Clinical trial results:
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	2022-000439-22
Trial protocol	SE CZ ES HU BE BG PT PL
Global end of trial date	18 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	67953964MDD3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05455684
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	18 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2024
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 an 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	22 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: 34
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Brazil: 41
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Czechia: 38
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 37
Country: Number of subjects enrolled	United States: 230
Worldwide total number of subjects	511
EEA total number of subjects	193

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)	425
From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 513 participants were enrolled in the study, of whom 511 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	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm 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 (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.

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

Arm description:

During DB treatment phase, participants received aticaprant 10 milligrams (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.

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	258	253
Participants who entered follow-up phase	24 [1]	14 [2]
Completed	244	240
Not completed	14	13
Consent withdrawn by subject	7	4
Adverse event, non-fatal	2	3
Unspecified	1	2
Lost to follow-up	3	2
Non-Compliant with study drug	-	1
Protocol deviation	1	1

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 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.	
Reporting group title	Aticaprant 10 mg
Reporting group description:	
During DB treatment phase, participants received aticaprant 10 milligrams (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.	

Reporting group values	Placebo	Aticaprant 10 mg	Total
Number of subjects	258	253	511
Age categorical Units: participants			
<18 years	0	0	0
Between 18 and 64 years	213	212	425
Between 65 to 74 years	45	41	86
Age continuous Units: Years			
arithmetic mean	51.4	50.2	
standard deviation	± 13.3	± 14.6	-
Gender categorical Units: participants			
Female	185	184	369
Male	72	69	141
Undifferentiated	1	0	1
Region of Enrollment Units: Subjects			
Argentina	18	16	34
Australia	6	7	13
Belgium	12	12	24
Brazil	23	18	41
Bulgaria	17	16	33
Czech Republic	20	18	38
Hungary	2	4	6
Italy	2	1	3
Poland	14	17	31
Portugal	2	3	5
Spain	7	9	16
Sweden	19	18	37
United States	116	114	230
Race, Customized			

Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	1	4	5
Native Hawaiian or Other Pacific Islander	5	3	8
Black or African American	25	24	49
White	222	213	435
More than one race	1	1	2
Missing or Not reported	3	8	11
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	73	71	144
Not Hispanic or Latino	179	176	355
Unknown or Not Reported	6	6	12

Subject analysis sets

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 DB treatment phase, participants received aticaprant 10 milligrams (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).

Reporting group values	DB: Placebo	DB: Aticaprant 10 mg	FU: Placebo
Number of subjects	258	253	24
Age categorical Units: participants			
<18 years Between 18 and 64 years Between 65 to 74 years			
Age continuous Units: Years arithmetic mean standard deviation	 0 ± 0	 ±	 ±
Gender categorical Units: participants			
Female Male			

Undifferentiated			

Region of Enrollment Units: Subjects			
Argentina Australia Belgium Brazil Bulgaria Czech Republic Hungary Italy Poland Portugal Spain Sweden United States			
Race, Customized Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Missing or Not reported			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			

Reporting group values	FU: Aticaprant 10 mg		
Number of subjects	14		
Age categorical Units: participants			
<18 years Between 18 and 64 years Between 65 to 74 years			
Age continuous Units: Years arithmetic mean standard deviation	 ±		
Gender categorical Units: participants			
Female Male Undifferentiated			

Region of Enrollment Units: Subjects			
Argentina Australia Belgium Brazil Bulgaria Czech Republic Hungary Italy Poland Portugal Spain Sweden United States			
Race, Customized Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Missing or Not reported			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	Placebo

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 (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.

Reporting group title	Aticaprant 10 mg

Reporting group description:

During DB treatment phase, participants received aticaprant 10 milligrams (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.

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 DB treatment phase, participants received aticaprant 10 milligrams (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 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	155	158		
Units: Units on a scale				
least squares mean (standard error)	-11.4 (± 0.98)	-12.3 (± 0.95)		

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	= 0.467
Method	Mixed Model for Repeated Measures
Parameter estimate	Least Square Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	1.49
Variability estimate	Standard error of the mean
Dispersion value	1.2

Secondary: Change from Baseline Over Time in MADRS Total Score

End point title	Change from Baseline Over Time in 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 total score indicates improvement. Full analysis set (ANH+) included all adult randomized participants 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

End point timeframe:

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

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	166		
Units: Units on a scale				
least squares mean (standard error)				
Day 15 (n= 163, 166)	-5.4 (± 0.76)	-6.6 (± 0.72)		
Day 29 (n=156, 161)	-9.4 (± 0.90)	-11.1 (± 0.87)		
Day 43 (n=155, 158)	-11.4 (± 0.98)	-12.3 (± 0.95)		

Statistical analyses

No statistical analyses for this end point

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

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 (ranges from 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 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:

Baseline (Day 1) to Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	147		
Units: Units on a scale				
least squares mean (standard error)	10.5 (± 1.50)	12.0 (± 1.43)		

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

End point description:

Responders are defined as participants with a greater than or equal to (>=)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. Full analysis set (ANH+) included all adult randomized participants with MDD ANH+ who received at least 1 dose of study intervention.

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	167	170		
Units: Percentage of participants				
number (not applicable)	22.8	29.4		

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

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 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:

Baseline (Day 1) to Day 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	149		
Units: Units on a scale				
least squares mean (standard error)	-5.9 (± 0.58)	-6.7 (± 0.55)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Aticaprant 10 mg
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Square Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.21
upper limit	0.52
Variability estimate	Standard error of the mean
Dispersion value	0.69

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

End point description:

Percentage of participants with remission of depressive symptoms based on MADRS total score at Day 43 is reported. Participant is defined as a remitter at a given time point if the MADRS total score is less than or equal to (<=)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. Full analysis set (ANH+) included all adult randomized participants with MDD ANH+ who received at least 1 dose of study intervention.

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	167	170		
Units: Percentage of participants				
number (not applicable)	12.6	17.6		

Statistical analyses

No statistical analyses for this end point

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:

Change from baseline over time in DARS total score is reported. 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 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.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	147		
Units: Units on a scale				
least squares mean (standard error)				
Day 15 (n=152, 138)	4.8 (± 1.22)	5.9 (± 1.20)		
Day 29 (n=135, 139)	8.3 (± 1.38)	10.0 (± 1.32)		
Day 43 (n=139, 147)	10.5 (± 1.50)	12.0 (± 1.43)		

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)

End point description:

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 total score indicate improvement. Full analysis set (ANH+) included all adult randomized participants 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.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	149		
Units: Units on a scale				
least squares mean (standard error)				
Day 15 (n=154, 143)	-3.1 (± 0.49)	-3.9 (± 0.48)		
Day 29 (n=138, 143)	-4.6 (± 0.53)	-6.0 (± 0.51)		
Day 43 (n=141, 149)	-5.9 (± 0.58)	-6.7 (± 0.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline Over Time in Work Productivity and Activity Impairment: Depression (WPAI:D)

End point title	Percent Change from Baseline Over Time in Work Productivity and Activity Impairment: Depression (WPAI:D)

End point description:

The WPAI:D questionnaire is a validated short instrument that assesses impairment in work and other regular activities over the past 7 days. The WPAI yields four types of scores: (a) Absenteeism (work time missed); (b) Presenteeism (impairment at work / reduced on-the-job effectiveness); (c) Work productivity loss (overall work impairment / absenteeism plus presenteeism); (d) Activity Impairment. Each score ranges from 0 to 100 with higher scores indicating greater impairment and less productivity. Negative changes in score indicates less impairment and greater productivity. As planned overall work impairment (absenteeism plus presenteeism) and activity impairment is reported. Full analysis set (ANH+): all adult randomized participants with MDD ANH+ who received at least 1 dose of study intervention. 'N' (overall number of participants analyzed)=participants evaluable for this outcome measure; 'n' (number analyzed)=number of participants who were analyzed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Days 29 and 43

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	154		
Units: Percent Change				
least squares mean (standard error)				
Overall work impairment: Day 29 (n=46, 52)	-5.8 (± 4.59)	-14.2 (± 4.71)		
Overall work impairment: Day 43 (n=42, 46)	-13.9 (± 5.07)	-12.9 (± 5.09)		
Activity impairment: Day29 (n=149, 154)	-9.2 (± 2.12)	-13.9 (± 2.03)		
Activity impairment: Day43 (n=147, 150)	-13.9 (± 2.28)	-18.1 (± 2.20)		

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

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). Full analysis set (ANH+) included all adult randomized participants 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	119	128		
Units: Percentage of participants				
number (not applicable)	41.2	52.3		

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)

End point description:

This 8-item measure assesses participants' ability to participate in social roles and activities. The items measures the 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 including 1=always, 2=usually, 3=sometimes, 4=rarely and 5=never, with higher scores indicating better social functioning. The total scores ranges from 8 to 40 and is transformed using a T-score metric with a mean of 50 and a standard deviation of 10. 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 with MDD ANH+ who received at least 1 dose of study intervention. Here, 'N' (overall 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

End point timeframe:

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

End point values	Placebo	Aticaprant 10 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	150		
Units: T-score				
least squares mean (standard error)				
Day 15 (n=145, 150)	2.3 (± 0.48)	2.6 (± 0.46)		
Day 29 (n=143, 150)	2.8 (± 0.54)	3.9 (± 0.52)		
Day 43 (n=143, 148)	4.3 (± 0.63)	5.5 (± 0.61)		

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:

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 who entered the follow-up phase after the double-blind 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	24	14		
Units: Percentage of participants				
number (not applicable)	8.3	7.1		

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 AEs 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. TEAEs included both serious and non serious adverse events. TEAEs are defined as AEs with onset during the DB Treatment Phase, or AEs that are a consequence of a pre-existing condition that has worsened since baseline (Day 1). Safety analysis set included all randomized participants (adults and elderly) 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	258	253		
Units: Percentage of participants				
number (not applicable)	39.5	45.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB treatment phase: start of treatment (Day 1) up to Day 43, FU Phase: From Day 44 up to Day 57

Adverse event reporting additional description:

DB phase: Safety analysis set included all randomized participants (adults and elderly) who received at least 1 dose of study treatment. FU phase: FU population included all randomized participants who entered the FU phase after the double-blind treatment phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	DB: Aticaprant 10 mg

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	DB: Placebo

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).

Serious adverse events	DB: Aticaprant 10 mg	DB: Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 253 (1.19%)	1 / 258 (0.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Pancreatitis Acute			
subjects affected / exposed	1 / 253 (0.40%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal Behaviour			

subjects affected / exposed	1 / 253 (0.40%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DB: Aticaprant 10 mg	DB: Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 253 (20.55%)	29 / 258 (11.24%)	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 253 (6.72%)	22 / 258 (8.53%)	
occurrences (all)	24	25	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 253 (5.53%)	8 / 258 (3.10%)	
occurrences (all)	17	8	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	31 / 253 (12.25%)	6 / 258 (2.33%)	
occurrences (all)	39	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2022	The overall reason for this amendment was to make updates based on feedback received from interactions with health authorities, key opinion leaders in the MDD field and potential investigational sites involved in the study feasibility, to ensure alignment across the program and to improve patient selection. Minor changes were made throughout the protocol for compliance with updated protocol template text, for clarification, and to correct errors.
22 February 2023	The overall reason for this amendment was to make updates based on feedback received from interactions with health authorities, to ensure alignment across the program and to improve participant selection. Minor changes were made throughout the protocol for clarification and to correct errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported