Clinical trial results:
A Randomized, Double-Blind, Parallel-Group, Placebo- and Active-Controlled Study to Evaluate the Efficacy and Safety of 2 doses of MIN-117 in Adult Subjects with Major Depressive Disorder

Summary

EudraCT number	2015-000306-18
Trial protocol	LV PL FI
Global end of trial date	05 April 2016

Results information

Result version number	v1 (current)
This version publication date	15 August 2018
First version publication date	15 August 2018

Trial information

Trial identification

Sponsor protocol code	MIN-117C01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 6176007373, jreilly@minervaneurosciences.com
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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	05 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2016
Global end of trial reached?	Yes
Global end of trial date	05 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of MIN-117 0.5 mg and 2.5 mg compared to placebo in reducing the symptoms of a major depressive episode as measured by the change from Baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score over 6 weeks of treatment.

Protection of trial subjects:

Prior to study initiation, the protocol and associated documents were approved by an Independent Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practices.

Throughout the trial, safety assessments were performed and evaluated to ensure subject safety.

Background therapy: -

Evidence for comparator:

Paroxetine was used as a positive control based on having a reference molecule that had a demonstrated antidepressant effect and one that exhibited some side effects like cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117.

Actual start date of recruitment	26 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 34
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Moldova, Republic of: 30
Country: Number of subjects enrolled	Poland: 14
Worldwide total number of subjects	84
EEA total number of subjects	54

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	82
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrolled subjects were recruited for this study at 10 study centers in 4 countries (Finland, Poland, Latvia, and Moldova).

Pre-assignment

Screening details:

Subjects were screened for eligibility to participate in the study within 28 days before dosing.

Period 1

Period 1 title	Overall Trial (Overall Period) (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: -

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:

Placebo was matched in appearance to MIN-117 capsules. Placebo was administered in a single dose in the morning at approximately the same time each day with or without food according to the food intake habit of the subject. Capsules were to be swallowed with water and not divided, crushed, chewed, or placed in water.

Arm title	MIN-117 0.5 mg

Arm description: -

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

Dosage and administration details:

A single dose was administered in the morning at approximately the same time each day with or without food according to food intake habit of the subject. Capsules were to be swallowed whole with water.

Arm title	MIN-117 2.5 mg

Arm description: -

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

Dosage and administration details:

A single dose was administered in the morning at approximately the same time each day with or without food according to food intake habit of the subject. Capsules were to be swallowed whole with water.

Arm title	Paroxetine 20 mg

Arm description:

A Paroxetine treatment group was included as a positive control because of its demonstrated antidepressant effect with some side effects like cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. The Paroxetine group was compared to Placebo separately to assess assay sensitivity.

Arm type	Active comparator
Investigational medicinal product name	Paroxetine
Investigational medicinal product code	
Other name	Deroxat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A single dose was administered in the morning at approximately the same time each day with or without food according to food intake habit of the subject. Capsules were to be swallowed whole with water.

Number of subjects in period 1	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg
Started	21	21	21
Completed	18	20	20
Not completed	3	1	1
Consent withdrawn by subject	2	1	1
Randomized but not treated	1	-	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Paroxetine 20 mg
Started	21
Completed	16
Not completed	5
Consent withdrawn by subject	1
Randomized but not treated	1
Adverse event, non-fatal	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	MIN-117 0.5 mg
Reporting group description: -	
Reporting group title	MIN-117 2.5 mg
Reporting group description: -	
Reporting group title	Paroxetine 20 mg

Reporting group description:

A Paroxetine treatment group was included as a positive control because of its demonstrated antidepressant effect with some side effects like cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. The Paroxetine group was compared to Placebo separately to assess assay sensitivity.

Reporting group values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg
Number of subjects	21	21	21
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	48.4	50.0	46.3
standard deviation	± 13.3	± 11.9	± 13.0
Gender categorical Units: Subjects			
Female	14	16	12
Male	7	5	9
Race Units: Subjects			
Caucasian	21	21	21
Body Mass Index Units: kg/m2			
arithmetic mean	24.75	26.51	25.45
standard deviation	± 4.06	± 5.27	± 4.14
Height Units: cm			
arithmetic mean	167.7	166.4	170.0
standard deviation	± 8.7	± 9.0	± 7.8

Weight			
Units: kg			
arithmetic mean	69.81	73.51	73.18
standard deviation	± 13.99	± 16.82	± 13.28

Reporting group values	Paroxetine 20 mg	Total	
Number of subjects	21	84	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	48.5		
standard deviation	± 11.5	-	
Gender categorical			
Units: Subjects			
Female	15	57	
Male	6	27	
Race			
Units: Subjects			
Caucasian	21	84	
Body Mass Index			
Units: kg/m2			
arithmetic mean	24.94		
standard deviation	± 2.92	-	
Height			
Units: cm			
arithmetic mean	168.8		
standard deviation	± 8.7	-	
Weight			
Units: kg			
arithmetic mean	71.85		
standard deviation	± 12.48	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	MIN-117 0.5 mg
Reporting group description: -	
Reporting group title	MIN-117 2.5 mg
Reporting group description: -	
Reporting group title	Paroxetine 20 mg

Reporting group description:

A Paroxetine treatment group was included as a positive control because of its demonstrated antidepressant effect with some side effects like cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. The Paroxetine group was compared to Placebo separately to assess assay sensitivity.

Primary: Change from Baseline to Week 6 in MADRS Total Score

End point title	Change from Baseline to Week 6 in MADRS Total Score[1]

End point description:

Adjusted least-squares mean change from Baseline to Week 6 in Montogomery-Asberg-Depression Rating Scale Total Score from Mixed Model Repeated Measures (MMRM) analysis, intent-to-treat (ITT) population.

End point type	Primary

End point timeframe:

Baseline to Week 6

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	21	21	
Units: NA				
least squares mean (standard error)	-9.27 (± 1.92)	-11.26 (± 1.86)	-12.08 (± 1.83)	

Statistical analyses

Statistical analysis title	Change from Baseline to Wk 6 in MADRS Total Score

Statistical analysis description:

MMRM with treatment (placebo, MIN-117 0.5 mg, MIN-117 2.5 mg), visit, pooled study center, and treatment-by-visit interaction terms as fixed effects, subject nested in treatment as a random effect with baseline value as covariates. An unstructured covariance matrix is used.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	≤ 0.4453 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)

Notes:

[2] - MMRM: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[3] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.4453
MIN-117 2.5 mg vs. Placebo: p ≤ 0.2841

Secondary: Change from Baseline to Week 6 in CGI-S

End point title	Change from Baseline to Week 6 in CGI-S[4]

End point description:

Change from Baseline to Week 6 in Clinical Global Impression-Severity of Illness Scale Score (CGI-S), intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline to Week 6

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	21	
Units: NA				
arithmetic mean (standard deviation)	-1.2 (± 1.0)	-1.1 (± 1.2)	-1.2 (± 1.0)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 6 in CGI-S

Statistical analysis description:

Analysis of covariance of ranked data with treatment as a factor and Baseline CGI-S value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	≤ 0.8877 [6]
Method	ANCOVA

Notes:

[5] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[6] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.8877
MIN-117 2.5 mg vs. Placebo: p ≤ 0.8944

Secondary: Observed Data to Week 6 in CGI-I

End point title	Observed Data to Week 6 in CGI-I[7]

End point description:

Observed data to Week 6 in Clinical Global Impression-Global Improvement Scale Score (CGI-I) intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline to Week 6

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	21	
Units: NA				
arithmetic mean (standard deviation)	7.6 (± 11.3)	5.6 (± 11.8)	9.3 (± 9.7)	

Statistical analyses

Statistical analysis title	Observed Data to Week 6 in CGI-I ANCOVA

Statistical analysis description:

Analysis of covariance of ranked data with treatment as a factor and Baseline CGI-I value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	≤ 0.9514 [9]
Method	ANCOVA

Notes:

[8] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[9] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.9514
MIN-117 2.5 mg vs. Placebo: p ≤ 0.4258

Secondary: Change from Baseline to Week 6 in A-SEX

End point title	Change from Baseline to Week 6 in A-SEX[10]

End point description:

Mean change from Baseline to Week 6 in Arizona Sexual Experience Scale Total Score (A-SEX), intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline to Week 6

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	21	
Units: NA				
arithmetic mean (standard deviation)	-0.5 (± 3.1)	-1.9 (± 3.3)	-1.6 (± 4.7)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 6 in A-SEX ANCOVA

Statistical analysis description:

Analysis of covariance of ranked data with treatment as a factor and Baseline Arizona Sexual Experience Scale Total Score (A-SEX) value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	≤ 0.2236 [12]
Method	ANCOVA

Notes:

[11] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[12] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.2236
MIN-117 2.5 mg vs. Placebo: p ≤ 0.1719

Secondary: Change from Baseline to Week 2 in MADRS Total Score

End point title	Change from Baseline to Week 2 in MADRS Total Score[13]

End point description:

Adjusted least-squares mean change from Baseline to Week 2 in Montogomery-Asberg-Depression Rating Scale (MADRS) Total Score from MMRM analysis, ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 2

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which

might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	21	21	
Units: NA				
least squares mean (standard error)	-9.81 (± 1.90)	-11.83 (± 1.85)	-11.88 (± 1.82)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 2 in MADRS

Statistical analysis description:

MMRM with treatment (placebo, MIN-117 0.5 mg, MIN-117 2.5 mg), visit, pooled study center, and treatment-by-visit interaction terms as fixed effects, subject nested in treatment as a random effect with baseline value as covariates. An unstructured covariance matrix is used.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	≤ 0.4264 [15]
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Notes:

[14] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[15] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.4264
MIN-117 2.5 mg vs. Placebo: p ≤ 0.4190

Secondary: Change from Baseline to Week 6 in DSST Cognition Score

End point title	Change from Baseline to Week 6 in DSST Cognition Score[16]

End point description:

Change from Baseline to Week 6 in Digit-Symbol Substitution Test (DSST) Cognition Score, intent-to-treat (ITT) population

End point type	Secondary

End point timeframe:

Baseline to Week 6

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	20	
Units: NA				
arithmetic mean (standard deviation)	7.6 (± 11.3)	5.6 (± 11.8)	9.3 (± 9.7)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 6 in DSST ANCOVA

Statistical analysis description:

Analysis of covariance of ranked data with treatment as a factor and Baseline Digit-Symbol Substitution Test (DSST) Cognition Score value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	≤ 0.9848 [18]
Method	ANCOVA

Notes:

[17] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[18] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.9848
MIN-117 2.5 mg vs. Placebo: p ≤ 0.3461

Secondary: Change from Baseline to Week 6 in Digit Span Backwards Task

End point title	Change from Baseline to Week 6 in Digit Span Backwards

End point description:

Mean change from Baseline to Week 6 in Digit Span Backwards Task Cognition Score, intent-to-treat (ITT) population

End point type	Secondary

End point timeframe:

Baseline to Week 6

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	20	
Units: NA				
arithmetic mean (standard deviation)	0 (± 4.6)	2.8 (± 11.3)	0.6 (± 1.4)	

Statistical analyses

Statistical analysis title	Change from Baseline to Week 6 in DSBT

Statistical analysis description:

Analysis of covariance of ranked data with treatment as a factor and Baseline in Digit Scan Backwards task value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	≤ 0.4269 [21]
Method	ANCOVA

Notes:

[20] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[21] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.4269
MIN-117 2.5 mg vs. Placebo: p ≤ 0.8548

Other pre-specified: Change from Baseline to Week 6 in Sleep Efficiency

End point title	Change from Baseline to Week 6 in Sleep Efficiency[22]

End point description:

Change from Baseline to Week 6 in summary of sleep efficiency (percent time in bed), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: Percent Time in Bed				
arithmetic mean (standard deviation)	0.2 (± 14.8)	-4.9 (± 18.8)	-1.0 (± 7.1)	

Statistical analyses

Statistical analysis title	Sleep Efficiency -- ANCOVA for ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	≤ 0.0501 [24]
Method	ANCOVA

Notes:

[23] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[24] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.0501
MIN-117 2.5 mg vs. Placebo: p ≤ 0.3873

Other pre-specified: Change from Baseline to Week 6 in Latency to Sleep Onset

End point title	Change from Baseline to Week 6 in Latency to Sleep Onset[25]

End point description:

Change from Baseline to Week 6 in Latency to Sleep Onset (minutes), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: Minutes				
arithmetic mean (standard deviation)	-2.8 (± 39.4)	2.6 (± 32.7)	-1.2 (± 26.2)	

Statistical analyses

Statistical analysis title	Latency to Sleep - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.4022 [26]
Method	ANCOVA

Notes:

[26] - 0.5 mg vs. placebo p ≤ 0.4022
2.5 mg vs. placebo p ≤ 0.6637

Other pre-specified: Change from Baseline to Week 6 in Latency to Continuous Sleep

End point title	Change from Baseline to Week 6 in Latency to Continuous Sleep[27]

End point description:

Change from Baseline to Week 6 in Latency to Continuous Sleep (minutes), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	8.9 (± 42.7)	10.3 (± 41.0)	-3.7 (± 33.2)	

Statistical analyses

Statistical analysis title	Latency to Continuous Sleep-ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	≤ 0.5297 [29]
Method	ANCOVA

Notes:

[28] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[29] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.5297
MIN-117 2.5 mg vs. Placebo: p ≤ 0.9399

Other pre-specified: Change from Baseline to Week 6 in Stage REM Latency	
End point title	Change from Baseline to Week 6 in Stage REM Latency[30]
End point description:	
Change from Baseline to Week 6 in Stage REM Latency (minutes), intent-to-treat (ITT) population	
End point type	Other pre-specified
End point timeframe:	
Baseline to Week 6	

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	-1.1 (± 67.5)	22.4 (± 67.8)	-7.8 (± 57.5)	

Statistical analyses

Statistical analysis title	Stage REM Latency - ANCOVA of ranked data
Statistical analysis description:	
Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.	
Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	≤ 0.1188 [32]
Method	ANCOVA

Notes:

[31] - MIN-117 0.5 mg vs. Placebo
MIN-117 2.5 mg vs. Placebo

[32] - MIN-117 0.5 mg vs. Placebo: $p \leq 0.1188$
MIN-117 2.5 mg vs. Placebo: $p \leq 0.6120$

Other pre-specified: Change from Baseline to Week 6 in Total Sleep Time	
End point title	Change from Baseline to Week 6 in Total Sleep Time[33]
End point description:	
Change from Baseline to Week 6 in Total Sleep Time (minutes), intent-to-treat (ITT) population	
End point type	Other pre-specified
End point timeframe:	
Baseline to Week 6	

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	3.1 (± 70.5)	-23.5 (± 90.9)	-5.1 (± 34.8)	

Statistical analyses

Statistical analysis title	Total Sleep Time - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	≤ 0.0347 [35]
Method	ANCOVA

Notes:

[34] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[35] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.0347
MIN-117 2.5 mg vs. Placebo: p ≤ 0.2725

Other pre-specified: Change from Baseline to Week 6 in Wake After Sleep Onset

End point title	Change from Baseline to Week 6 in Wake After Sleep Onset[36]

End point description:

Change from Baseline to Week 6 in Wake After Sleep Onset (minutes), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	2.5 (± 41.9)	21.0 (± 70.6)	5.7 (± 36.9)	

Statistical analyses

Statistical analysis title	Wake After Sleep Onset - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	≤ 0.1086 [38]
Method	ANCOVA

Notes:

[37] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[38] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.1086
MIN-117 2.5 mg vs. Placebo: p ≤ 0.4767

Other pre-specified: Change from Baseline to Week 6 in Time in Stage N3

End point title	Change from Baseline to Week 6 in Time in Stage N3[39]

End point description:

Change from Baseline to Week 6 in Time in Stage N3 (minutes), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	-2.3 (± 29.1)	1.5 (± 55.4)	-2.6 (± 17.9)	

Statistical analyses

Statistical analysis title	Time in Stage N3 - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	≤ 0.7525 [41]
Method	ANCOVA

Notes:

[40] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[41] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.7525
MIN-117 2.5 mg vs. Placebo: p ≤ 0.9088

Other pre-specified: Change from Baseline to Week 6 in Percent of Time in Stage N3

End point title	Change from Baseline to Week 6 in Percent of Time in Stage N3[42]

End point description:

Change from Baseline to Week 6 in Percent of Time in Stage N3 (% total sleep time), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: % total sleep time				
arithmetic mean (standard deviation)	-0.1 (± 5.8)	0.9 (± 12.7)	-0.7 (± 4.0)	

Statistical analyses

Statistical analysis title	% Time in Stage N3 - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	≤ 0.9272 [44]
Method	ANCOVA

Notes:

[43] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[44] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.9272
MIN-117 2.5 mg vs. Placebo: p ≤ 0.8988

Other pre-specified: Change from Baseline to Week 6 in Time in Stage N2

End point title	Change from Baseline to Week 6 in Time in Stage N2[45]

End point description:

Change from Baseline to Week 6 in Time in Stage N2 (minutes), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	22.0 (± 51.2)	-7.7 (± 60.6)	-2.4 (± 46.8)	

Statistical analyses

Statistical analysis title	Time in Stage N2 (min) - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	≤ 0.1982 [47]
Method	ANCOVA

Notes:

[46] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[47] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.1982
MIN-117 2.5 mg vs. Placebo: p ≤ 0.0880

Other pre-specified: Change from Baseline to Week 6 in Percent Time in Stage N2

End point title	Change from Baseline to Week 6 in Percent Time in Stage

End point description:

Change from Baseline to Week 6 in Percent Time in Stage N2 (% total sleep time), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: % total sleep time				
arithmetic mean (standard deviation)	2.9 (± 13.2)	2.2 (± 12.2)	0.1 (± 9.5)	

Statistical analyses

Statistical analysis title	% Time in Stage N2 - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	≤ 0.7308 [50]
Method	ANCOVA

Notes:

[49] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[50] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.7308
MIN-117 2.5 mg vs. Placebo: p ≤ 0.1641

Other pre-specified: Change from Baseline to Week 6 in Time in Stage REM

End point title	Change from Baseline to Week 6 in Time in Stage REM[51]

End point description:

Change from Baseline to Week 6 in Time in Stage REM (minutes), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	-17.4 (± 35.9)	-14.2 (± 33.7)	-6.1 (± 37.0)	

Statistical analyses

Statistical analysis title	Time in Stage REM (min) - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	≤ 0.5658 [53]
Method	ANCOVA

Notes:

[52] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[53] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.5658
MIN-117 2.5 mg vs. Placebo: p ≤ 0.5747

Other pre-specified: Change from Baseline to Week 6 in Percentage of Time in REM Stage

End point title	Change from Baseline to Week 6 in Percentage of Time in REM Stage[54]

End point description:

Change from Baseline to Week 6 in Percentage of Time in REM Stage (% total sleep time), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to

evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: % total sleep time				
arithmetic mean (standard deviation)	-3.8 (± 9.8)	-3.3 (± 6.4)	-1.4 (± 10.8)	

Statistical analyses

Statistical analysis title	% Time in Stage REM - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	≤ 0.8823 [56]
Method	ANCOVA

Notes:

[55] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[56] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.8823
MIN-117 2.5 mg vs. Placebo: p ≤ 0.3716

Other pre-specified: Change from Baseline to Week 6 in Certain Density in Stage REM

End point title	Change from Baseline to Week 6 in Certain Density in Stage REM[57]

End point description:

Change from Baseline to Week 6 in Certain Density in Stage REM (number per minute), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: number per minute				
arithmetic mean (standard deviation)	-2.9 (± 4.6)	-3.3 (± 5.6)	-0.4 (± 7.1)	

Statistical analyses

Statistical analysis title	Certain Density in Stage REM - ANCOVA ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	≤ 0.6097 [59]
Method	ANCOVA

Notes:

[58] - ANCOVA for ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[59] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.6097
MIN-117 2.5 mg vs. Placebo: p ≤ 0.1647

Other pre-specified: Change from Baseline to Week 6 in Total Sleep Period

End point title	Change from Baseline to Week 6 in Total Sleep Period[60]

End point description:

Change from Baseline to Week 6 in Total Sleep Period (minutes), intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: minutes				
arithmetic mean (standard deviation)	14.9 (± 77.3)	-21.0 (± 55.3)	-3.8 (± 28.3)	

Statistical analyses

Statistical analysis title	Total Sleep Period - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	≤ 0.0172 [62]
Method	ANCOVA

Notes:

[61] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[62] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.0172
MIN-117 2.5 mg vs. Placebo: p ≤ 0.3344

Other pre-specified: Change from Baseline to Week 6 in Awakening Index

End point title	Change from Baseline to Week 6 in Awakening Index[63]

End point description:

Change from Baseline to Week 6 in Awakening Index, intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	16	17	
Units: NA				
arithmetic mean (standard deviation)	1.0 (± 3.7)	0.4 (± 1.5)	0.1 (± 1.4)	

Statistical analyses

Statistical analysis title	Awakening Index - ANCOVA of ranked data

Statistical analysis description:

Changes from Baseline in Somno-Art- and PSG-derived sleep parameters were analyzed using an ANCOVA of ranked data, with treatment (MIN-117 0.5 mg, MIN-117 2.5 mg, and Placebo) as a factor and Baseline value as a covariate.

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	≤ 0.6869 [65]
Method	ANCOVA

Notes:

[64] - MIN-117 0.5 mg vs. Placebo
MIN-117 2.5 mg vs. Placebo
[65] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.6869
MIN-117 2.5 mg vs. Placebo: p ≤ 0.4591

Other pre-specified: Change from Baseline to Week 6 in Hamilton Anxiety Rating Scale-A Total Scores

End point title	Change from Baseline to Week 6 in Hamilton Anxiety Rating Scale-A Total Scores[66]

End point description:

Change from Baseline to Week 6 in Hamilton Anxiety Rating Scale-A Total Scores, intent-to-treat (ITT) population

End point type	Other pre-specified

End point timeframe:

Baseline to Week 6

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for the Paroxetine group vs. Placebo are not presented. Study objectives were to evaluate the efficacy of MIN-117 0.5 and 2.5 mg compared to Placebo in reducing symptoms of a major depressive episode. The Paroxetine group was included as a positive control because of its demonstrated antidepressant effect with some side effects of cognitive impairment and sexual dysfunctions, which might be preserved or improved by MIN-117. Paroxetine was compared to Placebo to test assay sensitivity.

End point values	Placebo	MIN-117 0.5 mg	MIN-117 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	21	
Units: NA				
arithmetic mean (standard deviation)	-7.4 (± 5.5)	-10.1 (± 5.4)	-9.9 (± 8.0)	

Statistical analyses

Statistical analysis title	Hamilton Anxiety Scale A - ANCOVA of ranked data

Statistical analysis description:

Analysis of change from Baseline in Hamilton Anxiety Scale using ANCOVA of ranked data

Comparison groups	Placebo v MIN-117 0.5 mg v MIN-117 2.5 mg

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	≤ 0.2871 [68]
Method	ANCOVA

Notes:

[67] - ANCOVA on ranked data: MIN-117 0.5 mg vs. Placebo; MIN-117 2.5 mg vs. Placebo

[68] - MIN-117 0.5 mg vs. Placebo: p ≤ 0.2871
MIN-117 2.5 mg vs. Placebo: p ≤ 0.2751

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were reported from the time of signed informed consent until completion of last study-related procedure. Serious adverse events including spontaneously reported events within 30 days after the last dose were reported.

Adverse event reporting additional description:

AEs were classified as treatment-emergent AEs (TEAEs) if the AEs were not present before the first dose of double-blind study medication or were present before the first dose but increased in severity on or after the first dose. AEs occurring >14 days after last dose were not considered TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Safety Population - Placebo
Reporting group description: -	
Reporting group title	Safety Population - MIN-117 0.5 mg
Reporting group description: -	
Reporting group title	Safety Population - MIN-117 2.5 mg
Reporting group description: -	
Reporting group title	Safety Population - Paroxetine 20 mg
Reporting group description: -	

Serious adverse events	Safety Population - Placebo	Safety Population - MIN-117 0.5 mg	Safety Population - MIN-117 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Safety Population - Paroxetine 20 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Safety Population - Placebo	Safety Population - MIN-117 0.5 mg	Safety Population - MIN-117 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 20 (45.00%)	11 / 21 (52.38%)	11 / 21 (52.38%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pallor			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Dyspareunia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Fibrocystic breast disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Libido decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Tension			

subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 20 (0.00%)	3 / 21 (14.29%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Blood pressure systolic increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram PR prolongation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Venous injury			

subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Sinus arrhythmia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
QTcF Interval Increased	Additional description: 12-lead ECG data - QTcF interval increase between 30 and 50 ms or greater than 60 ms from Baseline.		
subjects affected / exposed	3 / 20 (15.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Headache			
subjects affected / exposed	3 / 20 (15.00%)	3 / 21 (14.29%)	1 / 21 (4.76%)
occurrences (all)	3	3	1
Restless legs syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	3 / 21 (14.29%)
occurrences (all)	1	1	3
Diarrhoea			

subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Muscle tightness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 21 (4.76%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Upper respiratory tract infection			

subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Safety Population - Paroxetine 20 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 20 (65.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pallor			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dyspareunia			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Fibrocystic breast disease			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Libido decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Investigations			
Blood triglycerides increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood pressure systolic increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Low density lipoprotein increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Transaminases increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Blood cholesterol increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Venous injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Sinus arrhythmia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
QTcF Interval Increased	Additional description: 12-lead ECG data - QTcF interval increase between 30 and 50 ms or greater than 60 ms from Baseline.		
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Restless legs syndrome			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Salivary hypersecretion			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Rash macular			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Muscle tightness			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2015	Protocol version 1.4 was issued: genotype was individualized among all pharmacodynamic parameters and was made optional. Protocol was submitted and approved in Finland, Latvia, Moldova, and Poland. All subjects were randomized under version 1.4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported