Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of ITI-007 Adjunctive to Lithium or Valproate in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression)

Summary

EudraCT number	2018-002749-12
Trial protocol	BG
Global end of trial date	02 July 2020

Results information

Result version number	v1 (current)
This version publication date	27 October 2021
First version publication date	27 October 2021

Trial information

Trial identification

Sponsor protocol code	ITI-007-402

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02600507
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Intra-Cellular Therapies, Inc.
Sponsor organisation address	430 East 29th Street, New York, NY, United States, 10016
Public contact	ITI Clinical Trials, Intra-Cellular Therapies, Inc. (ITI), +1 646-440-9333, ITCIClinicalTrials@itci-inc.com
Scientific contact	ITI Clinical Trials, Intra-Cellular Therapies, Inc. (ITI), +1 646-440-9333, ITCIClinicalTrials@itci-inc.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	14 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2020
Global end of trial reached?	Yes
Global end of trial date	02 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare efficacy of 2 doses of ITI-007 adjunctive to treatment with lithium or valproate, administered orally once daily, to that of placebo adjunctive to treatment with lithium or valproate as measured by mean change from baseline to Day 43 in total score of the rater administered Montgomery-Åsberg Depression Rating Scale (MADRS) in patients with bipolar depression.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study complied with the ICH Guidance on General Considerations for Clinical Trials and GCP, as well as CFR Part 312.

Background therapy:

Lithium or Valproate

Evidence for comparator: -

Actual start date of recruitment	07 March 2016
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: 142
Country: Number of subjects enrolled	Russian Federation: 104
Country: Number of subjects enrolled	Serbia: 52
Country: Number of subjects enrolled	Ukraine: 57
Country: Number of subjects enrolled	United States: 173
Worldwide total number of subjects	528
EEA total number of subjects	142

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)	501
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Screening phase begins once the Informed Consent Form is signed. Patients are evaluated during the screening period lasting up to 2 weeks to ensure sufficient washout of restricted medications.

Period 1

Period 1 title	Double-Blind Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Lumateperone 42 mg

Arm description: -

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

Dosage and administration details:

Once daily oral administration

Arm title	Lumateperone 28 mg

Arm description: -

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

Dosage and administration details:

Once oral daily administration

Arm title	Placebo

Arm description: -

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:

Once daily oral administration

Number of subjects in period 1	Lumateperone 42 mg	Lumateperone 28 mg	Placebo
Started	177	176	175
Completed	133	147	150
Not completed	44	29	25
Unwillingness to attend visits related to COVID-19	1	-	1
Consent withdrawn by subject	11	7	7
Physician decision	-	1	1
Adverse event, non-fatal	15	3	5
Lost to follow-up	5	3	2
Lack of efficacy	8	3	5
Protocol deviation	4	12	4

Baseline characteristics

Reporting groups	
Reporting group title	Lumateperone 42 mg
Reporting group description: -	
Reporting group title	Lumateperone 28 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Lumateperone 42 mg	Lumateperone 28 mg	Placebo
Number of subjects	177	176	175
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)	173	163	165
From 65-84 years	4	13	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.7	44.0	45.1
standard deviation	± 12.60	± 13.56	± 12.93
Gender categorical Units: Subjects			
Female	109	101	98
Male	68	75	77

Reporting group values	Total		
Number of subjects	528		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	501		
From 65-84 years	27		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	308		
Male	220		

End points

End points reporting groups

Reporting group title	Lumateperone 42 mg
Reporting group description: -	
Reporting group title	Lumateperone 28 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Lumateperone 42 mg (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients who received at least one dose of study medication and who had a valid baseline (pre-dose) measurement and at least one valid post-baseline measurement of MADRS total score.

Subject analysis set title	Lumateperone 28 mg (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients who received at least one dose of study medication and who had a valid baseline (pre-dose) measurement and at least one valid post-baseline measurement of MADRS total score.

Subject analysis set title	Placebo (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients who received at least one dose of study medication and who had a valid baseline (pre-dose) measurement and at least one valid post-baseline measurement of MADRS total score.

Primary: Change from baseline to Day 43 in the MADRS total score.

End point title	Change from baseline to Day 43 in the MADRS total score.

End point description:

End point type	Primary

End point timeframe:

Baseline to Day 43

End point values	Lumateperone 42 mg (ITT)	Lumateperone 28 mg (ITT)	Placebo (ITT)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	174	171	174	
Units: Units				
least squares mean (confidence interval 95%)	-16.9 (-18.52 to -15.34)	-16.2 (-17.75 to -14.66)	-14.5 (-16.08 to -12.99)	

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis
Comparison groups	Lumateperone 42 mg (ITT) v Placebo (ITT)
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0206
Method	Mixed-effect Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.42
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	1.03

Statistical analysis title	Primary Efficacy Analysis
Comparison groups	Lumateperone 28 mg (ITT) v Placebo (ITT)
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0994
Method	Mixed-effect Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.65
upper limit	0.32
Variability estimate	Standard error of the mean
Dispersion value	1.01

Secondary: Change from baseline to Day 43 in the CGI-BP-S depression score	
End point title	Change from baseline to Day 43 in the CGI-BP-S depression score
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to Day 43	

End point values	Lumateperone 42 mg (ITT)	Lumateperone 28 mg (ITT)	Placebo (ITT)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	174	171	174	
Units: Units				
least squares mean (confidence interval 95%)	-1.8 (-2.01 to -1.63)	-1.7 (-1.93 to -1.56)	-1.5 (-1.67 to -1.30)	

Statistical analyses

Statistical analysis title	Key Secondary Efficacy Analysis
Comparison groups	Lumateperone 42 mg (ITT) v Placebo (ITT)
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0082
Method	Mixed-effect Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Key Secondary Efficacy Analysis
Comparison groups	Lumateperone 28 mg (ITT) v Placebo (ITT)
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [1]
Method	Mixed-effect Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[1] - Nominal p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the subject gives study-specific informed consent until the end of study procedures being completed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Lumateperone 42 mg
Reporting group description: -	
Reporting group title	Lumateperone 28 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Lumateperone 42 mg	Lumateperone 28 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	0 / 175 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Lithium Toxicity			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	0 / 175 (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

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

Non-serious adverse events	Lumateperone 42 mg	Lumateperone 28 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 177 (26.55%)	50 / 176 (28.41%)	28 / 175 (16.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 177 (11.30%)	23 / 176 (13.07%)	20 / 175 (11.43%)
occurrences (all)	23	25	22
Somnolence			

subjects affected / exposed	20 / 177 (11.30%)	13 / 176 (7.39%)	6 / 175 (3.43%)
occurrences (all)	20	13	6
Dizziness			
subjects affected / exposed	19 / 177 (10.73%)	18 / 176 (10.23%)	4 / 175 (2.29%)
occurrences (all)	21	20	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 177 (8.47%)	10 / 176 (5.68%)	7 / 175 (4.00%)
occurrences (all)	15	10	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2018	To add conduct of the protocol to countries outside of the United States.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported