Clinical trial results:
A Double-Blind, Placebo-Controlled Trial of Asenapine in the Prevention of Recurrence of a Mood Episode After Stabilization of an Acute Manic/Mixed Episode in Subjects With Bipolar 1 Disorder (Phase 3B, Protocol P06384)

Summary

EudraCT number	2010-018671-20
Trial protocol	BG
Global end of trial date	30 April 2015

Results information

Result version number	v1 (current)
This version publication date	12 June 2016
First version publication date	12 June 2016

Trial information

Trial identification

Sponsor protocol code	P06384

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01396291
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Research Institute, Inc., an affiliate of Allergan, plc
Sponsor organisation address	185 Hudson Street, Jersey City, United States, NJ 07302
Public contact	Willie Earley, Forest Research Institute, Inc., an affiliate of Allergan, plc, +1 201-427-8257, Willie.Earley@Allergan.com
Scientific contact	Willie Earley, Forest Research Institute, Inc., an affiliate of Allergan, plc, +1 201-427-8257, Willie.Earley@Allergan.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	30 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and safety of asenapine compared with placebo in preventing the recurrence of any mood episodes.

Protection of trial subjects:

This trial had investigator meetings at the outset to review all protocol procedures and investigator responsibilities under Good Clinical Practice (GCP). At the meeting, the conduct of the trial was explained and instructions were provided to ensure accuracy and consistency in data collection. This trial was conducted in conformance with GCP standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. One trial site participating in this trial was identified as having issues related to significant non-compliance associated with some/all requirements of GCP and hence their participation was terminated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 57
Country: Number of subjects enrolled	Croatia: 25
Country: Number of subjects enrolled	India: 46
Country: Number of subjects enrolled	Philippines: 29
Country: Number of subjects enrolled	Romania: 34
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Serbia: 57
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	Ukraine: 32
Country: Number of subjects enrolled	United States: 229
Worldwide total number of subjects	549
EEA total number of subjects	116

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)	532
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at 87 trial centers: 7 in Bulgaria, 6 in Croatia, 7 in Romania, 6 in Russia, 7 in Serbia, 3 in Turkey, 7 in the Ukraine, 4 in the Philippines, 8 in India, and 32 in the United States.

Pre-assignment

Screening details:

This trial consisted of a Screening/2-day Wait Period; a 12-16-week, open-label, asenapine active treatment period followed by a 26-week, double-blind, placebo-controlled period; and a 30-day Follow-up Period.

Period 1

Period 1 title	Open-Label Treatment Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label treatment period.

Arms

Arm title	Open-Label Treatment

Arm description:

For the Open-Label Treatment Period, participants were assigned to asenapine 10 mg BID (flexible-dosing of asenapine 5 mg BID -10 mg BID was to begin on Day 2) for a period of at least 12 and up to 16 weeks. In the event of intolerability during the Open-Label Treatment Period, down-titration to asenapine 5 mg BID was permitted. Participants who cannot tolerate an asenapine 5 mg BID dose were discontinued from the trial. For participants who were down-titrated, subsequent rechallenge with asenapine 10 mg BID was attempted as the final target dose for the stabilization phase of the Open-Label Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Asenapine 10 mg BID
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Participants were treated initially with open-label asenapine, with a starting and target dose of asenapine 10 mg BID (flexible dosing asenapine 5 -10 mg BID) for a period of at least 12 and up to 16 weeks.

Number of subjects in period 1	Open-Label Treatment
Started	549
Completed	253
Not completed	296
Consent withdrawn by subject	35
Administrative	8
Adverse event	91
Lost to follow-up	29

Lack of efficacy	45
Protocol deviation	88

Period 2

Period 2 title	Double-Blind Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Blinding implementation details:

The packaging and labeling of the study medication were designed to maintain the double-blind design of the trial. The study medication included active and placebo fast-dissolving asenapine tablets. Asenapine and asenapine-matched placebo tablets were made to look identical in appearance. The interactive voice response system was used to assign a starting dose of asenapine based on the participant's last dose during Open-Label Treatment Period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Treatment Period - Placebo

Arm description:

During the Double-Blind Treatment Period, participants randomized to placebo received placebo tablets. In the event of intolerability, down-titration was permitted starting at Day 2, but no subsequent rechallenge during the Double-Blind Treatment Period was permitted.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Participants randomized to placebo received sub-lingual asenapine-matched placebo tablets 5-10 mg BID up to 26 Weeks.

Arm title	Double-Blind Treatment Period - Asenapine

Arm description:

During the Double-Blind Treatment Period, participants randomized to asenapine received sub-lingual asenapine tablets 5-10 mg BID up to 26 Weeks. The starting dose of double-blind trial medication was the final asenapine dose used in the Open-Label Treatment Period. The starting dose of double-blind trial medication was the evening dose of the Double-Blind Baseline Visit. In the event of intolerability, down-titration was permitted starting at Day 2, but no subsequent rechallenge during the Double-Blind Treatment Period was permitted.

Arm type	Experimental
Investigational medicinal product name	Asenapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Participants randomized to asenapine received sub-lingual asenapine tablets 5-10 mg BID up to 26 Weeks.

Number of subjects in period 2[1]	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine
Started	126	126
Completed	70	101
Not completed	56	25
Consent withdrawn by subject	6	7
Adverse event	25	9
Recurrence	18	4
Lost to follow-up	3	3
Protocol deviation	4	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Please note that one participant completed the Open-Label period and was randomized in the Double-Blind period. The patient discontinued the study due to an AE in the Double–Blind period however did not start Double-Blind study medication. Therefore, this participant and their AE, including the AE leading to the discontinuation is included in the Open–Label period.

Baseline characteristics

Reporting groups	
Reporting group title	Open-Label Treatment

Reporting group description:

For the Open-Label Treatment Period, participants were assigned to asenapine 10 mg BID (flexible-dosing of asenapine 5 mg BID -10 mg BID was to begin on Day 2) for a period of at least 12 and up to 16 weeks. In the event of intolerability during the Open-Label Treatment Period, down-titration to asenapine 5 mg BID was permitted. Participants who cannot tolerate an asenapine 5 mg BID dose were discontinued from the trial. For participants who were down-titrated, subsequent rechallenge with asenapine 10 mg BID was attempted as the final target dose for the stabilization phase of the Open-Label Treatment Period.

Reporting group values	Open-Label Treatment	Total	
Number of subjects	549	549	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	532	532	
From 65-84 years	17	17	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	41.8		
standard deviation	± 12.9	-	
Gender categorical Units: Subjects			
Female	310	310	
Male	239	239	

End points

End points reporting groups

Reporting group title	Open-Label Treatment

Reporting group description:

For the Open-Label Treatment Period, participants were assigned to asenapine 10 mg BID (flexible-dosing of asenapine 5 mg BID -10 mg BID was to begin on Day 2) for a period of at least 12 and up to 16 weeks. In the event of intolerability during the Open-Label Treatment Period, down-titration to asenapine 5 mg BID was permitted. Participants who cannot tolerate an asenapine 5 mg BID dose were discontinued from the trial. For participants who were down-titrated, subsequent rechallenge with asenapine 10 mg BID was attempted as the final target dose for the stabilization phase of the Open-Label Treatment Period.

Reporting group title	Double-Blind Treatment Period - Placebo

Reporting group description:

During the Double-Blind Treatment Period, participants randomized to placebo received placebo tablets. In the event of intolerability, down-titration was permitted starting at Day 2, but no subsequent rechallenge during the Double-Blind Treatment Period was permitted.

Reporting group title	Double-Blind Treatment Period - Asenapine

Reporting group description:

During the Double-Blind Treatment Period, participants randomized to asenapine received sub-lingual asenapine tablets 5-10 mg BID up to 26 Weeks. The starting dose of double-blind trial medication was the final asenapine dose used in the Open-Label Treatment Period. The starting dose of double-blind trial medication was the evening dose of the Double-Blind Baseline Visit. In the event of intolerability, down-titration was permitted starting at Day 2, but no subsequent rechallenge during the Double-Blind Treatment Period was permitted.

Primary: Percentage of participants with recurrence of any mood event during the Double-Blind (DB) Treatment Period.

End point title	Percentage of participants with recurrence of any mood event during the Double-Blind (DB) Treatment Period.

End point description:

The primary efficacy endpoint for the current trial is time to recurrence of any mood event during the Double-Blind Treatment Period, defined as any of the following: 1) Requirement or initiation of any non-study medication to treat mixed, manic, or depressive symptoms, including an antipsychotic, antidepressant, or mood-stabilizing agent; 2) Requirement or initiation of psychiatric hospitalization; 3) Discontinuation from the study because of a mood event (as determined by the investigator); or 4) Young Mania Rating Scale (Y-MRS) and/ or Montgomery Asberg Depression Rating Scale (MADRS) score ≥16. The assignment of the specific mood episode type (manic or depressed or mixed) were made by the study investigator, based on clinical judgment and verified by the rating scale data.

End point type	Primary

End point timeframe:

From Week 12 or 16 to Week 38 or 42

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: percentage of participants				
number (not applicable)				
With Recurrence	33.3	8.7		

Initiation of any non-study medication	23.8	5.6		
Initiation of psychiatric hospitalization	4.8	1.6		
Discontinuation from the study due to mood event	23	5.6		
Y-MRS and/or MADRS score ≥16	30.2	8.7		

Statistical analyses

Statistical analysis title	Time to first recurrence of any mood episode
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.43

Secondary: Mean change from Baseline in Y-MRS total score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in Y-MRS total score by visit in Open-Label Treatment Period.

End point description:

Y-MRS instrument consists of 11 items. Each item is rated on a defined step scale of 0 to 4 (Elevated mood; Increased motor activity–energy; Sexual interest; Sleep; Language thought disorder; Appearance; Insight) or 0 to 8 (Irritability; Speech; Content; Disruptive-aggressive behavior). The total score ranges from 0 (all symptoms absent) to 60 (all symptoms extreme).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 447)	-6.4 (± 6)			
Week 2 (N= 484)	-10.4 (± 7.6)			
Week 4 (N= 427)	-14.6 (± 7.6)			

Week 6 (N= 389)	-17.5 (± 7.4)			
Week 8 (N= 353)	-20.2 (± 7)			
Week 10 (N=323)	-21.5 (± 6.5)			
Week 12 (N= 293)	-22.5 (± 6.3)			
Week 14 (N= 229)	-23.2 (± 6.4)			
Week 16 (N= 142)	-23.3 (± 6.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in MADRS total score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in MADRS total score by visit in Open-Label Treatment Period.

End point description:

MADRS is a 10-item, clinician-rated scale for assessing the severity of symptoms of depression. The MADRS interview was conducted early in each applicable visit to avoid negatively impacting diagnostic and primary outcome data due to participant fatigue. A structured interview for the MADRS (structured interview guide for the Montgomery-Åsberg Depression Rating Scale [SIGMA]) was used. The MADRS total score is the sum of the 10 items and ranges from 0 to 60. A high numeric rating implies a greater degree of symptom severity.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 427)	-4.4 (± 6.2)			
Week 6 (N= 389)	-5.1 (± 6.8)			
Week 8 (N= 353)	-5.8 (± 6.5)			
Week 10 (N= 323)	-6.1 (± 6.1)			
Week 12 (N= 293)	-6.7 (± 5.9)			
Week 14 (N= 229)	-6.5 (± 5.6)			
Week 16 (N= 142)	-7 (± 6.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS total score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS total score by visit in Open-Label Treatment Period.

End point description:

The PANSS is a 30-item, clinician rate instrument for assessing the symptoms of schizophrenia and consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 427)	-9.6 (± 10.8)			
Week 16 (N= 141)	-15.6 (± 10.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS positive score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS positive score by visit in Open-Label Treatment Period.

End point description:

The PANSS is a 30-item, clinician rate instrument for assessing the symptoms of schizophrenia and consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms). The 7 positive symptom constructs were delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS Positive Score ranged from 7 (best possible outcome) to 49 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427) Week 16 (N=141)	-4.2 (± 4.4) -6.3 (± 4.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS negative score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS negative score by visit in Open-Label Treatment Period.

End point description:

The PANSS is a 30-item, clinician rate instrument for assessing the symptoms of schizophrenia and consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms).The 7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The PANSS Negative Score ranged from 7(best possible outcome) to 49 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427) Weel 16 (N= 141)	-0.5 (± 2.5) -1 (± 1.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS general psychopathology score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS general psychopathology score by visit in Open-Label Treatment Period.

End point description:

The PANSS is a 30-item, clinician rate instrument for assessing the symptoms of schizophrenia and consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms). The 16 general psychopathology symptom constructs were Somatic concern, Anxiety, Guilt feelings, Tension, Mannerisms and posturing, Depression, Motor retardation, Uncooperativeness, Unusual thought content, Disorientation, Poor attention, Lack of judgment and insight, Disturbance of volition, Poor impulse control, Preoccupation, and Active social avoidance. The PANSS general psychopathology score ranged from 16 (best possible outcome) to 112 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427)	-5 (± 6)			
Week 16 (N=141)	-8.4 (± 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS marder factor positive symptom score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor positive symptom score by visit in Open-Label Treatment Period.

End point description:

PANSS marder factor positive symptom factor score defined by the sum of (PANSS Items P1, P3, P5, P6, N7, G1, G9, G12). If any one of the component items has a missing value then the Marder Factor Positive Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 8 to 56. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427)	-2.9 (± 4.1)			
Week 16 (N=141)	-4.6 (± 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS marder factor negative symptom score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor negative symptom score by visit in Open-Label Treatment Period.

End point description:

PANSS marder factor negative symptom factor score defined by sum of (PANSS items N1, N2, N3, N4, N6, G7, G16). If any one of the component items has a missing value then the Marder Factor Negative Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 7 to 49. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427)	-0.3 (± 2.5)			
Week 16 (N=141)	-0.5 (± 2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS marder factor disorganized thought symptom score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor disorganized thought symptom score by visit in Open-Label Treatment Period.

End point description:

PANSS marder factor disorganized thought symptom factor score defined by sum of (PANSS items P2, N5, G5, G10, G11, G13, G15). If any one of the component items has a missing value then the Marder Factor Disorganized Thought Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 7 to 49. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427) Week 16 (N=141)	-1.9 (± 3) -3.2 (± 3.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS marder factor hostility/excitement symptom score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor hostility/excitement symptom score by visit in Open-Label Treatment Period.

End point description:

PANSS marder factor hostility/ excitement symptom score is defined as the sum of (items P4, P7, G8, G14). If any one of the component items has a missing value then the Marder Factor Hostility/Excitement Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 4 to 28. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427) Week 16 (N=141)	-3.1 (± 3) -4.9 (± 3.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS marder factor anxiety/depression symptom score by visit in Open-Label Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor anxiety/depression symptom score by visit in Open-Label Treatment Period.

End point description:

PANSS marder factor anxiety/depression symptom score is defined as the sum of (items G2, G3, G4, G6). If any one of the component items has a missing value then the Marder Factor Anxiety/Depression Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 4 to 28. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N=427)	-1.5 (± 2.7)			
Week 16 (N= 141)	-2.3 (± 2.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Clinical Global Impression Scale-Improvement for Bipolar Disorder (CGI-BP) severity of mania by visit during Open-Label Treatment Period.

End point title	Mean change from Baseline in Clinical Global Impression Scale-Improvement for Bipolar Disorder (CGI-BP) severity of mania by visit during Open-Label Treatment Period.

End point description:

It is a 7-point scale where, for each condition, 1 = Not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; and 7 = Among the most extremely ill.

End point type	Secondary

End point timeframe:

Baseline in Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 447)	-0.6 (± 0.8)			

Week 2 (N= 484)	-1 (± 1)			
Week 4 (N= 427)	-1.6 (± 1)			
Week 6 (N= 389)	-2 (± 1.1)			
Week 8 (N= 353)	-2.4 (± 1)			
Week 10 (N=323)	-2.6 (± 0.9)			
Week 12 (N= 293)	-2.7 (± 0.9)			
Week 14 (N= 229)	-2.8 (± 0.9)			
Week 16 (N= 142)	-2.9 (± 0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in CGI-BP severity of depression by visit during Open-Label Treatment Period.

End point title	Mean change from Baseline in CGI-BP severity of depression by visit during Open-Label Treatment Period.

End point description:

It is a 7-point scale where, for each condition, 1 = Not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; and 7 = Among the most extremely ill.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 447)	-0.2 (± 0.7)			
Week 2 (N= 484)	-0.3 (± 0.9)			
Week 4 (N= 427)	-0.3 (± 1.1)			
Week 6 (N= 389)	-0.4 (± 1.1)			
Week 8 (N= 353)	-0.4 (± 1.1)			
Week 10 (N=323)	-0.4 (± 1.1)			
Week 12 (N= 293)	-0.4 (± 1.1)			
Week 14 (N= 229)	-0.4 (± 1)			
Week 16 (N= 142)	-0.6 (± 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in CGI-BP severity of overall bipolar illness

by visit during Open-Label Treatment Period.

End point title	Mean change from Baseline in CGI-BP severity of overall bipolar illness by visit during Open-Label Treatment Period.

End point description:

It is a 7-point scale where, for each condition, 1 = Not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; and 7 = Among the most extremely ill.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 447)	-0.6 (± 0.8)			
Week 2 (N= 482)	-1 (± 0.9)			
Week 4 (N= 427)	-1.6 (± 1)			
Week 6 (N= 389)	-2 (± 1)			
Week 8 (N= 353)	-2.3 (± 1)			
Week 10 (N=323)	-2.5 (± 0.9)			
Week 12 (N= 293)	-2.7 (± 0.9)			
Week 14 (N= 229)	-2.7 (± 0.9)			
Week 16 (N= 142)	-2.8 (± 0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with remission of mania by visit in Open-Label Treatment Period.

End point title	Percentage of participants with remission of mania by visit in Open-Label Treatment Period.

End point description:

Remission of mania is defined as Y-MRS total score of ≤12 at 2 consecutive post open-label baseline visits.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: percentage of participants				
number (not applicable)				
Week 1 (N= 447)	0			
Week 2 (N= 484)	8.3			
Week 4 (N= 427)	25.8			
Week 6 (N= 389)	43.7			
Week 8 (N= 353)	62.6			
Week 10 (N=323)	88.5			
Week 12 (N= 293)	90.8			
Week 14 (N= 229)	90.4			
Week 16 (N= 142)	86.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants of Y-MRS 50% responders by visit in Open-Label Treatment Period.

End point title	Percentage of participants of Y-MRS 50% responders by visit in Open-Label Treatment Period.

End point description:

Y-MRS 50% responder is defined as a Y-MRS total score reduction of at least 50% compared to open-label baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: Percentage of participants				
number (not applicable)				
Week 1 (N= 447)	13			
Week 2 (N= 484)	31			
Week 4 (N= 427)	56.2			
Week 6 (N= 389)	75.6			
Week 8 (N= 353)	90.9			
Week 10 (N=323)	97.2			
Week 12 (N= 293)	96.2			
Week 14 (N= 229)	96.9			
Week 16 (N= 142)	97.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with remission of depression by visit in Open-Label Treatment Period.

End point title	Percentage of participants with remission of depression by visit in Open-Label Treatment Period.

End point description:

Remission of depression is defined as MADRS total score of 12 or lower at 2 consecutive post open-label baseline visits during the open-label treatment period for participants with an open-label baseline MADRS of 16 or higher.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: percentage of participants				
number (not applicable)				
Week 4 (N= 427)	0			
Week 6 (N= 389)	9.3			
Week 8 (N= 353)	9.3			
Week 10 (N=323)	11.8			
Week 12 (N= 293)	11.6			
Week 14 (N= 229)	10.9			
Week 16 (N= 142)	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants of MADRS 50% responder by visit in Open-Label Treatment Period.

End point title	Percentage of participants of MADRS 50% responder by visit in Open-Label Treatment Period.

End point description:

MADRS 50% responder is defined as a MADRS total score reduction of at least 50%, compared to open-label baseline in subset of participants with open-label baseline MADRS score of 16 or higher.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: percentage of participants				
number (not applicable)				
Week 4 (N= 414)	10.1			
Week 6 (N= 377)	11.1			
Week 8 (N= 342)	10.8			
Week 10 (N= 314)	11.8			
Week 12 (N= 285)	11.6			
Week 14 (N= 221)	10.4			
Week 16 (N= 138)	16.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants in CGI-BP mania responder rates by visit in Open-Label Treatment Period.

End point title	Percentage of participants in CGI-BP mania responder rates by visit in Open-Label Treatment Period.

End point description:

CGI-BP mania responder rate is defined as change of much improved or very much improved in mania from open-label baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: percentage of participants				
number (not applicable)				
Week 1 (N= 447)	24.4			
Week 2 (N= 482)	41.7			
Week 4 (N= 427)	69.8			
Week 6 (N= 389)	81.7			
Week 8 (N= 353)	91.2			
Week 10 (N=323)	95.4			
Week 12 (N= 293)	96.9			

Week 14 (N= 229)	96.5			
Week 16 (N= 142)	97.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants in CGI-BP depression responder rates by visit in Open-Label Treatment Period.

End point title	Percentage of participants in CGI-BP depression responder rates by visit in Open-Label Treatment Period.

End point description:

CGI-BP depression responder rate is defined as change of much improved or very much improved in depression from open-label baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: percentage of participants				
number (not applicable)				
Week 1 (N= 447)	13			
Week 2 (N= 482)	18.3			
Week 4 (N= 427)	23.2			
Week 6 (N= 389)	23.9			
Week 8 (N= 353)	26.9			
Week 10 (N=323)	28.8			
Week 12 (N= 293)	30			
Week 14 (N= 229)	26.6			
Week 16 (N= 142)	29.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants in CGI-BP bipolar illness responder rates by visit in Open-Label Treatment Period.

End point title	Percentage of participants in CGI-BP bipolar illness responder rates by visit in Open-Label Treatment Period.

End point description:

The CGI-I is a 7-point scale where, 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; and 7 = Very much worse.

End point type	Secondary
End point timeframe: Baseline to Week 16	

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	516			
Units: percentage of participants				
number (not applicable)				
Week 1 (N= 447)	23.9			
Week 2 (N= 482)	39.8			
Week 4 (N= 427)	65.1			
Week 6 (N= 389)	78.4			
Week 8 (N= 353)	87.8			
Week 10 (N=323)	92			
Week 12 (N= 293)	95.6			
Week 14 (N= 229)	94.3			
Week 16 (N= 142)	95.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Y-MRS total score by visit in DB Treatment Period.

End point title	Mean change from Baseline in Y-MRS total score by visit in DB Treatment Period.
End point description: Y-MRS instrument consists of 11 items. Each item is rated on a defined step scale of 0 to 4 (Elevated mood; Increased motor activity–energy; Sexual interest; Sleep; Language thought disorder; Appearance; Insight) or 0 to 8 (Irritability; Speech; Content; Disruptive-aggressive behavior). The total score ranges from 0 (all symptoms absent) to 60 (all symptoms extreme).	
End point type	Secondary
End point timeframe: Baseline to DB Week 26	

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: units on a scale				
least squares mean (standard error)				
DB Week 2 (N= 123, 119)	0.1 (± 0.2)	0 (± 0.2)		

DB Week 4 (N= 109, 115)	0.4 (± 0.3)	0 (± 0.3)		
DB Week 6 (N= 104, 113)	-0.2 (± 0.3)	-0.3 (± 0.3)		
DB Week 8 (N= 98, 106)	0.3 (± 0.4)	-0.3 (± 0.4)		
DB Week 10 (N= 99, 105)	-0.1 (± 0.3)	-0.8 (± 0.3)		
DB Week 12 (N= 88, 101)	0.4 (± 0.4)	-0.9 (± 0.4)		
DB Week 16 (N= 76, 101)	-0.5 (± 0.3)	-1.2 (± 0.3)		
DB Week 20 (N= 73, 103)	-0.7 (± 0.4)	-0.5 (± 0.4)		
DB Week 24 (N= 69, 98)	-0.5 (± 0.4)	-0.7 (± 0.3)		
DB Week 26 (N= 60, 92)	-0.9 (± 0.3)	-0.8 (± 0.3)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 2.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9834 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.6

Notes:

[1] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 4.
Comparison groups	Double-Blind Treatment Period - Asenapine v Double-Blind Treatment Period - Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4427 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.6

Notes:

[2] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 6.

Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7512 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.6

Notes:

[3] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 8.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3022 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.5

Notes:

[4] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 10.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.121 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.2

Notes:

[5] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 12.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0135 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.3

Notes:

[6] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 12.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0597 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0

Notes:

[7] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 20.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6801 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.3

Notes:

[8] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 24.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7173 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.8

Notes:

[9] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8121 [10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.9

Notes:

[10] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Secondary: Mean change from Baseline in MADRS total score by visit in DB Treatment Period.

End point title	Mean change from Baseline in MADRS total score by visit in DB Treatment Period.

End point description:

MADRS is a 10-item, clinician-rated scale for assessing the severity of symptoms of depression. The MADRS interview was conducted early in each applicable visit to avoid negatively impacting diagnostic

and primary outcome data due to participant fatigue. A structured interview for the MADRS (SIGMA) was used. The MADRS total score is the sum of the 10 items and ranges from 0 to 60. A high numeric rating implies a greater degree of symptom severity.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: units on a scale				
least squares mean (standard error)				
DB Week 2 (N= 123, 119)	1.5 (± 0.3)	0.5 (± 0.4)		
DB Week 4 (N= 109, 115)	1 (± 0.3)	0.1 (± 0.3)		
DB Week 6 (N= 104, 113)	0.6 (± 0.2)	0.1 (± 0.2)		
DB Week 8 (N= 98, 106)	0.6 (± 0.3)	0.3 (± 0.3)		
DB Week 10 (N= 99, 105)	0.2 (± 0.3)	0.3 (± 0.3)		
DB Week 12 (N= 88, 101)	1 (± 0.4)	0.2 (± 0.4)		
DB Week 16 (N= 76, 101)	-0.1 (± 0.3)	0 (± 0.3)		
DB Week 20 (N= 73, 103)	-0.1 (± 0.3)	0.3 (± 0.2)		
DB Week 24 (N= 69, 98)	0.1 (± 0.3)	0.2 (± 0.3)		
DB Week 26 (N= 60, 92)	-0.5 (± 0.3)	0.1 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 2.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0473 [11]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0

Notes:

[11] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 4.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind

	Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039 [12]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0

Notes:

[12] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 6.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1725 [13]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.2

Notes:

[13] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 8.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4351 [14]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.5

Notes:

[14] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 10.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7124 [15]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.8

Notes:

[15] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 12.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1148 [16]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.2

Notes:

[16] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 16.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7879 [17]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.9

Notes:

[17] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 20.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2559 [18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	1.1

Notes:

[18] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 24.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8241 [19]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.9

Notes:

[19] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097 [20]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.2

Notes:

[20] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases.

Secondary: Mean change from Baseline in PANSS total score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS total score by visit in DB Treatment Period.

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	-0.4 (± 0.6)	0.9 (± 0.5)		

Statistical analyses

Statistical analysis title	Statistcal analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1225 [21]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2.9

Notes:

[21] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS positive score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS positive score by visit in DB Treatment Period.

End point description:

The PANSS consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms). The 7 positive symptom constructs were delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS Positive Score ranged from 7(best possible outcome) to 49 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	-0.1 (± 0.2)	0.1 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3326 [22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.8

Notes:

[22] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS negative score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS negative score by visit in DB Treatment Period.

End point description:

The PANSS consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms).The 7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The PANSS Negative Score ranged from 7(best possible outcome) to 49 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to DB Week 26.

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	-0.1 (± 0.2)	0.4 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0651 [23]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[23] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS general psychopathology score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS general psychopathology score by visit in DB Treatment Period.

End point description:

The PANSS consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms). The 16 general psychopathology symptom constructs were Somatic concern, Anxiety, Guilt feelings, Tension, Mannerisms and posturing, Depression, Motor retardation, Uncooperativeness, Unusual thought content, Disorientation, Poor attention, Lack of judgment and insight, Disturbance of volition, Poor impulse control, Preoccupation, and Active social avoidance. The PANSS general psychopathology score ranged from 16 (best possible outcome) to 112 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	-0.2 (± 0.4)	0.3 (± 0.3)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Asenapine v Double-Blind Treatment Period - Placebo

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2599 [24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.5

Notes:

[24] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS marder factor positive symptom score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor positive symptom score by visit in DB Treatment Period.

End point description:

PANSS marder factor positive symptom factor score defined by the sum of (PANSS Items P1, P3, P5, P6, N7, G1, G9, G12). If any one of the component items has a missing value then the Marder Factor Positive Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 8 to 56. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	0 (± 0.2)	0.3 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.209 [25]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.8

Notes:

[25] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS marder factor negative symptom score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor negative symptom score by visit in DB Treatment Period.

End point description:

PANSS marder factor negative symptom factor score defined by sum of (PANSS items N1, N2, N3, N4, N6, G7, G16). If any one of the component items has a missing value then the Marder Factor Negative Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 7 to 49. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	0.1 (± 0.2)	0.4 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2059 [26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.8

Notes:

[26] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS marder factor disorganized thought symptom score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor disorganized thought symptom score by visit in DB Treatment Period.

End point description:

PANSS marder factor disorganized thought symptom factor score defined by sum of (PANSS items P2, N5, G5, G10, G11, G13, G15). If any one of the component items has a missing value then the Marder Factor Disorganized Thought Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 7 to 49. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	-0.3 (± 0.2)	-0.1 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3326 [27]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.7

Notes:

[27] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS marder factor hostility/excitement symptom score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor hostility/excitement symptom score by visit in DB Treatment Period.

End point description:

PANSS marder factor hostility/ excitement symptom score is defined as the sum of (items P4, P7, G8, G14). If any one of the component items has a missing value then the Marder Factor Hostility/Excitement Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 4 to 28. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	-0.1 (± 0.2)	0 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6243 [28]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.6

Notes:

[28] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in PANSS marder factor anxiety/depression symptom score by visit in DB Treatment Period.

End point title	Mean change from Baseline in PANSS marder factor anxiety/depression symptom score by visit in DB Treatment Period.

End point description:

PANSS marder factor anxiety/depression symptom score is defined as the sum of (items G2, G3, G4, G6). If any one of the component items has a missing value then the Marder Factor Anxiety/Depression Symptom Score is missing. Each item is rated from 1 (absent) to 7 (extreme) and the symptom score ranges from 4 to 28. Higher scores indicate greater severity of illness.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	91		
Units: units on a scale				
least squares mean (standard error)	0 (± 0.2)	0.3 (± 0.2)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2632 [29]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.8

Notes:

[29] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in CGI-BP severity of mania by visit in DB Treatment Period.

End point title	Mean change from Baseline in CGI-BP severity of mania by visit in DB Treatment Period.

End point description:

CGI-BP score ranged from 1 (normal, not at all ill) to 7 (very severely ill). Decreases from baseline within a treatment group were indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: units on a scale				
least squares mean (standard error)				
DB Week 2 (N= 123, 119)	0 (± 0)	0 (± 0)		
DB Week 4 (N= 109, 115)	0 (± 0.1)	0 (± 0.1)		
DB Week 6 (N= 104, 113)	-0.1 (± 0)	0 (± 0)		
DB Week 8 (N= 98, 106)	0 (± 0.1)	-0.1 (± 0.1)		
DB Week 10 (N= 99, 105)	-0.1 (± 0.1)	-0.1 (± 0.1)		
DB Week 12 (N= 88, 100)	0 (± 0.1)	-0.1 (± 0.1)		
DB Week 16 (N= 76, 101)	-0.1 (± 0.1)	-0.2 (± 0)		
DB Week 20 (N= 73, 103)	-0.2 (± 0.1)	-0.1 (± 0.1)		
DB Week 24 (N= 69, 98)	-0.1 (± 0.1)	-0.1 (± 0.1)		
DB Week 26 (N= 60, 92)	-0.2 (± 0.1)	-0.2 (± 0)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 2
Comparison groups	Double-Blind Treatment Period - Asenapine v Double-Blind Treatment Period - Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6977 [30]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[30] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 4.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2568 [31]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[31] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 6.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4852 [32]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[32] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 8.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2192 [33]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[33] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 10.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8268 [34]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[34] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 12.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2266 [35]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[35] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 16.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3759 [36]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[36] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 20.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1998 [37]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[37] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 24.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7865 [38]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[38] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7952 [39]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[39] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in CGI-BP severity of depression by visit in DB Treatment Period.

End point title	Mean change from Baseline in CGI-BP severity of depression by visit in DB Treatment Period.

End point description:

CGI-BP score ranged from 1 (normal, not at all ill) to 7 (very severely ill). Decreases from baseline within a treatment group were indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: units on a scale				
least squares mean (standard error)				
DB Week 2 (N= 123, 119)	0.2 (± 0.1)	0.1 (± 0.1)		
DB Week 4 (N= 109, 115)	0.1 (± 0)	0 (± 0)		
DB Week 6 (N= 104, 113)	0 (± 0)	0 (± 0)		
DB Week 8 (N= 98, 106)	0.1 (± 0)	0 (± 0)		
DB Week 10 (N= 99, 105)	0 (± 0)	0.1 (± 0)		
DB Week 12 (N= 88, 100)	0.1 (± 0.1)	0.1 (± 0.1)		
DB Week 16 (N= 76, 101)	0 (± 0.1)	0.1 (± 0)		
DB Week 20 (N= 73, 103)	0 (± 0)	0 (± 0)		
DB Week 24 (N= 69, 98)	0.1 (± 0.1)	0.1 (± 0)		
DB Week 26 (N= 60, 92)	-0.1 (± 0)	0 (± 0)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 2.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4488 [40]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[40] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 4.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9279 [41]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[41] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 6.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7011 [42]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[42] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 8.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6188 [43]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[43] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 10.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.258 [44]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.2

Notes:

[44] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 12.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5861 [45]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[45] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 16.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4592 [46]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[46] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 20.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8219 [47]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[47] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 24.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9939 [48]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[48] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1157 [49]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.2

Notes:

[49] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Mean change from Baseline in CGI-BP severity of overall bipolar illness by visit in DB Treatment Period.

End point title	Mean change from Baseline in CGI-BP severity of overall bipolar illness by visit in DB Treatment Period.

End point description:

CGI-BP score ranged from 1 (normal, not at all ill) to 7 (very severely ill). Decreases from baseline within a treatment group were indicative of an improvement.

End point type	Secondary

End point timeframe:

Baseline to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: units on a scale				
least squares mean (standard error)				
DB Week 2 (N= 123, 119)	0.1 (± 0.1)	0.1 (± 0.1)		
DB Week 4 (N= 109, 115)	0 (± 0.1)	0 (± 0.1)		
DB Week 6 (N= 104, 113)	-0.1 (± 0)	0 (± 0)		
DB Week 8 (N= 98, 106)	0 (± 0.1)	-0.1 (± 0.1)		
DB Week 10 (N= 99, 105)	0 (± 0.1)	0 (± 0.1)		
DB Week 12 (N= 88, 100)	0.1 (± 0.1)	-0.1 (± 0.1)		
DB Week 16 (N= 76, 101)	-0.1 (± 0.1)	-0.1 (± 0.1)		
DB Week 20 (N= 73, 103)	-0.1 (± 0.1)	-0.1 (± 0.1)		
DB Week 24 (N= 69, 98)	-0.1 (± 0.1)	-0.1 (± 0.1)		
DB Week 26 (N= 60, 92)	-0.2 (± 0.1)	-0.2 (± 0)		

Statistical analyses

Statistical analysis title	Statistical analysis at DB Week 2.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5974 [50]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[50] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 4.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5887 [51]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[51] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 6.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.342 [52]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[52] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 8.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2196 [53]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[53] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 10.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9776 [54]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[54] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 12.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1241 [55]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0

Notes:

[55] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 16.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8295 [56]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[56] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 20.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4173 [57]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[57] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 24.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine

Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3891 [58]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[58] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Statistical analysis title	Statistical analysis at DB Week 26.
Comparison groups	Double-Blind Treatment Period - Placebo v Double-Blind Treatment Period - Asenapine
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8337 [59]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Notes:

[59] - Based on ANCOVA model with treatment and pooled site as fixed effects and double-blind baseline as a covariate for the observed cases data.

Secondary: Percentage of participants in CGI-BP mania responder rates by visit in DB Treatment Period.

End point title	Percentage of participants in CGI-BP mania responder rates by visit in DB Treatment Period.

End point description:

CGI-BP mania responder rate is defined as change of much improved or very much improved in mania from double-blind baseline.

End point type	Secondary

End point timeframe:

DB Week 2 to DB Week 16

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: percentage of participants				
number (not applicable)				
DB Week 2	39	46.2		
DB Week 4	37.6	46.1		
DB Week 6	38.5	46		
DB Week 8	33.7	47.2		
DB Week 10	36.4	43.8		
DB Week 12	33	48		
DB Week 16	36.8	50.5		
DB Week 20	35.6	51.5		
DB Week 24	33.3	57.1		
DB Week 26	31.7	55.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants in CGI-BP depression responder rates by visit in DB Treatment Period.

End point title	Percentage of participants in CGI-BP depression responder rates by visit in DB Treatment Period.

End point description:

CGI-BP depression responder rate is defined as change of much improved or very much improved in depression from double-blind baseline.

End point type	Secondary

End point timeframe:

DB Week 2 to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: percentage of participants				
number (not applicable)				
DB Week 2	7.3	13.4		
DB Week 4	5.5	15.7		
DB Week 6	5.8	15		
DB Week 8	5.1	16		
DB Week 10	6.1	14.3		
DB Week 12	4.5	15		
DB Week 16	9.2	12.9		

DB Week 20	9.6	15.5		
DB Week 24	7.2	16.3		
DB Week 26	8.3	15.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants in CGI-BP overall bipolar illness responder rates by visit in DB Treatment Period.

End point title	Percentage of participants in CGI-BP overall bipolar illness responder rates by visit in DB Treatment Period.

End point description:

CGI-BP overall bipolar illness responder rate is defined as change of much improved or very much improved in overall bipolar illness from double-blind baseline.

End point type	Secondary

End point timeframe:

DB Week 2 to DB Week 26

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: percentage of participants				
number (not applicable)				
DB Week 2	36.6	45.4		
DB Week 4	36.7	43.5		
DB Week 6	38.5	44.2		
DB Week 8	32.7	46.2		
DB Week 10	36.4	41.9		
DB Week 12	31.8	47		
DB Week 16	36.8	47.5		
DB Week 20	35.6	51.5		
DB Week 24	30.4	58.2		
DB Week 26	31.7	56.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall recurrence rate of any mood episode by visit in DB Treatment Period.

End point title	Overall recurrence rate of any mood episode by visit in DB Treatment Period.

End point description:

Overall recurrence rates (any mood episode) defined as number of participants with recurrences divided by the number of participants in full analysis set.

End point type	Secondary

End point timeframe:

DB Visit 10 to DB Visit 19

End point values	Double-Blind Treatment Period - Placebo	Double-Blind Treatment Period - Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	126		
Units: percentage of participants				
number (not applicable)				
Visit 10 (1 ≤ Day ≤ 21)	7.1	2.4		
Visit 11 (22 ≤ Day ≤ 35)	3.5	2.5		
Visit 12 (36 ≤ Day ≤ 49)	3.7	0.8		
Visit 13 (50 ≤ Day ≤ 63)	2.9	0.9		
Visit 14 (64 ≤ Day ≤ 77)	5	0.9		
Visit 15 (78 ≤ Day ≤ 98)	8.6	0		
Visit 16 (99 ≤ Day ≤ 126)	4.8	0.9		
Visit 17 (127 ≤ Day ≤ 154)	3.9	0.9		
Visit 18 (155 ≤ Day ≤ 175)	2.7	0		
Visit 19 (176 ≤ Day)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signing of the informed consent through the study until the follow-up visit at least 7 days after last dose of study medication; For serious adverse events, at least 30 days after last dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Open-Label Treatment Period

Reporting group description:

For the Open-Label Treatment Period, participants were assigned to asenapine 10 mg BID (flexible-dosing of asenapine 5 mg BID -10 mg BID was to begin on Day 2) for a period of at least 12 and up to 16 weeks. In the event of intolerability during the Open-Label Treatment Period, down-titration to asenapine 5 mg BID was permitted. Participants who cannot tolerate an asenapine 5 mg BID dose were discontinued from the trial. For participants who were down-titrated, subsequent rechallenge with asenapine 10 mg BID was attempted as the final target dose for the stabilization phase of the Open-Label Treatment Period.

Reporting group title	Placebo - Double-Blind Treatment Period

Reporting group description:

During the Double-Blind Treatment Period, participants randomized to placebo received placebo tablets. In the event of intolerability, down-titration was permitted starting at Day 2, but no subsequent rechallenge during the Double-Blind Treatment Period was permitted.

Reporting group title	Asenapine - Double-Blind Treatment Period

Reporting group description:

During the Double-Blind Treatment Period, participants randomized to asenapine received sub-lingual asenapine tablets 5-10 mg BID up to 26 Weeks. The starting dose of double-blind trial medication was the final asenapine dose used in the Open-Label Treatment Period. The starting dose of double-blind trial medication was the evening dose of the Double-Blind Baseline Visit. In the event of intolerability, down-titration was permitted starting at Day 2, but no subsequent rechallenge during the Double-Blind Treatment Period was permitted.

Serious adverse events	Open-Label Treatment Period	Placebo - Double-Blind Treatment Period	Asenapine - Double-Blind Treatment Period
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 549 (5.46%)	11 / 126 (8.73%)	6 / 126 (4.76%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 549 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 549 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Vomiting			

subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Asthma			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 549 (0.00%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mania			
subjects affected / exposed	6 / 549 (1.09%)	1 / 126 (0.79%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	4 / 549 (0.73%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	3 / 549 (0.55%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptom			
subjects affected / exposed	3 / 549 (0.55%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bipolar I disorder			
subjects affected / exposed	2 / 549 (0.36%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Psychotic disorder			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Depression			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dependence			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Panic attack			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Suicide attempt			
subjects affected / exposed	1 / 549 (0.18%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 549 (0.00%)	1 / 126 (0.79%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Appendicitis perforated			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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
Pneumonia			
subjects affected / exposed	1 / 549 (0.18%)	0 / 126 (0.00%)	0 / 126 (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

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

Non-serious adverse events	Open-Label Treatment Period	Placebo - Double-Blind Treatment Period	Asenapine - Double-Blind Treatment Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	192 / 549 (34.97%)	14 / 126 (11.11%)	4 / 126 (3.17%)
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	39 / 549 (7.10%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences (all)	47	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	55 / 549 (10.02%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences (all)	65	0	0
Akathisia			
subjects affected / exposed	42 / 549 (7.65%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences (all)	45	0	0
Sedation			
subjects affected / exposed	42 / 549 (7.65%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences (all)	46	0	0
Headache			
subjects affected / exposed	32 / 549 (5.83%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences (all)	40	0	0
Gastrointestinal disorders			
Hypoaesthesia oral			
subjects affected / exposed	33 / 549 (6.01%)	0 / 126 (0.00%)	0 / 126 (0.00%)
occurrences (all)	34	0	0

Psychiatric disorders Mania subjects affected / exposed occurrences (all)	0 / 549 (0.00%) 0	14 / 126 (11.11%) 15	4 / 126 (3.17%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2010	The first protocol amendment, included the following changes: Key secondary trial objectives were deleted; Specification that there would be no hypothesis testing of safety data; Added exclusion criteria related to hepatic condition to exclusion criterion #4; Added previous diagnosis of epilepsy or seizure disorder to exclusion criterion #7; Added previous or current diagnosis of schizophrenia or schizoaffective disorder or other psychotic disorder to exclusion criterion #10; Added diagnosis of primary Axis I disorder other than bipolar I disorder to exclusion criterion #11; Added previous allergy to asenapine to exclusion criterion #22; Added inability of the participant to reduce his/her benzodiazepine intake as specified in the protocol to exclusion criterion #24; Added time points (at least 8 weeks) related to the failure to respond to marketed antipsychotic agents and the intake of an investigational drug to exclusion criterion #25; Added discontinuation criteria related to absolute neutrophil count; Changes and additional information were added to Table 4 (allowed medications); Additional details were added to trial procedures; Key secondary efficacy endpoints were deleted; Added Table 6; Changes and additional information to endpoints and analyses were added; Additional details were added to the timing of dose administration (Section 7.4.1.3.2), labeling (Section 7.4.1.5.3), and packaging (Section 7.7.1.2); Additional details were added to statistical analysis sections of protocol; Other editorial corrections, minor clarifications, and additional information were provided.
03 August 2011	The second protocol amendment, included the following changes: Trial Flow Charts, Open-Label Treatment Period, removed the "x" for the Columbia Suicidal Severity Rating Scale (C-SSRS) at Day 1; Participant Exclusion Criteria, 7.3.2.1 Open-Label Treatment Period, Medical, under criteria #3, the second paragraph was given a new designation: 3A; Subject Exclusion Criteria, 7.3.2.1 Open-Label Treatment Period, Psychiatric, under criterion #17: revision to C-SSRS text; Participant Discontinuation Criteria, inclusion of new criterion #4 (Y-MRS/MADRS ≥16) for participant discontinuation from treatment; Concomitant Medications, Supplements, and Other Substances Allowed During Trial, Table 4, text for benzodiazepine and diazepam dosing was revised and clarified; Screening and Administrative Procedures Not Including Safety and Efficacy Baseline Measurements, had new text added to item #10 header; Procedures for Safety Assessments, Table 5 Laboratory Tests to include the following tests under Urinalysis: urine pregnancy test, urine drug screen, nitrite, urobilinogen, leukocyte esterase, and the deletion of microscopic exam; Serious Adverse Event, had "cancer" added as serious adverse event outcome #6; CME, #1, replacement of Drug Induced Liver Injury (DILI) text per Sponsor standards and latest Food and Drug Administration (FDA) guidance; CME, #5, a new event (suicidal ideation and/or behavior) was added; Deletion of the following sections: Section 7.7.2.2.7, Medication Error; 7.7.2.2.8; Potential Medication Error; and 7.7.2.2.9, Incident; Expedited Reporting of Safety Observations by the Investigator to the Sponsor,"5. Incidents associated with the device" was deleted; Statistical Method for Exploratory Safety Analysis, Table 6, Tier 3, the safety endpoint "heart rate" was replaced with "pulse rate."

06 October 2011	The third protocol amendment, included the following changes: Trial Flow Chart, Open-Label Treatment Period, footnote b example was corrected; Trial Flow Chart, Open-Label Treatment Period, footnote i was deleted; Trial Flow Chart, Open-Label Treatment Period, footnote j was clarified by adding text specific to urine drug screen requirements for participants who meet stabilization and enter double-blind period; Trial Flow Chart, Open-Label Treatment Period, footnote o was clarified by adding text specific to C-SSRS completion on Day 3 of open-label; Trial Flow Chart, Open-Label Treatment Period, footnote q was revised to clarify fasting blood draw requirements; Trial Flow Chart, Double-Blind Treatment Period, footnote e was deleted; Procedures for Efficacy Assessments, text specific to monitoring of the Mini International Neuropsychiatric Interview (MINI), the Y-MRS, and the MADRS was removed; Monitoring Liver Enzymes was updated to be consistent with FDA DILI guidance and; Pharmacogenetic Specimen Handling and Shipping Instructions were updated in Appendix 1 to reflect ambient shipping on the day of collection.
20 August 2014	The fourth protocol amendment, included the following changes: Sponsor's name, Schering Plough, Schering, Schering Plough Research Institute, and Merck was changed to Forest Research Institute, Inc. (as well as Sponsor address where required); Global Pharmacovigilance was changed to Pharmacovigilance and Risk Management and; Section 12 was amended to clarify the specimen sampling, processing, labeling, storage, and shipment according to Forest Research Institute, Inc. SOPs due to the Sponsor change.
05 December 2014	The fifth protocol amendment included the following changes: Title Page, trial physician/director was changed from Maju Mathews to Armin Szegedi, MD, due to personnel changes; Amended Section 2 to reflect changes to the sample size within Statistical Methods; Added three additional references and; Sections 7.3.4 and 8.4 were updated to reflect the changes in the sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported