



Clinical trial results:

A Randomized, Double-blind, Multicenter, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aticaprant 10 mg as Adjunctive Therapy in Adult Participants with Major Depressive Disorder (MDD) with Moderate-to-severe Anhedonia and Inadequate Response to Current Antidepressant Therapy

Summary

EudraCT number	2022-000461-41
Trial protocol	CZ BG FR SK
Global end of trial date	02 April 2025

Results information

Result version number	v1 (current)
This version publication date	27 November 2025
First version publication date	27 November 2025

Trial information

Trial identification

Sponsor protocol code	67953964MDD3002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05550532
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.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	12 November 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 April 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in adult participants with major depressive disorder (MDD) with moderate-to-severe anhedonia (ANH+) who have had an inadequate response to current antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitors (SNRI).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 June 2022
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	Argentina: 72
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Czechia: 18
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Slovakia: 36
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United States: 178
Country: Number of subjects enrolled	South Africa: 26
Worldwide total number of subjects	440
EEA total number of subjects	119

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)	392
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 444 participants were enrolled in the study, of whom 440 received the treatment and were included in the analysis.

Pre-assignment

Screening details:

Adult participants aged 18 to 64 years who had major depressive disorder (MDD) with or without moderate-to-severe anhedonia (ANH+ or ANH-) and elderly participants aged 65 to 74 years with MDD (ANH+ and ANH-) who had an inadequate response to an ongoing antidepressant therapy were randomized in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

During double blind (DB) treatment phase, participants received placebo matching to aticaprant tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor [SSRI/SNRI]). Participants were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57). Participants who completed the DB phase (at Day 43) and were compliant to the study intervention were eligible to participate in a separate 52-week open-label long-term safety study 67953964MDD3003 (NCT05518149).

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:

Participants received placebo matching to aticaprant tablet orally once daily from Day 1 to Day 42.

Arm title	Aticaprant 10 mg
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Arm description:

During DB treatment phase, participants received aticaprant 10 milligram (mg) tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (SSRI/SNRI). Participants were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57). Participants who completed the DB phase (at Day 43) and were compliant to the study intervention were eligible to participate in a separate 52-week open-label long-term safety study 67953964MDD3003 (NCT05518149).

Arm type	Experimental
Investigational medicinal product name	Aticaprant 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received aticaprant 10 mg tablet orally once daily from Day 1 to Day 42.

Number of subjects in period 1	Placebo	Aticaprant 10 mg
Started	223	217
Participants who entered follow-up phase	21 ^[1]	18 ^[2]
Completed	210	207
Not completed	13	10
Consent withdrawn by subject	7	3
Adverse event, non-fatal	2	3
Unspecified	-	4
Lost to follow-up	4	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only reported subjects were planned to be included in this milestone.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only reported subjects were planned to be included in this milestone.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
During double blind (DB) treatment phase, participants received placebo matching to aticaprant tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor [SSRI/SNRI]). Participants were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57). Participants who completed the DB phase (at Day 43) and were compliant to the study intervention were eligible to participate in a separate 52-week open-label long-term safety study 67953964MDD3003 (NCT05518149).	
Reporting group title	Aticaprant 10 mg
Reporting group description:	
During DB treatment phase, participants received aticaprant 10 milligram (mg) tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (SSRI/SNRI). Participants were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57). Participants who completed the DB phase (at Day 43) and were compliant to the study intervention were eligible to participate in a separate 52-week open-label long-term safety study 67953964MDD3003 (NCT05518149).	

Reporting group values	Placebo	Aticaprant 10 mg	Total
Number of subjects	223	217	440
Age categorical			
Units: Subjects			
Adults (18-64 years)	200	192	392
From 65 to 74 years	23	25	48
Age continuous			
Units: Years			
arithmetic mean	49.3	49.1	
standard deviation	± 13.11	± 13.14	-
Gender categorical			
Units: Subjects			
Female	168	161	329
Male	55	56	111
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	15	16	31
Native Hawaiian or Other Pacific Islander	2	1	3
Black or African American	9	9	18
White	182	177	359
More than one race	2	2	4
Unknown or Not Reported	13	11	24
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	74	74	148
Not Hispanic or Latino	141	137	278
Unknown or Not Reported	8	6	14
Region of enrollment			
Units: Subjects			

Argentina	35	37	72
Brazil	8	4	12
Bulgaria	9	9	18
Czech Republic	11	7	18
France	10	10	20
Poland	13	14	27
Slovakia	19	17	36
South Africa	12	14	26
Korea, Republic of	9	10	19
Taiwan	3	2	5
United Kingdom	4	5	9
United States	90	88	178

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: During double blind (DB) treatment phase, participants received placebo matching to aticaprant tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (selective serotonin reuptake inhibitor/serotonin–norepinephrine reuptake inhibitor [SSRI/SNRI]). Participants were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57). Participants who completed the DB phase (at Day 43) and were compliant to the study intervention were eligible to participate in a separate 52-week open-label long-term safety study 67953964MDD3003 (NCT05518149).	
Reporting group title	Aticaprant 10 mg
Reporting group description: During DB treatment phase, participants received aticaprant 10 milligram (mg) tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (SSRI/SNRI). Participants were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57). Participants who completed the DB phase (at Day 43) and were compliant to the study intervention were eligible to participate in a separate 52-week open-label long-term safety study 67953964MDD3003 (NCT05518149).	
Subject analysis set title	DB: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: During DB treatment phase, participants received placebo matching to aticaprant tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (SSRI/SNRI).	
Subject analysis set title	DB: Aticaprant 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description: During the DB treatment phase, participants received aticaprant 10 mg tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (SSRI/SNRI).	
Subject analysis set title	FU: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Participants who received placebo and completed DB phase entered the follow-up phase and were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57).	
Subject analysis set title	FU: Aticaprant 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Participants who received aticaprant 10 mg and completed DB phase entered the follow-up phase and were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57).	

Primary: Change from Baseline to Day 43 in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change from Baseline to Day 43 in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score
End point description: The MADRS is a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The scale consists of 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS total score is the sum of scores from individual question items, which ranges from 0 to 60; higher scores represent a more severe condition. Negative change in MADRS total score indicates improvement. Full analysis set (ANH+) included all adult randomized participants in rest of the world (ROW; countries/territories other than China) with MDD ANH+ who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) signifies number of participants evaluable for this outcome measure.	
End point type	Primary

End point timeframe:

Baseline (Day 1) to Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	154		
Units: Units on a scale				
least squares mean (standard error)	-9.4 (± 0.96)	-10.0 (± 0.96)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Aticaprant 10 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Mixed Model for Repeated Measures Model
Parameter estimate	Least Square Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.95
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	1.23

Secondary: Change from Baseline to Day 43 in Dimensional Anhedonia Rating Scale (DARS) Total Score

End point title	Change from Baseline to Day 43 in Dimensional Anhedonia Rating Scale (DARS) Total Score
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End point description:

The DARS is a 17-item self-report questionnaire that is designed to assess anhedonia in MDD across the 4 domains: hobbies, social activities, food/drink, and sensory experience. The DARS scale measures desire, motivation, effort, and consummatory pleasure. The DARS is rated on a 5-point Likert scale (0=not at all, 1=slightly, 2=moderately, 3=mostly, 4=very much) and responses are summed to generate the total score (range of 0 to 68). A lower total score is indicative of greater anhedonia. Positive changes in DARS total score indicate improvement. Full analysis set (ANH+) included all adult randomized participants in ROW (countries/territories other than China) with MDD ANH+ who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) signifies number of participants evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	147		
Units: Units on a scale				
least squares mean (standard error)	8.2 (\pm 1.39)	8.8 (\pm 1.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in MADRS Total Score

End point title	Change from Baseline Over Time in MADRS Total Score
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End point description:

The MADRS is a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The scale consists of 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS total score is the sum of scores from individual question items, which ranges from 0 to 60; higher scores represent a more severe condition. Negative change indicates improvement. Full analysis set (ANH+) included all adult randomized participants in ROW with MDD ANH+ who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) signifies participants evaluable for this outcome measure and 'n' (number analyzed) signifies number of participants analyzed at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline (Day 1), Day 15, Day 29, and Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	160		
Units: Units on a scale				
least squares mean (standard error)				
Day 15 (n= 161, 160)	-4.4 (\pm 0.75)	-5.4 (\pm 0.74)		
Day 29 (n=159, 157)	-7.5 (\pm 0.89)	-8.0 (\pm 0.89)		
Day 43 (n=159, 154)	-9.4 (\pm 0.96)	-10.0 (\pm 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved Response on Depressive

Symptoms Scale Based on MADRS Total Score at Day 43

End point title	Percentage of Participants who Achieved Response on Depressive Symptoms Scale Based on MADRS Total Score at Day 43
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End point description:

Responders are defined as participants with a ≥ 50 percent (%) improvement in the MADRS total score from baseline to a given timepoint. The MADRS is a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The scale consists of 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS total score is the sum of scores from individual question items, which ranges from 0 to 60; higher scores represent a more severe condition. Negative change in MADRS total score indicates improvement. Full analysis set (ANH+) included all adult randomized participants in ROW (countries/territories other than China) with MDD ANH+ who received at least 1 dose of study intervention.

End point type	Secondary
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End point timeframe:

At Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Percentage of participants				
number (not applicable)	28.3	27.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Remission of Depressive Symptoms Based on MADRS Total Score at Day 43

End point title	Percentage of Participants With Remission of Depressive Symptoms Based on MADRS Total Score at Day 43
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End point description:

Participant is defined as a remitter at a given time point if the MADRS total score is less than or equal to (\leq)10 at that time point. The MADRS is a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The scale consists of 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of symptoms). MADRS total score is the sum of scores from individual question items, which ranges from 0 to 60; higher scores represent a more severe condition. Negative change in MADRS total score indicates improvement. Full analysis set (ANH+) included all adult randomized participants in ROW (countries/territories other than China) with MDD ANH+ who received at least 1 dose of study intervention.

End point type	Secondary
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End point timeframe:

At Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	165		
Units: Percentage of participants				
number (not applicable)	16.3	15.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 43 in Patient Health Questionnaire, 9-Item (PHQ-9) Total Score

End point title	Change from Baseline to Day 43 in Patient Health Questionnaire, 9-Item (PHQ-9) Total Score
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End point description:

The PHQ-9 is a 9-item, participant reported outcome measure to assess depressive symptoms. The scale scores each of the 9 symptom domains of the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) MDD criteria. Each item is rated on a 4 point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). Negative changes in PHQ-9 total score indicate improvement. Full analysis set (ANH+) included all adult randomized participants in ROW with MDD ANH+ who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) signifies number of participants evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: Units on a scale				
least squares mean (standard error)	-5.5 (\pm 0.58)	-5.2 (\pm 0.58)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Aticaprant 10 mg
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Square Mean Difference
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	1.71
Variability estimate	Standard error of the mean
Dispersion value	0.72

Secondary: Change from Baseline Over Time in DARS Total Score

End point title	Change from Baseline Over Time in DARS Total Score
End point description:	
<p>The DARS is a 17-item self-report questionnaire that is designed to assess anhedonia in MDD across the 4 domains: hobbies, social activities, food/drink, and sensory experience. The DARS scale measures desire, motivation, effort, and consummatory pleasure. The DARS is rated on a 5-point Likert scale (0=not at all, 1=slightly, 2=moderately, 3=mostly, 4=very much) and responses are summed to generate the total score (range of 0 to 68). A lower total score is indicative of greater anhedonia. Positive changes in DARS total score indicate improvement. Full analysis set (ANH+) included all adult randomized participants in ROW (countries/territories other than China) with MDD ANH+ who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) signifies participants evaluable for this outcome measure and 'n' (number analyzed) signifies number of participants who were analyzed at specified timepoints.</p>	
End point type	Secondary
End point timeframe:	
Baseline (Day 1), Day 15, Day 29, and Day 43	

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	149		
Units: Units on a scale				
least squares mean (standard error)				
Day 15 (n=152, 149)	3.5 (± 1.17)	4.2 (± 1.17)		
Day 29 (n=148, 146)	6.9 (± 1.27)	7.1 (± 1.27)		
Day 43 (n=150, 147)	8.2 (± 1.39)	8.8 (± 1.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in the PHQ-9 Anhedonia-specific Item (PHQ-9, item 1)

End point title	Change from Baseline Over Time in the PHQ-9 Anhedonia-specific Item (PHQ-9, item 1)
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End point description:

The PHQ-9 is a 9-item, participant reported outcome measure to assess depressive symptoms. The scale scores each of the 9 symptom domains of the DSM-5 MDD criteria. Each item is rated on a 4 point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range of 0 to 27), with higher scores indicating

greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). Negative changes in PHQ-9 total score indicate improvement. Full analysis set (ANH+) included all adult randomized participants in ROW who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) signifies participants evaluable for this outcome measure and 'n' (number analyzed) signifies number of participants who were analyzed at specified timepoints.

End point type	Secondary
End point timeframe:	
Baseline (Day 1), Day 15, Day 29, and Day 43	

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	152		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day 15 (n=157, 152)	-0.4 (± 0.93)	-0.6 (± 1.08)		
Day 29 (n=149, 149)	-0.7 (± 1.00)	-0.8 (± 1.05)		
Day 43 (n=150, 150)	-0.9 (± 1.12)	-0.9 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Score Less Than (<) 2 in the PHQ-9 Anhedonia-specific Item (PHQ-9, item 1) at Day 43

End point title	Percentage of Participants With a Score Less Than (<) 2 in the PHQ-9 Anhedonia-specific Item (PHQ-9, item 1) at Day 43
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End point description:

The PHQ-9 is a 9-item, participant reported outcome measure to assess depressive symptoms. The scale scores each of the 9 symptom domains of the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) MDD criteria. Each item is rated on a 4 point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The severity of the PHQ-9 is categorized as follows: none-minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27). Full analysis set (ANH+) included all adult randomized participants in ROW (countries/territories other than China) with MDD ANH+ who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) signifies number of participants evaluable for this outcome measure.

End point type	Secondary
End point timeframe:	
At Day 43	

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	136		
Units: Percentage of participants				
number (not applicable)	50.8	46.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in Patient Reported Outcomes Measurement Information System Short Form - Ability to Participate in Social Roles and Activities - 8a (PROMIS-APS 8a)

End point title	Change from Baseline Over Time in Patient Reported Outcomes Measurement Information System Short Form - Ability to Participate in Social Roles and Activities - 8a (PROMIS-APS 8a)
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End point description:

This 8-item measure assesses participants' ability to participate in social roles and activities with degree of involvement in social roles, activities, and responsibilities, including work, family, friends, and leisure. Each item is rated on a 5-point ordinal scale (1=always, 2=usually, 3=sometimes, 4=rarely, 5=never), with higher scores indicating better social functioning. The total scores of PROMIS-APS 8a are scaled on a T-score metric with a mean of 50 and a standard deviation of 10. The total score ranges from 8 to 40 and T-score ranges from 25.9 to 65.4, a higher score indicates better social functioning. Positive change in score indicates improvement. Full analysis set (ANH+) included all adult randomized participants in ROW who received at least 1 dose of study intervention. Here, 'N' (overall number of participants analyzed) is participants evaluable for this outcome measure and 'n' (number analyzed) is number of participants analyzed at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline (Day 1), Day 15, Day 29, and Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	134		
Units: T-score				
least squares mean (standard error)				
Day 15 (n=141, 132)	1.4 (± 0.54)	1.5 (± 0.55)		
Day 29 (n=139, 130)	3.2 (± 0.57)	3.1 (± 0.59)		
Day 43 (n=142, 134)	3.9 (± 0.63)	4.3 (± 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Treatment Phase: Percentage of Participants With Treatment Emergent Adverse Events (TEAEs)

End point title	DB Treatment Phase: Percentage of Participants With Treatment Emergent Adverse Events (TEAEs)
End point description: Percentage of participants with TEAEs during DB treatment phase are reported. An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. TEAE is defined as any AE occurring at or after the initial administration of study intervention through the end of DB phase. Safety analysis set included all randomized participants (adults and elderly) in ROW (countries/territories other than China) who received at least 1 dose of study intervention.	
End point type	Secondary
End point timeframe: From start of treatment (Day 1) up to Day 43	

End point values	DB: Placebo	DB: Aticaprant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	223	217		
Units: Percentage of participants				
number (not applicable)	38.1	44.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up (FU) Phase: Percentage of Participants With AEs

End point title	Follow-up (FU) Phase: Percentage of Participants With AEs
End point description: Percentage of participants with AEs during FU phase are reported. An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. Follow-up analysis set included all randomized participants in ROW (countries/territories other than China) who entered the follow-up phase after the doubleblind treatment phase.	
End point type	Secondary
End point timeframe: From Day 44 up to Day 57	

End point values	FU: Placebo	FU: Aticaprant 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	18		
Units: Percentage of participants				
number (not applicable)	0	5.6		

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB Treatment Phase: From Day 1 (start of treatment) up to Day 43; Follow-up Phase: From Day 44 up to Day 57

Adverse event reporting additional description:

DB phase: Safety analysis set: all randomized participants (adults and elderly) in ROW (countries/territories other than China) who received at least 1 dose of study treatment. FU phase population: all randomized participants in ROW (countries/territories other than China) who entered the FU phase after the DB treatment phase.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	DB: Placebo
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Reporting group description:

During DB treatment phase, participants received placebo matching to aticaprant tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (SSRI/SNRI).

Reporting group title	DB: Aticaprant 10 mg
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Reporting group description:

During the DB treatment phase, participants received aticaprant 10 mg tablet orally once daily from Day 1 to Day 42 in addition to the ongoing antidepressant therapy (SSRI/SNRI).

Reporting group title	FU: Placebo
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Reporting group description:

Participants who received placebo and completed DB phase entered follow-up phase and were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57).

Reporting group title	FU: Aticaprant 10 mg
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Reporting group description:

Participants who received aticaprant 10 mg and completed DB phase entered follow-up phase and were then followed up for safety up to 7 to 14 days after end of DB phase at Day 43 (up to Day 57).

Serious adverse events	DB: Placebo	DB: Aticaprant 10 mg	FU: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 223 (0.45%)	0 / 217 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 223 (0.45%)	0 / 217 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	FU: Aticaprant 10 mg		
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Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DB: Placebo	DB: Aticaprant 10 mg	FU: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 223 (8.07%)	39 / 217 (17.97%)	0 / 21 (0.00%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 223 (4.04%)	17 / 217 (7.83%)	0 / 21 (0.00%)
occurrences (all)	9	19	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 223 (4.04%)	25 / 217 (11.52%)	0 / 21 (0.00%)
occurrences (all)	9	32	0
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	1 / 223 (0.45%)	1 / 217 (0.46%)	0 / 21 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	FU: Aticaprant 10 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Pruritus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0		
Psychiatric disorders Suicidal Ideation subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2023	The overall rationale for the amendment was to made updates based on feedback received from interactions with health authorities, to ensure alignment across the program and to improve participant selection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported