Clinical trial results:
A Randomized, Double-Blind, Parallel-Group, Placebo Controlled Study to Evaluate the Efficacy and Safety of 2 Fixed Doses (5.0 mg or 2.5 mg) of MIN-117 in Adult Patients with Major Depressive Disorder

Summary

EudraCT number	2017-005149-64
Trial protocol	FI PL BG
Global end of trial date	13 December 2019

Results information

Result version number	v1 (current)
This version publication date	06 December 2020
First version publication date	06 December 2020

Trial information

Trial identification

Sponsor protocol code	MIN-117C03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03446846
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Minerva Neurosciences, Inc.
Sponsor organisation address	1601 Trapelo Road, Suite 286, Waltham, United States, 02451
Public contact	Joseph Reilly, Minerva Neurosciences, Inc., 1 6176007380, jsaoud@minervaneurosciences.com
Scientific contact	Jay Saoud, Minerva Neurosciences, Inc., 1 6176007375, jreilly@minervaneurosciences.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	10 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2019
Global end of trial reached?	Yes
Global end of trial date	13 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo in reducing the symptoms of major depression measured by the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score over 6 weeks of treatment in adult patients with major depressive disorder (MDD).

Protection of trial subjects:

Prior to initiation of the study, the study protocol and associated documentation were reviewed and approved by an Independent Ethics Committee (IEC). This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP) and applicable regulatory requirements. Patients provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. Personal data from subjects enrolled in this study was limited to those data necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study, and were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Safety and tolerability assessments were evaluated by an analysis of AEs throughout the study, and vital signs, ECGs, physical and neurological examinations, and clinical laboratory tests at specified time points during the study.

Background therapy:

Women were to remain on a highly effective method of birth control for the duration of the study.

Evidence for comparator: -

Actual start date of recruitment	30 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Bulgaria: 78
Country: Number of subjects enrolled	Finland: 55
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Ukraine: 111
Country: Number of subjects enrolled	Georgia: 15
Country: Number of subjects enrolled	Moldova, Republic of: 3
Worldwide total number of subjects	360
EEA total number of subjects	185

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)	350
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrolled patients were recruited at study centers in 7 countries (Ukraine, Bulgaria, United States, Poland, Finland, Georgia, and Moldova).

Pre-assignment

Screening details:

Patients were screened for eligibility to participate in the study within 21 days before dosing.

Period 1

Period 1 title	Patient Disposition - ITT Population
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study drugs were packaged using a double-dummy, double-blind design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (ITT)

Arm description:

Patients received Placebo every day for 6 weeks.

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

Dosage and administration details:

Patients received Placebo as a daily dose consisting of 2 capsules containing the intended dose (placebo).

Arm title	2.5 mg MIN-117 (ITT)

Arm description:

Patients received 2.5 mg MIN-117 every day for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	MIN-117
Investigational medicinal product code	MIN-117
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received 2.5 mg MIN-117 as a daily dose consisting of 2 capsules containing the intended dose (1 capsule of 2.5 mg MIN-117 and 1 capsule of Placebo).

Arm title	5.0 mg MIN-117 (ITT)

Arm description:

Patients received 5.0 mg MIN-117 every day for 6 weeks.

Arm type	Experimental

Investigational medicinal product name	MIN-117
Investigational medicinal product code	MIN-117
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received 5.0 mg MIN-117 as a daily dose consisting of 2 capsules containing the intended dose (2 capsules of 2.5 mg MIN-117).

Number of subjects in period 1	Placebo (ITT)	2.5 mg MIN-117 (ITT)	5.0 mg MIN-117 (ITT)
Started	178	92	90
Completed	162	87	83
Not completed	16	5	7
Consent withdrawn by subject	11	2	5
Noncompliance with study drug	2	1	1
Lost to follow-up	3	2	1

Period 2

Period 2 title	Safety Population
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study drugs were packaged using a double-dummy, double-blind design.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo (Safety Population)

Arm description:

Patients received Placebo every day for 6 weeks.

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

Dosage and administration details:

Patients received Placebo as a daily dose consisting of 2 capsules containing the intended dose (placebo).

Arm title	2.5 mg MIN-117 (Safety Population)

Arm description:

Patients received 2.5 mg MIN-117 every day for 6 weeks

Arm type	Experimental
Investigational medicinal product name	MIN-117
Investigational medicinal product code	MIN-117
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received 2.5 mg MIN-117 as a daily dose consisting of 2 capsules containing the intended dose (1 capsule of 2.5 mg MIN-117 and 1 capsule of Placebo).

Arm title	5.0 mg MIN-117 (Safety Population)

Arm description:

Patients received 5.0 mg MIN-117 every day for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	MIN-117
Investigational medicinal product code	MIN-117
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received 5.0 mg MIN-117 as a daily dose consisting of 2 capsules containing the intended dose (2 capsules of 2.5 mg MIN-117).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: One patient was randomized to a particular kit# in the Electronic Data Capture system, however, the site dispensed another kit# instead in error. Consequently, the patient was randomized to placebo but received 5.0 mg MIN-117 and was, therefore, included in the (Intent-to-Treat) ITT population based on the randomized treatment to placebo and in the safety population based on the actual treatment they received (5.0 mg MIN-117). Period 1 (ITT) created to support Baseline Characteristics entry.

Number of subjects in period 2	Placebo (Safety Population)	2.5 mg MIN-117 (Safety Population)	5.0 mg MIN-117 (Safety Population)
Started	177	92	91
Completed	161	87	84
Not completed	16	5	7
Consent withdrawn by subject	11	2	5
Noncompliance with study drug	2	1	1
Lost to follow-up	3	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (Safety Population)
Reporting group description:	
Patients received Placebo every day for 6 weeks.	
Reporting group title	2.5 mg MIN-117 (Safety Population)
Reporting group description:	
Patients received 2.5 mg MIN-117 every day for 6 weeks	
Reporting group title	5.0 mg MIN-117 (Safety Population)
Reporting group description:	
Patients received 5.0 mg MIN-117 every day for 6 weeks.	

Reporting group values	Placebo (Safety Population)	2.5 mg MIN-117 (Safety Population)	5.0 mg MIN-117 (Safety Population)
Number of subjects	177	92	91
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)	171	90	89
From 65-84 years	6	2	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47	47	48
standard deviation	± 12.5	± 12.7	± 11.5
Gender categorical Units: Subjects			
Female	136	60	62
Male	41	32	29
Race Units: Subjects			
White	165	87	85
Black or African American	11	4	5
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	1	1	1
American Indian or Alaska Native	0	0	0

Reporting group values	Total		
Number of subjects	360		

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)	350		
From 65-84 years	10		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	258		
Male	102		
Race Units: Subjects			
White	337		
Black or African American	20		
Native Hawaiian or Other Pacific Islander	0		
Asian	3		
American Indian or Alaska Native	0		

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population is the population of all patients who received at least 1 dose of study treatment. Patients in this population were analyzed according to the treatment they received, regardless of which treatment they were randomly assigned.

Reporting group values	Safety Population		
Number of subjects	360		
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)	350		
From 65-84 years	10		

85 years and over	0		

Age continuous Units: years			
arithmetic mean	48		
standard deviation	± 12.3		
Gender categorical Units: Subjects			
Female	258		
Male	102		
Race Units: Subjects			
White	337		
Black or African American	20		
Native Hawaiian or Other Pacific Islander	0		
Asian	3		
American Indian or Alaska Native	0		

End points

End points reporting groups

Reporting group title	Placebo (ITT)
Reporting group description:	
Patients received Placebo every day for 6 weeks.	
Reporting group title	2.5 mg MIN-117 (ITT)
Reporting group description:	
Patients received 2.5 mg MIN-117 every day for 6 weeks.	
Reporting group title	5.0 mg MIN-117 (ITT)
Reporting group description:	
Patients received 5.0 mg MIN-117 every day for 6 weeks.	
Reporting group title	Placebo (Safety Population)
Reporting group description:	
Patients received Placebo every day for 6 weeks.	
Reporting group title	2.5 mg MIN-117 (Safety Population)
Reporting group description:	
Patients received 2.5 mg MIN-117 every day for 6 weeks	
Reporting group title	5.0 mg MIN-117 (Safety Population)
Reporting group description:	
Patients received 5.0 mg MIN-117 every day for 6 weeks.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population is the population of all patients who received at least 1 dose of study treatment. Patients in this population were analyzed according to the treatment they received, regardless of which treatment they were randomly assigned.	

Primary: Change in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score
End point description:	
The Montgomery-Asberg Depression Rating Scale (MADRS) is a validated, physician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The test consists of 10 items, each scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total score of 60. Higher scores represent a more severe condition. MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability and its capacity to differentiate between responders and nonresponders to antidepressant treatment has been shown to be comparable to the Hamilton Rating Scale for Depression.	
End point type	Primary
End point timeframe:	
Week 6	

End point values	Placebo (ITT)	2.5 mg MIN-117 (ITT)	5.0 mg MIN-117 (ITT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	76	70	
Units: Score on a scale				
arithmetic mean (standard deviation)	-12 (± 9.2)	-12 (± 9.2)	-12 (± 9.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis - Primary Endpoint

Statistical analysis description:

The adjustment for multiplicity within the family of primary hypotheses will utilize the Hochberg procedure for the purpose of reporting of results.

Comparison groups	Placebo (ITT) v 2.5 mg MIN-117 (ITT) v 5.0 mg MIN-117 (ITT)
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Hochberg procedure

Secondary: Change in Hamilton Anxiety Scale (HAM-A)

End point title	Change in Hamilton Anxiety Scale (HAM-A)

End point description:

Hamilton Anxiety Scale (HAM-A) measures the severity of a participant's anxiety, based on 14 parameters, including anxious mood, tension, fears, insomnia, somatic complaints and behavior at the interview. The participant is asked to rate the gravity of each item using a 5-level scale, from 0 to 4, with 4 being the most severe, and afterwards the results are collated and tabulated to determine the severity of anxiety.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo (ITT)	2.5 mg MIN-117 (ITT)	5.0 mg MIN-117 (ITT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	76	70	
Units: Score on a scale				
arithmetic mean (standard deviation)	-11 (± 8.5)	-11 (± 9.1)	-12 (± 8.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Clinical Global Impression of Severity Scale (CGI-S)

End point title	Change in Clinical Global Impression of Severity Scale (CGI-S)

End point description:

The Clinical Global Impression of Severity (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the participant's illness at the time of assessment, relative to the clinician's past experience with participants who have the same diagnosis: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" which is rated on the following scale: 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. The CGI-S will provide an overall clinician-determined summary measure that takes into account all available information including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function.

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo (ITT)	2.5 mg MIN-117 (ITT)	5.0 mg MIN-117 (ITT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	76	70	
Units: Score on a scale				
arithmetic mean (standard deviation)	-1 (± 1.2)	-1 (± 1.1)	-1 (± 1.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Clinical Global Impression of Improvement Scale (CGI-I)

End point title	Change in Clinical Global Impression of Improvement Scale (CGI-I)

End point description:

The Clinical Global Impression of Improvement Scale (CGI-I) will provide an overall clinician-determined summary measure that takes into account all available information including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. The CGI-I consists of a 7-point scale that evaluates the change from initiation of treatment similar to the Clinical Global Impression of Severity Scale (CGI-S).

End point type	Secondary

End point timeframe:

Week 6

End point values	Placebo (ITT)	2.5 mg MIN-117 (ITT)	5.0 mg MIN-117 (ITT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	76	70	
Units: Score on a scale				
arithmetic mean (standard deviation)	3 (± 1.1)	3 (± 1.2)	3 (± 1.0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Approximately up to 11 weeks	
Adverse event reporting additional description:	
Treatment-emergent adverse events were those that were reported on or after the initiation of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients received Placebo every day for 6 weeks.	
Reporting group title	2.5 mg MIN-117
Reporting group description:	
Patients received 2.5 mg MIN-117 every day for 6 weeks.	
Reporting group title	5.0 mg MIN-117
Reporting group description:	
Patients received 5.0 mg MIN-117 every day for 6 weeks.	

Serious adverse events	Placebo	2.5 mg MIN-117	5.0 mg MIN-117
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 177 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Feeling guilty			
subjects affected / exposed	0 / 177 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 177 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			

subjects affected / exposed	0 / 177 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	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	Placebo	2.5 mg MIN-117	5.0 mg MIN-117
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 177 (7.34%)	11 / 92 (11.96%)	11 / 91 (12.09%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 177 (7.34%)	11 / 92 (11.96%)	11 / 91 (12.09%)
occurrences (all)	13	11	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No notable study limitations were identified.

Notes: