considering your total clinical experience, how mentally ill is the participant at this time?" The clinician's answer was based on the following scale: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill participants. Negative changes from Baseline indicate less mental illness.

Analysis population: Modified Intent-to-Treat population (mITT): All randomized participants who received at least 1 dose of investigational medicinal product (IMP) and have both a Baseline and at least

End point type	Secondary
End point timeframe:	
Baseline; Weeks 1, 2, 3, 4, 5, and 6	

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	124	127	
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 1 (n=127, 124, 127)	-0.18 (-0.29 to -0.06)	-0.17 (-0.29 to -0.05)	-0.21 (-0.32 to -0.09)	
Week 2 (n=114, 114, 118)	-0.36 (-0.50 to -0.21)	-0.39 (-0.54 to -0.25)	-0.35 (-0.50 to -0.21)	
Week 3 (n=108, 107, 110)	-0.48 (-0.64 to -0.32)	-0.42 (-0.58 to -0.26)	-0.52 (-0.67 to -0.36)	
Week 4 (n=99, 102, 104)	-0.54 (-0.71 to -0.36)	-0.53 (-0.70 to -0.36)	-0.70 (-0.87 to -0.53)	
Week 5 (n=92, 96, 97)	-0.67 (-0.85 to -0.49)	-0.64 (-0.82 to -0.46)	-0.74 (-0.92 to -0.56)	
Week 6 (n=87, 90, 93)	-0.70 (-0.89 to -0.51)	-0.75 (-0.94 to -0.56)	-0.84 (-1.03 to -0.65)	

Statistical analyses

Statistical analysis title	Week 1-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5822 ^[17]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.061

Notes:

[17] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 1-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9244 ^[18]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.061

Notes:

[18] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 2-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9348 ^[19]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.088

Notes:

[19] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 2-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Emraclidine 10 mg, Once Daily (QD) v Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.716 ^[20]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.089
Notes:	
[20] - Emraclidine 10 mg - Placebo	

Statistical analysis title	Week 3-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6883 ^[21]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.1
Notes:	
[21] - Emraclidine 30 mg - Placebo	

Statistical analysis title	Week 3-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit	

interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5973 ^[22]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.1

Notes:

[22] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 4-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1392 ^[23]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[23] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 4-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9421 ^[24]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.111

Notes:

[24] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 5-- Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5431 ^[25]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.116

Notes:

[25] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 5-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
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Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.816 ^[26]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.117

Notes:

[26] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2534 ^[27]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.124

Notes:

[27] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
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Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6774 ^[28]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.125

Notes:

[28] - Emraclidine 10 mg - Placebo

Secondary: Percentage of Responders at Week 6 (Responders Defined as $\geq 30\%$ Reduction From Baseline in Positive and Negative Syndrome Scale [PANSS] Total Score)

End point title	Percentage of Responders at Week 6 (Responders Defined as $\geq 30\%$ Reduction From Baseline in Positive and Negative Syndrome Scale [PANSS] Total Score)
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End point description:

The PANSS measures symptom severity of participants with schizophrenia and contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Participants are rated from 1 to 7 on each symptom scale with a total minimum score of 30 and a maximum score of 210. A decrease in PANSS total score correlates with an improvement in schizophrenia symptoms. A PANSS responder is defined as a participant with at least a 30% decrease in PANSS total score compared to Baseline at Week 6 visit or the early termination visit. If a participant discontinued and did not have an early termination visit, the participant's last assessment was considered.

Analysis population: Modified Intent-to-Treat population (mITT): All randomized participants who received at least 1 dose of investigational medicinal product (IMP) and have both a Baseline and at least 1 post-Baseline PANSS assessment; participants with available data

End point type	Secondary
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End point timeframe:

Baseline through Week 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	125	127	
Units: percentage of participants				
number (not applicable)	10.2	17.6	17.3	

Statistical analyses

Statistical analysis title	Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Odds ratio, 95% confidence interval, and p-value were from a logistic regression with treatment group, geographic region and Baseline value as a covariate.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0904
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.99

Statistical analysis title	Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Odds ratio, 95% confidence interval, and p-value were from a logistic regression with treatment group, geographic region and Baseline value as a covariate.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0756
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	4.13

Secondary: Number of Participants With Treatment Emergent Adverse Event (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment Emergent Adverse Event (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)
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End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. The investigator assesses the relationship of each event to the use of study drug. A serious adverse event (SAE) is an event that results in death, is life-threatening, requires or prolongs hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an important medical event that, based on medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed

above. Treatment-emergent adverse events/treatment-emergent serious adverse events (TEAEs/TESAEs) are defined as any event that began or worsened in severity on or after the first dose of study drug.

Analysis population: Full analysis set: All randomized subjects who rcvd ≥ 1 dose of IMP

End point type	Secondary
End point timeframe:	
From first dose of study drug until 28 days following last dose of study drug (up to Week 10)	

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	128	129	
Units: participants				
Any TEAE	73	78	82	
TESAE	2	4	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes in Electrocardiogram (ECGs)

End point title	Number of Participants With Clinically Significant Changes in Electrocardiogram (ECGs)
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End point description:

12-lead electrocardiogram (ECG) recordings were obtained after the participant had been supine and at rest for at least 3 minutes.

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP)

End point type	Secondary
End point timeframe:	
Baseline; from first dose of study drug up to Week 6	

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	128	129	
Units: participants				
QTcF value > 450 - 480 msec	5	3	1	
QTcF value > 480 - 500 msec	0	0	0	
QTcF value > 500 msec	0	0	0	
QTcF increase from Baseline > 30 - 60 msec	13	8	8	
QTcF increase from Baseline > 60 msec	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Changes in Clinical Laboratory Assessments

End point title	Number of Participants with Clinically Significant Changes in Clinical Laboratory Assessments
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End point description:

Clinical laboratory tests were performed at scheduled study visits, and the investigator recorded any clinically significant changes.

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP)

End point type	Secondary
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End point timeframe:

Baseline; from first dose of study drug up to Week 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	128	129	
Units: participants	3	4	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes in Vital Sign Measurements

End point title	Number of Participants With Clinically Significant Changes in Vital Sign Measurements
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End point description:

Vital signs were obtained after the participant had been supine and at rest for 3 minutes and included temperature, systolic and diastolic blood pressure, respiratory rate, and heart rate. Participants' body weights were also measured and recorded.

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP)

End point type	Secondary
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End point timeframe:

Baseline; from first dose of study drug up to Week 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	128	129	
Units: participants				
Supine Systolic Blood Pressure < 90 mmHg	0	0	0	
Supine Systolic BP > 140 mmHg and ≤ 160 mmHg	15	9	11	
Supine Systolic BP > 160 mmHg and ≤ 200 mmHg	0	0	1	
Supine Systolic Blood Pressure > 200 mmHg	0	0	0	
Orthostatic Change in Systolic BP ≥ 20 mmHg down	4	2	5	
Supine Diastolic Blood Pressure < 50 mmHg	0	0	0	
Supine Diastolic BP > 90 mmHg and ≤ 100 mmHg	10	9	19	
Supine Diastolic BP > 100 mmHg and ≤ 120 mmHg	0	0	3	
Supine Diastolic Blood Pressure > 120 mmHg	0	0	0	
Orthostatic Change in Diastolic BP ≥ 10 mmHg down	9	7	14	
Supine Heart Rate < 50 bpm	1	0	0	
Supine Heart Rate ≥ 50 bpm and < 60 bpm	17	6	6	
Supine Heart Rate > 100 bpm and ≤ 120 bpm	8	18	24	
Supine Heart Rate > 120 bpm	0	0	3	
Temperature < 36 °C	1	3	5	
Temperature > 38 °C	1	0	0	
Respiratory Rate < 12 breaths/min	0	0	0	
Respiratory Rate > 20 breaths/min	3	5	6	
Body Weight ≥ 7% decrease	1	1	1	
Body Weight ≥ 7% increase	16	24	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes in Physical and Neurological Examination Results

End point title	Number of Participants With Clinically Significant Changes in Physical and Neurological Examination Results
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End point description:

The number of participants with clinically significant changes in physical and neurological examination results was documented.

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP)

End point type	Secondary
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End point timeframe:

Baseline; from first dose of study drug up to Week 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	128	129	
Units: participants				
Clinically Significant Changes: Physical Exam	1	1	3	
Clinically Significant Changes: Neurological Exam	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Suicide-Related Treatment-Emergent Events assessed using the Columbia Suicide-Severity Rating Scale (C-SSRS)

End point title	Number of Participants With Suicide-Related Treatment-Emergent Events assessed using the Columbia Suicide-Severity Rating Scale (C-SSRS)
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End point description:

The C-SSRS rates an individual's degree of suicidal ideation (SI) on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent." The scale identifies SI severity and intensity, which may be indicative of an individual's intent to commit suicide. C-SSRS SI severity subscale ranges from 0 (no SI) to 5 (active SI with plan and intent).

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP)

End point type	Secondary
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End point timeframe:

Baseline; from first dose of study drug up to Week 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128	128	129	
Units: participants				
Tx-Emergent Suicidal Ideation (Recently)	1	2	7	
Tx-Emergent Serious Suicidal Ideation (Recently)	0	0	0	

Emergence of Serious Suicidal Ideation (Recently)	0	0	0	
Emergence of Suicidal Behavior (Present vs Past)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Simpson Angus Scale (SAS) Total Score

End point title	Change from Baseline in Simpson Angus Scale (SAS) Total Score
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End point description:

The SAS consists of a list of 10 symptoms of Parkinsonism. Each item is rated on a 5-point scale, with a score of 0 representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items. Negative changes from Baseline indicate an improvement in symptoms.

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP); participants with available data

End point type	Secondary
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End point timeframe:

Baseline; Weeks 3 and 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	119	125	
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 3 (n=119, 119, 125)	0.0 (-0.1 to 0.1)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.2)	
Week 6 (n=89, 90, 95)	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.1)	

Statistical analyses

Statistical analysis title	Week 3-- Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
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Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2418 ^[29]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[29] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 3-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.572 ^[30]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[30] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
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Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7459 ^[31]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[31] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6729 ^[32]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[32] - Emraclidine 10 mg - Placebo

Secondary: Change from Baseline in Abnormal Involuntary Movement Scale (AIMS) Movement Rating Score

End point title	Change from Baseline in Abnormal Involuntary Movement Scale (AIMS) Movement Rating Score
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End point description:

The AIMS assessment consists of 10 items describing symptoms of dyskinesia. Each item is rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). In addition, the AIMS includes 2 yes/no questions that address the subject's dental status. Negative changes from Baseline indicate an improvement in symptoms.

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP); participants with available data

End point type	Secondary
End point timeframe:	
Baseline; Weeks 3 and 6	

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	119	125	
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 3 (n=119, 119, 125)	0.0 (-0.1 to 0.1)	-0.1 (-0.2 to 0.0)	0.1 (0.0 to 0.2)	
Week 6 (n=89, 90, 95)	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.1)	

Statistical analyses

Statistical analysis title	Week 3-- Emraclidine 30 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3783 ^[33]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[33] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 3-- Emraclidine 10 mg versus Placebo
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Statistical analysis description:

Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2242 ^[34]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[34] - Emraclidine 10 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8626 ^[35]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[35] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)

Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6106 ^[36]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[36] - Emraclidine 10 mg - Placebo

Secondary: Change From Baseline in Barnes Akathisia Rating Scale (BARS) Global Clinical Evaluation Score

End point title	Change From Baseline in Barnes Akathisia Rating Scale (BARS) Global Clinical Evaluation Score
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End point description:

The BARS consists of 4 items related to akathisia: The first 3 items are rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation is made on a 6-point scale, with a score of 0 representing absence of symptom and a score of 5 representing severe akathisia. Negative changes from Baseline indicate an improvement in symptoms.

Analysis population: Full analysis set: All randomized participants who received at least 1 dose of investigational medicinal product (IMP); participants with available data

End point type	Secondary
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End point timeframe:

Baseline; Weeks 3 and 6

End point values	Placebo	Emraclidine 10 mg, Once Daily (QD)	Emraclidine 30 mg, Once Daily (QD)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	119	125	
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 3 (n=119, 119, 125)	0.0 (-0.1 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	
Week 6 (n=89, 90, 95)	0.0 (0.0 to 0.0)	0.0 (-0.1 to 0.0)	0.0 (0.0 to 0.0)	

Statistical analyses

Statistical analysis title	Week 3-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4219 ^[37]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.03
Notes:	
[37] - Emraclidine 30 mg - Placebo	

Statistical analysis title	Week 3-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Emraclidine 10 mg, Once Daily (QD) v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3933 ^[38]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.03
Notes:	
[38] - Emraclidine 10 mg - Placebo	

Statistical analysis title	Week 6-- Emraclidine 30 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit	

interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.

Comparison groups	Placebo v Emraclidine 30 mg, Once Daily (QD)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7366 ^[39]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.02

Notes:

[39] - Emraclidine 30 mg - Placebo

Statistical analysis title	Week 6-- Emraclidine 10 mg versus Placebo
Statistical analysis description:	
Least-squares mean difference from Placebo and CIs were estimated using a mixed effects repeated measures model with fixed effects for treatment group, geographic region, visit, and treatment-by-visit interaction and Baseline value as a covariate. Participant was included as a random effect. An unstructured covariance structure was used.	
Comparison groups	Placebo v Emraclidine 10 mg, Once Daily (QD)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4639 ^[40]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.02

Notes:

[40] - Emraclidine 10 mg - Placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and adverse events reported from time informed consent was signed to end of the study. Median follow-up was 81.5 days for the Placebo group, 77 days for the Emraclidine 10 mg group, and 80 days for the Emraclidine 30 mg group.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received placebo tablets orally once daily (QD) through Day 45 of Week 6.

Reporting group title	Emraclidine 30 mg, Once Daily (QD)
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Reporting group description:

Participants received emraclidine 30 mg tablets orally once daily (QD) through Day 45 of Week 6.

Reporting group title	Emraclidine 10 mg, Once Daily (QD)
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Reporting group description:

Participants received emraclidine 10 mg tablets orally once daily (QD) through Day 45 of Week 6.

Serious adverse events	Placebo	Emraclidine 30 mg, Once Daily (QD)	Emraclidine 10 mg, Once Daily (QD)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 128 (1.56%)	1 / 129 (0.78%)	4 / 128 (3.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
DYSTONIA			
subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
AGGRESSION			
subjects affected / exposed	0 / 128 (0.00%)	1 / 129 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AGITATION			

subjects affected / exposed	0 / 128 (0.00%)	0 / 129 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCHIZOPHRENIA			
subjects affected / exposed	2 / 128 (1.56%)	0 / 129 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Emraclidine 30 mg, Once Daily (QD)	Emraclidine 10 mg, Once Daily (QD)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 128 (43.75%)	74 / 129 (57.36%)	66 / 128 (51.56%)
Investigations			
BLOOD PRESSURE INCREASED			
subjects affected / exposed	0 / 128 (0.00%)	4 / 129 (3.10%)	0 / 128 (0.00%)
occurrences (all)	0	4	0
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	3 / 128 (2.34%)	3 / 129 (2.33%)	4 / 128 (3.13%)
occurrences (all)	3	3	4
WEIGHT INCREASED			
subjects affected / exposed	11 / 128 (8.59%)	8 / 129 (6.20%)	22 / 128 (17.19%)
occurrences (all)	11	8	22
Cardiac disorders			
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 128 (0.78%)	6 / 129 (4.65%)	2 / 128 (1.56%)
occurrences (all)	1	8	2
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	4 / 128 (3.13%)	3 / 129 (2.33%)	1 / 128 (0.78%)
occurrences (all)	4	4	1
HEADACHE			
subjects affected / exposed	12 / 128 (9.38%)	17 / 129 (13.18%)	18 / 128 (14.06%)
occurrences (all)	14	18	20
SOMNOLENCE			

subjects affected / exposed occurrences (all)	6 / 128 (4.69%) 6	9 / 129 (6.98%) 9	9 / 128 (7.03%) 11
General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all)	1 / 128 (0.78%) 1	5 / 129 (3.88%) 5	0 / 128 (0.00%) 0
Gastrointestinal disorders TOOTHACHE subjects affected / exposed occurrences (all)	3 / 128 (2.34%) 3	3 / 129 (2.33%) 3	1 / 128 (0.78%) 1
NAUSEA subjects affected / exposed occurrences (all)	2 / 128 (1.56%) 2	6 / 129 (4.65%) 7	3 / 128 (2.34%) 4
GASTROOESOPHAGEAL REFLUX DISEASE subjects affected / exposed occurrences (all)	2 / 128 (1.56%) 2	4 / 129 (3.10%) 5	3 / 128 (2.34%) 3
DYSPEPSIA subjects affected / exposed occurrences (all)	4 / 128 (3.13%) 5	10 / 129 (7.75%) 10	5 / 128 (3.91%) 5
DRY MOUTH subjects affected / exposed occurrences (all)	3 / 128 (2.34%) 3	12 / 129 (9.30%) 12	5 / 128 (3.91%) 5
CONSTIPATION subjects affected / exposed occurrences (all)	4 / 128 (3.13%) 4	3 / 129 (2.33%) 3	3 / 128 (2.34%) 3
ABDOMINAL PAIN subjects affected / exposed occurrences (all)	4 / 128 (3.13%) 4	0 / 129 (0.00%) 0	0 / 128 (0.00%) 0
Psychiatric disorders AGITATION subjects affected / exposed occurrences (all)	4 / 128 (3.13%) 4	5 / 129 (3.88%) 8	1 / 128 (0.78%) 1
ANXIETY subjects affected / exposed occurrences (all)	3 / 128 (2.34%) 3	3 / 129 (2.33%) 3	1 / 128 (0.78%) 1
INSOMNIA			

subjects affected / exposed occurrences (all)	5 / 128 (3.91%) 5	3 / 129 (2.33%) 3	6 / 128 (4.69%) 7
PSYCHOTIC DISORDER subjects affected / exposed occurrences (all)	4 / 128 (3.13%) 4	2 / 129 (1.55%) 2	3 / 128 (2.34%) 3
SCHIZOPHRENIA subjects affected / exposed occurrences (all)	2 / 128 (1.56%) 2	4 / 129 (3.10%) 4	1 / 128 (0.78%) 1
SUICIDAL IDEATION subjects affected / exposed occurrences (all)	1 / 128 (0.78%) 1	4 / 129 (3.10%) 4	1 / 128 (0.78%) 1
Musculoskeletal and connective tissue disorders PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	0 / 128 (0.00%) 0	1 / 129 (0.78%) 1	4 / 128 (3.13%) 5
BACK PAIN subjects affected / exposed occurrences (all)	3 / 128 (2.34%) 3	8 / 129 (6.20%) 8	1 / 128 (0.78%) 2
ARTHRALGIA subjects affected / exposed occurrences (all)	1 / 128 (0.78%) 1	5 / 129 (3.88%) 6	3 / 128 (2.34%) 3
Infections and infestations TOOTH ABSCESS subjects affected / exposed occurrences (all)	1 / 128 (0.78%) 1	3 / 129 (2.33%) 4	0 / 128 (0.00%) 0
Metabolism and nutrition disorders INCREASED APPETITE subjects affected / exposed occurrences (all)	2 / 128 (1.56%) 2	0 / 129 (0.00%) 0	3 / 128 (2.34%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2022	<p>Version 2.0</p> <ul style="list-style-type: none">- Updated drug name to newly approved official INN for CVL-231, emraclidine- Increased upper limit of age range from 55 to 65 years- Added information regarding stratification by geographic region- Added flexibility to contact medical monitor if participant unable to return to facility on the same day as a day pass was given- Provided additional text to describe that some positive urine drug screen results may not require participant discontinuation after discussion and approval of medical monitor- Provided additional details regarding MMRM model analyses for primary and secondary estimands- Provided additional details regarding sensitivity analyses for primary and secondary estimands- Revised testing procedures for SARS-CoV-2 to require negative test prior to admission and to adhere to site procedures- Updated to have triplicate rather than duplicate vital sign measurements with average of last 2 values used for assessment of eligibility- Modified wording of footnote bb regarding future biospecimen research sample to indicate only collected from participants who are enrolled in trial- Minor wording modifications for clarity in describing changes in vital sign and ECG measurements- Modified Inclusion Criterion #9 regarding contraception requirements for men- Added requirement for participants using antihypertensive medications to have been on stable dose for 3 months or more to Exclusion Criterion #7 and Table 4. Added restriction that participants cannot be receiving more than 2 medications to treat hypertension to Table 4 for consistency.- Increased the exclusionary heart rate value from 90 to 100 bpm in Exclusion Criterion #19- Added in restriction for grapefruit- or Seville orange-containing foods and beverages while in trial- Added explanation and supporting references for the use of ALT (rather than ALT and AST) to detect and monitor liver injury
15 March 2023	<p>Version 3.0</p> <ul style="list-style-type: none">- In sentence referring to extending enrollment due to higher anticipated early terminations, removed language "due to COVID-19 or other reasons"- In description of statistical method, the strategies for addressing intercurrent events and missing values due to discontinuations were revised to provide further delineation of the intercurrent events of different nature- Modified language in footnotes y and z regarding PK sampling- Relaxed entry criterion (Exclusion Criterion #12) regarding COVID-19/SARS-CoV-2 testing- Removed exclusion of participants with positive result for hepatitis B core antibody at Screening and updated wording of "Note" in Exclusion Criterion #15- Reduced washout period for depot or long-acting injectable antipsychotic agents from 2 full cycles to 1.5 cycles- Allowed enrollment of participants who were involved in a long-term follow-up period of an interventional trial with no treatment within 12 months of signing ICF upon approval of medical monitor- Added instruction and table describing CTCAE grading of blood pressure-related adverse events- Added in clarification that "additional tests" for SARS-CoV-2 can be done at investigator discretion- Modified language to specify that follow-up not required for longer than 12 weeks beyond estimated delivery date for female participants who become pregnant

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported