



## Clinical trial results:

### **A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of Lumateperone Monotherapy in the Treatment of Patients with Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder (Bipolar Depression) Conducted Globally**

#### **Summary**

EudraCT number	2017-002317-58
Trial protocol	BG PL
Global end of trial date	01 March 2019

#### **Results information**

Result version number	v1 (current)
This version publication date	25 April 2020
First version publication date	25 April 2020

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	ITI-007-404
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03249376
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	Program Manager, Intra-Cellular Therapies, Inc. (ITI), 1 646-440-9333,
Scientific contact	Program Manager, Intra-Cellular Therapies, Inc. (ITI), 1 646-440-9333,

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	18 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2019
Global end of trial reached?	Yes
Global end of trial date	01 March 2019
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To compare the efficacy of lumateperone administered orally once daily to that of placebo as measured by mean change from baseline to Day 43 in the total score on the 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: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Russian Federation: 66
Country: Number of subjects enrolled	Bulgaria: 92
Country: Number of subjects enrolled	Serbia: 19
Country: Number of subjects enrolled	Ukraine: 87
Country: Number of subjects enrolled	United States: 114
Country: Number of subjects enrolled	Colombia: 3
Worldwide total number of subjects	381
EEA total number of subjects	92

Notes:

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**Subjects enrolled per age group**

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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)	358
From 65 to 84 years	23
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.

### Pre-assignment period milestones

Number of subjects started	546 <sup>[1]</sup>
Number of subjects completed	381

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Failure: 165
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Pre-assignment period includes all pts that are screened. Worldwide number enrolled are those patients that have been randomized.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Lumateperone 42mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Lumateperone
Investigational medicinal product code	
Other name	ITI-007
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily oral administration

<b>Arm title</b>	Placebo
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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

<b>Number of subjects in period 1</b>	Lumateperone 42mg	Placebo
Started	191	190
Completed	163	159
Not completed	28	31
Consent withdrawn by subject	7	11
Physician decision	-	2
Adverse event, non-fatal	11	5
Unavailable	1	1
Lost to follow-up	4	5
Lack of efficacy	2	4
Protocol deviation	3	3

## Baseline characteristics

### Reporting groups

Reporting group title	Lumateperone 42mg
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Reporting group description: -
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Reporting group title	Placebo
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Reporting group description: -
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Reporting group values	Lumateperone 42mg	Placebo	Total
Number of subjects	191	190	381
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)	175	183	358
From 65-84 years	16	7	23
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	45.7	44.1	
standard deviation	± 14.1	± 12.9	-
Gender categorical			
Units: Subjects			
Female	99	121	220
Male	92	69	161

## End points

### End points reporting groups

Reporting group title	Lumateperone 42mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Modified intent-to treat
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Includes all randomized subjects who received at least one dose of study medication and who had a valid (pre-dose) baseline measurement and at least one valid post-baseline measurement of MADRS.	

### Primary: Change from baseline to Day 43 in the total score on the Montgomery-Asberg Depression Rating Scale (MADRS)

End point title	Change from baseline to Day 43 in the total score on the Montgomery-Asberg Depression Rating Scale (MADRS)
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Day 43	

End point values	Lumateperone 42mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: Unit				
least squares mean (confidence interval 95%)	-16.7 (-18.06 to -15.34)	-12.1 (-13.45 to -10.79)		

### Statistical analyses

Statistical analysis title	Primary Efficacy Analysis
Comparison groups	Lumateperone 42mg v Placebo
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.34
upper limit	-2.83

Variability estimate	Standard error of the mean
Dispersion value	0.89

### Secondary: Change from baseline to Day 43 in the total score on the Clinical Global Impression Scale, Bipolar Version-Severity (CGI-BP-S)

End point title	Change from baseline to Day 43 in the total score on the Clinical Global Impression Scale, Bipolar Version-Severity (CGI-BP-S)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Day 43	

End point values	Lumateperone 42mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: Unit				
least squares mean (confidence interval 95%)	-3.5 (-3.81 to -3.14)	-2.5 (-2.86 to -2.21)		

### Statistical analyses

<b>Statistical analysis title</b>	Key Secondary Efficacy Analysis
Comparison groups	Lumateperone 42mg v Placebo
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	-0.51
Variability estimate	Standard error of the mean
Dispersion value	0.22



## 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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### Reporting groups

Reporting group title	Lumateperone 42mg
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Lumateperone 42mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 188 (0.53%)	0 / 189 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Mania			
subjects affected / exposed	1 / 188 (0.53%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lumateperone 42mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 188 (54.79%)	95 / 189 (50.26%)	
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 188 (17.55%)	19 / 189 (10.05%)	
occurrences (all)	33	19	
Somnolence			
subjects affected / exposed	16 / 188 (8.51%)	2 / 189 (1.06%)	
occurrences (all)	16	2	

Dizziness subjects affected / exposed occurrences (all)	9 / 188 (4.79%) 9	10 / 189 (5.29%) 10	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	12 / 188 (6.38%) 12	4 / 189 (2.12%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2018	Increase sample size from 250 subjects to 350 subjects.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported