Clinical trial results:
A Phase 3b, Multicenter, Double-Blind, Fixed-Dose, Parallel-Group, Three Week Placebo Controlled Trial Evaluating the Safety and Efficacy of Asenapine in Subjects With Bipolar 1 Disorder Experiencing an Acute Manic or Mixed Episode (Protocol P05691 [Formerly 041044])

Summary

EudraCT number	2010-018409-13
Trial protocol	BG
Global end of trial date	28 May 2014

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	10 April 2015

Trial information

Trial identification

Sponsor protocol code	P05691

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00764478
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: MK-8274-003

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	28 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial will study the efficacy and safety of a fixed dose of asenapine in participants diagnosed with Bipolar 1 Disorder. Participants who qualify for the study will be randomly assigned to receive a fixed dose of asenapine (either 5 mg or 10 mg twice daily [BID]) or placebo (BID) for 3 weeks. Throughout the trial, observations will be made on each participant at various times to assess the safety and effectiveness of the study treatment. The primary hypothesis is that there is at least one dose of asenapine that is superior to placebo in the change from baseline in manic symptoms (as measured by Young Mania Rating Scale [YMRS]) at Day 21 of the trial.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 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: 46
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Ukraine: 16
Country: Number of subjects enrolled	United States: 271
Worldwide total number of subjects	367
EEA total number of subjects	59

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)	360
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were 18 years of age with a current diagnosis of bipolar I disorder, with current manic or mixed episode, and who must have discontinued use of all prohibited psychotropic medication.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Asenapine 5 mg BID

Arm description:

Participants were administered one asenapine 5 mg tablet, sublingually twice daily (BID) for 21 days.

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:

Asenapine tablet, 5 mg sublingually, BID for 21 days

Arm title	Asenapine 10 mg BID

Arm description:

Participants were administered one asenapine 10 mg tablet, sublingually BID for 21 days.

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:

Asenapine tablet, 10 mg sublingually BID for 21 days.

Arm title	Placebo

Arm description:

Participants were administered one asenapine-matched placebo tablet sublingually BID for 21 days.

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:
Placebo sublingual tablet, administered BID for 21 days.

Number of subjects in period 1	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo
Started	122	119	126
Completed	107	97	118
Not completed	15	22	8
Consent withdrawn by subject	7	12	1
Adverse event, non-fatal	1	1	1
Lost to follow-up	7	8	5
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Asenapine 5 mg BID
Reporting group description:	
Participants were administered one asenapine 5 mg tablet, sublingually twice daily (BID) for 21 days.	
Reporting group title	Asenapine 10 mg BID
Reporting group description:	
Participants were administered one asenapine 10 mg tablet, sublingually BID for 21 days.	
Reporting group title	Placebo
Reporting group description:	
Participants were administered one asenapine-matched placebo tablet sublingually BID for 21 days.	

Reporting group values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo
Number of subjects	122	119	126
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 44.3 ± 10.82	 42.5 ± 11.06	 44.6 ± 11.54
Gender categorical Units: Subjects			
Female	65	64	72
Male	57	55	54

Reporting group values	Total		
Number of subjects	367		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	201		
Male	166		

End points

End points reporting groups

Reporting group title	Asenapine 5 mg BID
Reporting group description:	
Participants were administered one asenapine 5 mg tablet, sublingually twice daily (BID) for 21 days.	
Reporting group title	Asenapine 10 mg BID
Reporting group description:	
Participants were administered one asenapine 10 mg tablet, sublingually BID for 21 days.	
Reporting group title	Placebo
Reporting group description:	
Participants were administered one asenapine-matched placebo tablet sublingually BID for 21 days.	

Primary: Change from baseline in Young Mania Rating Scale (Y-MRS) total score at Day 21

End point title	Change from baseline in Young Mania Rating Scale (Y-MRS) total score at Day 21
End point description:	
Y-MRS consists of responses to the following 11 items: elevated mood, increased motor activity energy, sexual interest, sleep, language-thought disorder, appearance, insight, irritability, speech - rate and amount, content and disruptive-agressive behavior. The scores from the 11 items are summed to give a total score ranging from 0 to 60, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a mixed model repeated measures (MMRM) model. An improvement in symptoms is represented by change from baseline values that are negative.	
End point type	Primary
End point timeframe:	
Baseline and Day 21	

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Score on a scale				
least squares mean (standard error)	-14.4 (± 1.02)	-14.9 (± 1.04)	-10.9 (± 0.99)	

Statistical analyses

Statistical analysis title	Y-MRS total at Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0136 [1]
Method	MMRM
Parameter estimate	Least Square (LS) means difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	1.41

Notes:

[1] - Adjusted p-value from graphical approach to control Type 1 error rate among primary and secondary hypotheses

Statistical analysis title	Y-MRS total at day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [2]
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	-1.2
Variability estimate	Standard error of the mean
Dispersion value	1.43

Notes:

[2] - Adjusted p-value from graphical approach to control Type 1 error rate among primary and secondary hypotheses

Secondary: Change from baseline in Clinical Global Impression – Bipolar Mania – Severity of Illness (CGI-BP-S) overall score at Day 21

End point title	Change from baseline in Clinical Global Impression – Bipolar Mania – Severity of Illness (CGI-BP-S) overall score at Day 21

End point description:

The CGI-BP-S is a score that measures the severity of overall bipolar illness. The score ranges on a scale from 1 to 7, where 1 is normal, and 7 is very severely ill. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. One participant from the Placebo BID arm missed a baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	125	
Units: Score on a scale				
least squares mean (standard error)	-1.6 (± 0.12)	-1.7 (± 0.12)	-1.1 (± 0.11)	

Statistical analyses

Statistical analysis title	CGI-BP-S at Day 21: 5 mg Asenapine - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [3]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[3] - Adjusted p-value from Hochberg's method for testing two secondary efficacy hypotheses

Statistical analysis title	CGI-BP-S at Day 21: 10 mg Asenapine - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052 [4]
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[4] - Adjusted p-value from Hochberg's method for testing two secondary efficacy hypotheses

Secondary: Percentage of participants who are Y-MRS responders at Day 21

End point title	Percentage of participants who are Y-MRS responders at Day 21

End point description:

Y-MRS consists of responses to the following 11 items: elevated mood, increased motor activity energy, sexual interest, sleep, language-thought disorder, appearance, insight, irritability, speech - rate and amount, content and disruptive-agressive behavior. The scores from the 11 items are summed to give a total score ranging from 0 to 60, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. Missing data were imputed by Last Observation Carried Forward (LOCF). Y-MRS responders are defined as having a >= 50% decrease from baseline in Y-MRS total score.

End point type	Secondary

End point timeframe:

Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Percentage of participants				
number (not applicable)	45	46.9	39.7	

Statistical analyses

Statistical analysis title	Y-MRS responders Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5352 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - Overall adjusted p-value from Hochberg's method for testing two secondary efficacy hypotheses

Statistical analysis title	Y-MRS responders Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4274 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Overall adjusted p-value from Hochberg's method for testing two secondary efficacy hypotheses

Secondary: Change from baseline in Y-MRS total score at Day 2, Day 4, Day 7 and Day 14

End point title	Change from baseline in Y-MRS total score at Day 2, Day 4, Day 7 and Day 14

End point description:

Y-MRS consists of responses to the following 11 items: elevated mood, increased motor activity energy, sexual interest, sleep, language-thought disorder, appearance, insight, irritability, speech - rate and amount, content and disruptive-agressive behavior. The scores from the 11 items are summed to give a total score ranging from 0 to 60, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative

End point type	Secondary

End point timeframe:

Baseline and Day 2, Day 4, Day 7 and Day 14

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Score on a scale				
least squares mean (standard error)				
Day 2	-5.6 (± 0.57)	-5.8 (± 0.59)	-2.9 (± 0.56)	
Day 4	-8.6 (± 0.67)	-8.6 (± 0.68)	-4.9 (± 0.64)	
Day 7	-10 (± 0.81)	-10.7 (± 0.83)	-6.6 (± 0.79)	
Day 14	-11.1 (± 0.98)	-12.5 (± 1)	-9.4 (± 0.95)	

Statistical analyses

Statistical analysis title	Y-MRS total at Day 2: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	0.78

Statistical analysis title	Y-MRS total at Day 2: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	0.79

Statistical analysis title	Y-MRS total at Day 4: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	-1.8
Variability estimate	Standard error of the mean
Dispersion value	0.91

Statistical analysis title	Y-MRS total at Day 4: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	-1.9
Variability estimate	Standard error of the mean
Dispersion value	0.92

Statistical analysis title	Y-MRS total at Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	1.12

Statistical analysis title	Y-MRS total at Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	-2
Variability estimate	Standard error of the mean
Dispersion value	1.13

Statistical analysis title	Y-MRS total at Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1907
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	1.35

Statistical analysis title	Y-MRS total at Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0238
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	1.37

Secondary: Percentage of participants who are Y-MRS responders at Day 2, Day 4, Day 7, Day 14

End point title	Percentage of participants who are Y-MRS responders at Day 2, Day 4, Day 7, Day 14

End point description:

Y-MRS consists of responses to the following 11 items: elevated mood, increased motor activity energy, sexual interest, sleep, language-thought disorder, appearance, insight, irritability, speech - rate and amount, content and disruptive-agressive behavior. The scores from the 11 items are summed to give a total score ranging from 0 to 60, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement, and had evaluable post-baseline measurement at timepoint. Missing data were imputed by LOCF. Y-MRS responders are defined as having a >= 50% decrease from baseline in Y-MRS total score.

End point type	Secondary

End point timeframe:

Day 2, Day 4, Day 7, Day 14

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Percentage of participants				
number (not applicable)				
Day 2 (n=117,111,123)	12	14.4	8.9	
Day 4 (n=120,113,126)	21.7	23	8.7	
Day 7 (n=120,113,126)	31.7	28.3	19.8	
Day 14 (n=120,113,126)	36.7	40.7	33.3	

Statistical analyses

Statistical analysis title	Y-MRS Responders Day 2: Asenapine 5 mg - Placebo
Statistical analysis description: Number of participants analyzed = 240	
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2922
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS Responders Day 2: Asenapine 10 mg - Placebo
Statistical analysis description: Number of participants analyzed = 234	
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS Responders Day 4: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS Responders Day 4: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS Responders Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0194
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS responders Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0841
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS responders Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4858
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS responders Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2496
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of participants who are Y-MRS remitters at Day 21

End point title	Percentage of participants who are Y-MRS remitters at Day 21

End point description:

Y-MRS consists of responses to the following 11 items: elevated mood, increased motor activity energy, sexual interest, sleep, language-thought disorder, appearance, insight, irritability, speech - rate and amount, content and disruptive-agressive behavior. The 11 items are summed to give a total score ranging from 0 to 60, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one post-baseline measurement. Missing data were imputed by LOCF. Y-MRS remitters are defined as having a Y-MRS total score of 12 or lower.

End point type	Secondary

End point timeframe:

Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Percentage of participants				
number (not applicable)	34.2	38.1	30.2	

Statistical analyses

Statistical analysis title	Y-MRS remitters Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2912
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Y-MRS remitters Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1151
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of participants who are Y-MRS remitters at Day 2, Day 4, Day 7, Day 14, Day 21

End point title	Percentage of participants who are Y-MRS remitters at Day 2, Day 4, Day 7, Day 14, Day 21

End point description:

Y-MRS consists of responses to the following 11 items: elevated mood, increased motor activity energy, sexual interest, sleep, language-thought disorder, appearance, insight, irritability, speech - rate and amount, content and disruptive-agressive behavior. The scores from the 11 items are summed to give a total score ranging from 0 to 60, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one post-baseline measurement, and had evaluable post-baseline measurement at timepoint. The analysis is based on a generalized linear mixed model (GLMM). Y-MRS remitters are defined as having a Y-MRS total score of 12 or lower.

End point type	Secondary

End point timeframe:

Day 2, Day 4, Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Percentage of participants				
number (not applicable)				
Day 2 (n=117,111, 123)	8.5	11.7	5.7	
Day 4 (n= 104, 106,118)	17.3	15.1	10.2	
Day 7 (n= 104, 101,110)	26.9	24.8	17.3	
Day 14 (n= 96, 91,102)	28.1	27.5	24.5	
Day 21 (n= 86, 83,93)	40.7	43.4	34.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) total score

End point title	Change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) total score

End point description:

The MADRS measures depression and consists of 10 items, each rated on a scale from 0 to 6. The MADRS total score sums the scores from the 10 items, ranging from 0 to 60, with a higher numeric rating implying a greater degree of symptom severity. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline

measurement, and had evaluable post-baseline measurement at timepoint. Missing data were imputed by LOCF. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7 and Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7 (n=112,106, 117)	-4.3 (± 0.47)	-4.2 (± 0.48)	-2.3 (± 0.46)	
Day 21 (n =115, 110,123)	-4.6 (± 0.61)	-5.1 (± 0.63)	-2.5 (± 0.6)	

Statistical analyses

Statistical analysis title	MADRS Total Day 7: Asenapine 5 mg - Placebo

Statistical analysis description:

Number of participants analyzed = 229

Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	ANCOVA

Statistical analysis title	MADRS Total Day 7: Asenapine 10 mg - Placebo

Statistical analysis description:

Number of participants analyzed = 223

Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045
Method	ANCOVA

Statistical analysis title	MADRS Total Day 21: Asenapine 5 mg - Placebo

Statistical analysis description:

Number of participants analyzed = 238

Comparison groups	Asenapine 5 mg BID v Placebo

Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0112
Method	ANCOVA

Statistical analysis title	MADRS Total Day 21: Asenapine 10 mg - Placebo
Statistical analysis description: Number of participants analyzed = 233	
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	ANCOVA

Secondary: Change from baseline in CGI-BP-S overall score at Day 2, Day 4, Day 7, Day 14

End point title	Change from baseline in CGI-BP-S overall score at Day 2, Day 4, Day 7, Day 14

End point description:

The CGI-BP-S is a score that measures the severity of overall bipolar illness. The score ranges on a scale from 1 to 7, where 1 is normal, and 7 is very severely ill. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. One participant from the Placebo BID arm missed a baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 2, Day 4, Day 7, Day 14

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	125	
Units: Score on a scale				
least squares mean (standard error)				
Day 2	-0.5 (± 0.05)	-0.4 (± 0.06)	-0.2 (± 0.05)	
Day 4	-0.8 (± 0.07)	-0.7 (± 0.07)	-0.4 (± 0.07)	
Day 7	-1 (± 0.09)	-1.1 (± 0.09)	-0.7 (± 0.09)	
Day 14	-1.3 (± 0.1)	-1.3 (± 0.11)	-1 (± 0.1)	

Statistical analyses

Statistical analysis title	CGI-BP-S Overall Day 2: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	CGI-BP-S Overall Day 2: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0076
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	CGI-BP-S Overall Day 4: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	CGI-BP-S Overall Day 4: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	CGI-BP-S Overall Day 7: Asenapine 5 mg - Placebo
Comparison groups	Placebo v Asenapine 5 mg BID
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0061
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	CGI-BP-S Overall Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo

Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0031
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	CGI-BP-S Overall Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1086
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	CGI-BP-S Overall Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0376
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0

Variability estimate	Standard error of the mean
Dispersion value	0.15

Secondary: Change from baseline in CGI-BP-S mania score

End point title	Change from baseline in CGI-BP-S mania score

End point description:

The CGI-BP-S mania is a score that assesses the severity of the mania component of bipolar illness. The score ranges on a scale from 1 to 7, where 1 is normal, and 7 is very severely ill. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement, and had evaluable post-baseline measurement at timepoint. Missing data were imputed by LOCF. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 2, Day 4, Day 7, Day 14, and Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	125	
Units: Score on a scale				
least squares mean (standard error)				
Day 2 (n=118,111,122)	-0.4 (± 0.06)	-0.4 (± 0.06)	-0.1 (± 0.06)	
Day 4 (n=120,113,125)	-0.7 (± 0.07)	-0.7 (± 0.08)	-0.3 (± 0.07)	
Day 7 (n=120,113,125)	-0.9 (± 0.09)	-1 (± 0.09)	-0.7 (± 0.09)	
Day 14 (n=120,113,125)	-1.2 (± 0.1)	-1.3 (± 0.11)	-1 (± 0.1)	
Day 21 (n=120,113,125)	-1.4 (± 0.11)	-1.5 (± 0.12)	-1.1 (± 0.11)	

Statistical analyses

Statistical analysis title	CGI-BP-S Mania Day 2: Asenapine 5 mg - Placebo

Statistical analysis description:

Number of participants analyzed = 240

Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 2: Asenapine 10 mg - Placebo

Statistical analysis description:

Number of participants analyzed = 233

Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0026
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 4: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 4: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0387
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.311
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0613
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	ANCOVA

Statistical analysis title	CGI-BP-S Mania Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0139
Method	ANCOVA

Secondary: Change from baseline in CGI-BP-S depression score

End point title	Change from baseline in CGI-BP-S depression score

End point description:

The CGI-BP-S depression is a score that assesses the severity of the depression component of bipolar illness. The score ranges on a scale from 1 to 7, where 1 is normal, and 7 is very severely ill. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement, and had evaluable post-baseline measurement at timepoint. Missing data were imputed by LOCF. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:
Baseline and Day 2, Day 4, Day 7, Day 14, and Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	125	
Units: Score on a scale				
least squares mean (standard error)				
Day 2 (n=118,111,122)	-0.2 (± 0.06)	-0.2 (± 0.06)	-0.2 (± 0.06)	
Day 4 (n=120,113,125)	-0.3 (± 0.06)	-0.3 (± 0.06)	-0.3 (± 0.06)	
Day 7 (n=120,113,125)	-0.3 (± 0.07)	-0.4 (± 0.07)	-0.1 (± 0.07)	
Day 14 (n=120,113,125)	-0.4 (± 0.07)	-0.5 (± 0.07)	-0.2 (± 0.07)	
Day 21 (n=120,113,125)	-0.4 (± 0.08)	-0.5 (± 0.08)	-0.1 (± 0.08)	

Statistical analyses

Statistical analysis title	CGI-BP-S Depression Day 2: Asenapine 5 mg-Placebo
Statistical analysis description: Number of participants analyzed = 240	
Comparison groups	Placebo v Asenapine 5 mg BID
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9708
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 2: Asenapine 10 mg-Placebo
Statistical analysis description: Number of participants analyzed = 233	
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7891
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 4: Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5222
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 4: Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8686
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 7: Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0696
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 7: Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0049
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 14: Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0196
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 14:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 21: Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0061
Method	ANCOVA

Statistical analysis title	CGI-BP-S Depression Day 21:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	ANCOVA

Secondary: Percentage of participants who are CGI-BP Improvement (CGI-BP-I) Responders of Overall Bipolar Illness Score

End point title	Percentage of participants who are CGI-BP Improvement (CGI-BP-I) Responders of Overall Bipolar Illness Score

End point description:

The CGI-BP-I overall is a score on a 7-point scale for assessing the change from preceding phase of overall symptoms of bipolar disorder during the treatment of an acute episode or in longer term illness prophylaxis. Compared to the baseline, the CGI-BP-I overall score ranges from 1 = very much improved since initiating treatment, to 7 = very much worse since initiating treatment. Results reported for all randomized participants who received at least one dose of trial medication and had at least one post-baseline measurement, and had evaluable post-baseline measurement at timepoint. Missing data were imputed by LOCF. A CGI-BP-I responder had a score of 3 (minimally improved) or lower.

End point type	Secondary

End point timeframe:

Day 2, Day 4, Day 7, Day 14, and Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Percentage of participants				
number (not applicable)				
Day 2 (n=118,111,123)	50.8	45.9	37.4	
Day 4 (n=120,113,126)	64.2	64.6	55.6	
Day 7 (n=120,113,126)	73.3	78.8	61.1	
Day 14 (n=120,113,126)	70.8	83.2	65.1	
Day 21 (n=120,113,126)	74.2	82.3	64.3	

Statistical analyses

Statistical analysis title	CGI-BP-I Resp.Overall Day 2:Asenapine 5 mg-Placebo
Statistical analysis description: Number of participants analyzed = 241	
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0147
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 2:Asenapine 10mg-Placebo
Statistical analysis description: Number of participants analyzed = 234	
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 4:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1213
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 4:Asenapine 10mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0588
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 7:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 7:Asenapine 10mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 14:Asenapine 5mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2401
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 14:Asenapine10mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp.Overall Day 21:Asenapine 5mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0525
Method	Chi-squared corrected

Statistical analysis title	CGI-BP-I Resp.Overall Day 21:Asenapine10mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of participants who are CGI-BP-I Responders of Mania Score

End point title	Percentage of participants who are CGI-BP-I Responders of Mania Score

End point description:

The CGI-BP-I mania is a score on a 7-point scale for assessing the change from preceding phase of mania symptoms of bipolar disorder during the treatment of an acute episode or in longer term illness prophylaxis. Compared to the baseline, the CGI-BP-I mania score ranges from 1 = very much improved since initiating treatment, to 7 = very much worse since initiating treatment. Results reported for all randomized participants who received at least one dose of trial medication and had at least one post-baseline measurement, and had evaluable post-baseline measurement at timepoint. Missing data were imputed by LOCF. A CGI-BP-I responder had a score of 3 (minimally improved) or lower.

End point type	Secondary

End point timeframe:

Day 2, Day 4, Day 7, Day 14, and Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	113	126	
Units: Percentage of participants				
number (not applicable)				
Day 2 (n=118,111,123)	49.2	45.9	37.4	
Day 4 (n=120,113,126)	64.2	66.4	55.6	
Day 7 (n=120,113,126)	74.2	80.5	63.5	
Day 14 (n=120,113,126)	75.8	82.3	66.7	
Day 21 (n=120,113,126)	79.2	84.1	66.7	

Statistical analyses

Statistical analysis title	CGI-BP-I Resp. Mania Day 2:Asenapine 5 mg-Placebo
Statistical analysis description: Number of participants analyzed = 241	
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0377
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 2:Asenapine 10 mg-Placebo
Statistical analysis description: Number of participants analyzed = 234	
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0771
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 4:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1264
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 4:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 7:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0583
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 7:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 14:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0866
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 14:Asenapine 10mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0048
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 21:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0147
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Mania Day 21:Asenapine 10mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of participants who are CGI-BP-I Responders of Depression Score

End point title	Percentage of participants who are CGI-BP-I Responders of Depression Score

End point description:

The CGI-BP-I depression is a score on a 7-point scale for assessing the change from preceding phase of depression symptoms of bipolar disorder during the treatment of an acute episode or in longer term illness prophylaxis. Compared to the baseline, the CGI-BP-I depression score ranges from 1 = very much improved since initiating treatment, to 7 = very much worse since initiating treatment. Results reported for all randomized participants who received at least one dose of trial medication and had at least one post-baseline measurement, and had evaluable post-baseline measurement at timepoint. Missing data were imputed by LOCF. A CGI-BP-I responder had a score of 3 (minimally improved) or lower.

End point type	Secondary

End point timeframe:

Day 2, Day 4, Day 7, Day 14, and Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	106	121	
Units: Percentage of participants				
number (not applicable)				
Day 2 (n=113, 103, 116)	21.2	28.2	11.2	
Day 4 (n=116, 106, 119)	26.7	32.1	19.3	
Day 7 (n=117, 106, 119)	31.6	35.8	23.5	
Day 14 (n=117, 106, 120)	31.6	42.5	26.7	
Day 21 (n=117, 106, 121)	32.5	44.3	28.9	

Statistical analyses

Statistical analysis title	CGI-BP-I Resp. Depr. Day 2: Asenapine 5 mg-Placebo
Statistical analysis description: Number of participants analyzed = 229	
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0104
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 2:Asenapine 10 mg-Placebo
Statistical analysis description: Number of participants analyzed = 219	
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 4:Asenapine 5 mg-Placebo
Statistical analysis description: Number of participants analyzed = 235	
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0692
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 4:Asenapine 10 mg-Placebo
Statistical analysis description: Number of participants analyzed = 225	
Comparison groups	Asenapine 10 mg BID v Placebo

Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0128
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 7:Asenapine 5 mg-Placebo
Statistical analysis description: Number of participants analyzed = 236	
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0809
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 7:Asenapine 10 mg-Placebo
Statistical analysis description: Number of participants analyzed = 225	
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 14:Asenapine 5 mg-Placebo
Statistical analysis description: Number of participants analyzed = 237	
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2576
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 14:Asenapine 10mg-Placebo
Statistical analysis description: Number of participants analyzed = 226	
Comparison groups	Asenapine 10 mg BID v Placebo

Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 21:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.396
Method	Cochran-Mantel-Haenszel

Statistical analysis title	CGI-BP-I Resp. Depr. Day 21:Asenapine 10mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0141
Method	Cochran-Mantel-Haenszel

Secondary: Change from baseline in Positive And Negative Syndrome Scale (PANSS) total score

End point title	Change from baseline in Positive And Negative Syndrome Scale (PANSS) total score

End point description:

PANSS total score measures symptoms of schizophrenia and consists of responses to 30 items: 7 items from the positive subscale (P1-P7), 7 items from the negative subscale (N1-N7) and 16 items from the general psychopathology subscale (G1-G16). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS total score sums the scores from all 30 items, and ranges from 30 to 210, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-6.9 (± 0.77)	-6.9 (± 0.79)	-3.9 (± 0.76)	
Day 14	-7.5 (± 0.96)	-8.4 (± 0.99)	-5.2 (± 0.94)	
Day 21	-9.3 (± 1.02)	-8.8 (± 1.05)	-5.5 (± 1)	

Statistical analyses

Statistical analysis title	PANSS Total Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	1.06

Statistical analysis title	PANSS Total Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	-0.8
Variability estimate	Standard error of the mean
Dispersion value	1.08

Statistical analysis title	PANSS Total Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0743
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	1.33

Statistical analysis title	PANSS Total Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0177
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	1.35

Statistical analysis title	PANSS Total Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0081
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	-1
Variability estimate	Standard error of the mean
Dispersion value	1.41

Statistical analysis title	PANSS Total Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0247
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	1.43

Secondary: Change from baseline in PANSS Negative subscale score

End point title	Change from baseline in PANSS Negative subscale score

End point description:

PANSS Negative subscale measures symptoms of schizophrenia and consists of responses to 7 items (N1-N7). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS Negative subscale sums the scores from all 7 items and ranges from 7 to 49, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-0.5 (± 0.22)	-0.8 (± 0.22)	-0.5 (± 0.21)	
Day 14	-0.8 (± 0.23)	-0.7 (± 0.24)	-0.8 (± 0.23)	
Day 21	-0.4 (± 0.28)	0 (± 0.29)	-0.4 (± 0.27)	

Statistical analyses

Statistical analysis title	PANSS Negative Day 7: Asenapine 5 mg - Placebo
Comparison groups	Placebo v Asenapine 5 mg BID
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9808
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	PANSS Negative Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.31

Statistical analysis title	PANSS Negative Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9751
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	PANSS Negative Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7879
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.33

Statistical analysis title	PANSS Negative Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9654
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.38

Statistical analysis title	PANSS Negative Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3917
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.39

Secondary: Change from baseline in PANSS Positive subscale score

End point title	Change from baseline in PANSS Positive subscale score

End point description:

PANSS Positive subscale measures symptoms of schizophrenia and consists of responses to 7 items (P1-P7). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS Positive subscale sums the scores from all 7 items and ranges from 7 to 49, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-2.4 (± 0.3)	-2.8 (± 0.31)	-1.4 (± 0.29)	
Day 14	-2.3 (± 0.37)	-3.2 (± 0.38)	-2.1 (± 0.36)	
Day 21	-3.5 (± 0.37)	-3.9 (± 0.38)	-2.4 (± 0.36)	

Statistical analyses

Statistical analysis title	PANSS Positive Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.41

Statistical analysis title	PANSS Positive Day 7: Asenapine 10 mg - Placebo
Comparison groups	Placebo v Asenapine 10 mg BID
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.42

Statistical analysis title	PANSS Positive Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6885
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.51

Statistical analysis title	PANSS Positive Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0398
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.52

Statistical analysis title	PANSS Positive Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0258
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.51

Statistical analysis title	PANSS Positive Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0031
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.51

Secondary: Change from baseline in PANSS General Psychopathology subscale score

End point title	Change from baseline in PANSS General Psychopathology subscale score

End point description:

PANSS General Psychopathology subscale measures symptoms of schizophrenia and consists of responses to 16 items (G1-G16). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS General Psychopathology subscale sums the scores from all 16 items and ranges from 16 to 112, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-4 (± 0.46)	-3.3 (± 0.48)	-2.1 (± 0.46)	
Day 14	-4.5 (± 0.57)	-4.6 (± 0.59)	-2.4 (± 0.56)	
Day 21	-5.5 (± 0.61)	-4.9 (± 0.62)	-2.9 (± 0.59)	

Statistical analyses

Statistical analysis title	PANSS Gen. Psych. Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.64

Statistical analysis title	PANSS Gen. Psych. Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0622
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.65

Statistical analysis title	PANSS Gen. Psych. Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0083
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.79

Statistical analysis title	PANSS Gen. Psych. Day 14:Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0064
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.8

Statistical analysis title	PANSS Gen. Psych. Day 21:Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	0.84

Statistical analysis title	PANSS Gen. Psych. Day 21:Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0196
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.85

Secondary: Change from baseline in PANSS Marder Factor Positive symptom score

End point title	Change from baseline in PANSS Marder Factor Positive symptom score

End point description:

PANSS Marder Factor Positive symptom score measures symptoms of schizophrenia and consists of responses to 8 items (P1,P3,P5,P6,N7,G1,G9,G12). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS Marder Factor Positive symptom score sums the scores from all 8 items and ranges from 8 to 56, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-1.9 (± 0.29)	-1.9 (± 0.29)	-1.3 (± 0.28)	
Day 14	-1.6 (± 0.33)	-2.5 (± 0.34)	-1.6 (± 0.33)	
Day 21	-2.6 (± 0.34)	-2.9 (± 0.35)	-1.7 (± 0.33)	

Statistical analyses

Statistical analysis title	PANSS Mard. Pos. Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1883
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	PANSS Mard. Pos. Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1684
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	PANSS Mard. Pos. Day 14: Asenapine 5 mg - Placebo
Comparison groups	Placebo v Asenapine 5 mg BID
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9522
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.46

Statistical analysis title	PANSS Mard. Pos. Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0514
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.47

Statistical analysis title	PANSS Mard. Pos. Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0531
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.47

Statistical analysis title	PANSS Mard. Pos. Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.48

Secondary: Change from baseline in PANSS Marder Factor Negative symptom score

End point title	Change from baseline in PANSS Marder Factor Negative symptom score

End point description:

PANSS Marder Factor Negative symptom score measures symptoms of schizophrenia and consists of responses to 7 items (N1,N2,N3,N4,N6,G7,G16). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS Marder Factor Negative symptom score sums the scores from all 7 items and ranges from 7 to 49, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-0.5 (± 0.23)	-0.8 (± 0.24)	-0.5 (± 0.23)	
Day 14	-0.6 (± 0.24)	-0.5 (± 0.25)	-0.7 (± 0.24)	
Day 21	-0.1 (± 0.27)	0.1 (± 0.28)	-0.1 (± 0.27)	

Statistical analyses

Statistical analysis title	PANSS Mard. Neg. Day 7: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7746
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	PANSS Mard. Neg. Day 7: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2754
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	PANSS Mard. Neg. Day 14: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9109
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.34

Statistical analysis title	PANSS Mard. Neg. Day 14: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7295
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.34

Statistical analysis title	PANSS Mard. Neg. Day 21: Asenapine 5 mg - Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	0.38

Statistical analysis title	PANSS Mard. Neg. Day 21: Asenapine 10 mg - Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5122
Method	MMRM
Parameter estimate	LS means difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.38

Secondary: Change from baseline in PANSS Marder Factor Disorganized Thought symptom score

End point title	Change from baseline in PANSS Marder Factor Disorganized Thought symptom score

End point description:

PANSS Marder Factor Disorganized Thought symptom score measures symptoms of schizophrenia and consists of responses to 7 items (P2,N5,G5,G10,G11,G13,G15). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS Marder Factor Disorganized Thought symptom score sums the scores from all 7 items and ranges from 7 to 49, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-1.1 (± 0.21)	-1.3 (± 0.22)	-0.7 (± 0.21)	
Day 14	-1.5 (± 0.26)	-1.8 (± 0.27)	-1.2 (± 0.26)	
Day 21	-2 (± 0.28)	-1.7 (± 0.29)	-1.5 (± 0.27)	

Statistical analyses

Statistical analysis title	PANSS Mard. Disorg. Day 7:Asenapine 5mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2191
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.29

Statistical analysis title	PANSS Mard. Disorg. Day 7:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0589
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.29

Statistical analysis title	PANSS Mard. Disorg. Day 14:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3683
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.36

Statistical analysis title	PANSS Mard. Disorg. Day 14:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0982
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.37

Statistical analysis title	PANSS Mard. Disorg. Day 21:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1969
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.38

Statistical analysis title	PANSS Mard. Disorg. Day 21:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5615
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.39

Secondary: Change from baseline in PANSS Marder Factor Hostility/Excitement symptom score

End point title	Change from baseline in PANSS Marder Factor Hostility/Excitement symptom score

End point description:

PANSS Marder Factor Hostility/Excitement symptom score measures symptoms of schizophrenia and consists of responses to 4 items (P4,P7,G8,G14). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS Marder Factor Hostility/Excitement symptom score sums the score from all 4 items and ranges from 4 to 28, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-1.7 (± 0.24)	-1.7 (± 0.25)	-0.9 (± 0.24)	
Day 14	-1.8 (± 0.28)	-2 (± 0.29)	-1.2 (± 0.27)	
Day 21	-2.6 (± 0.29)	-2.5 (± 0.3)	-1.5 (± 0.28)	

Statistical analyses

Statistical analysis title	PANSS Mard. Hostil. Day 7:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0101
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.33

Statistical analysis title	PANSS Mard. Hostil. Day 7:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0146
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.34

Statistical analysis title	PANSS Mard. Hostil. Day 14:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0861
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.39

Statistical analysis title	PANSS Mard. Hostil. Day 14:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0342
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.39

Statistical analysis title	PANSS Mard. Hostil. Day 21:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	PANSS Mard. Hostil. Day 21:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0096
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.41

Secondary: Change from baseline in PANSS Marder Factor Anxiety/Depression symptom score

End point title	Change from baseline in PANSS Marder Factor Anxiety/Depression symptom score

End point description:

PANSS Marder Factor Anxiety/Depression symptom score measures symptoms of schizophrenia and consists of responses to 4 items (G2,G3,G4,G6). Responses to each item range from 1 = absence of symptom, to 7 = most extreme symptoms. The PANSS Marder Factor Anxiety/Depression symptom score sums the scores from all 4 items and ranges from 4 to 28, with a higher score indicating greater severity of symptoms. Results reported for all randomized participants who received at least one dose of trial medication and had at least one baseline and post-baseline measurement. The analysis is based on a MMRM model. An improvement in symptoms is represented by change from baseline values that are negative.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day14, Day 21

End point values	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	110	123	
Units: Score on a scale				
least squares mean (standard error)				
Day 7	-1.7 (± 0.24)	-1.3 (± 0.24)	-0.7 (± 0.23)	
Day 14	-2 (± 0.26)	-1.7 (± 0.27)	-0.7 (± 0.26)	
Day 21	-2.1 (± 0.3)	-1.9 (± 0.3)	-1 (± 0.29)	

Statistical analyses

Statistical analysis title	PANSS Mard. Anxiety Day 7:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.32

Statistical analysis title	PANSS Mard. Anxiety Day 7:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0791
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.33

Statistical analysis title	PANSS Mard. Anxiety Day 14:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.36

Statistical analysis title	PANSS Mard. Anxiety Day 14:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.37

Statistical analysis title	PANSS Mard. Anxiety Day 21:Asenapine 5 mg-Placebo
Comparison groups	Asenapine 5 mg BID v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.41

Statistical analysis title	PANSS Mard. Anxiety Day 21:Asenapine 10 mg-Placebo
Comparison groups	Asenapine 10 mg BID v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	MMRM
Parameter estimate	LS means difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.41

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 33 days after end of treatment (up to 54 days)	
Adverse event reporting additional description:	
Randomized participants who received at least one dose of trial medication	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Asenapine 5 mg BID
Reporting group description:	
Participants were administered one asenapine 5 mg tablet, sublingually twice daily (BID) for 21.	
Reporting group title	Asenapine 10 mg BID
Reporting group description:	
Participants were administered one asenapine 10 mg tablet, sublingually BID for 21 days.	
Reporting group title	Placebo
Reporting group description:	
Participants were administered one asenapine-matched placebo tablet sublingually BID for 21 days.	

Serious adverse events	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 122 (2.46%)	1 / 119 (0.84%)	2 / 126 (1.59%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 122 (0.00%)	0 / 119 (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
Foot fracture			
subjects affected / exposed	0 / 122 (0.00%)	0 / 119 (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
Road traffic accident			

subjects affected / exposed	0 / 122 (0.00%)	0 / 119 (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			
Bipolar I disorder			
subjects affected / exposed	2 / 122 (1.64%)	0 / 119 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 122 (0.82%)	0 / 119 (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
Suicidal ideation			
subjects affected / exposed	0 / 122 (0.00%)	1 / 119 (0.84%)	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
Suicide attempt			
subjects affected / exposed	0 / 122 (0.00%)	1 / 119 (0.84%)	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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 119 (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	Asenapine 5 mg BID	Asenapine 10 mg BID	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 122 (35.25%)	67 / 119 (56.30%)	24 / 126 (19.05%)
Nervous system disorders			
Akathisia			

subjects affected / exposed	5 / 122 (4.10%)	18 / 119 (15.13%)	1 / 126 (0.79%)
occurrences (all)	5	25	1
Dizziness			
subjects affected / exposed	4 / 122 (3.28%)	6 / 119 (5.04%)	6 / 126 (4.76%)
occurrences (all)	5	6	6
Dysgeusia			
subjects affected / exposed	4 / 122 (3.28%)	11 / 119 (9.24%)	0 / 126 (0.00%)
occurrences (all)	4	11	0
Headache			
subjects affected / exposed	9 / 122 (7.38%)	6 / 119 (5.04%)	9 / 126 (7.14%)
occurrences (all)	10	7	11
Sedation			
subjects affected / exposed	12 / 122 (9.84%)	18 / 119 (15.13%)	2 / 126 (1.59%)
occurrences (all)	12	19	2
Somnolence			
subjects affected / exposed	12 / 122 (9.84%)	14 / 119 (11.76%)	3 / 126 (2.38%)
occurrences (all)	12	15	3
Gastrointestinal disorders			
Hypoaesthesia oral			
subjects affected / exposed	15 / 122 (12.30%)	27 / 119 (22.69%)	2 / 126 (1.59%)
occurrences (all)	15	28	2
Nausea			
subjects affected / exposed	4 / 122 (3.28%)	6 / 119 (5.04%)	4 / 126 (3.17%)
occurrences (all)	4	6	6
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 122 (0.82%)	7 / 119 (5.88%)	3 / 126 (2.38%)
occurrences (all)	1	7	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2012	Amendment 3: clarified fasting blood draw requirement; updated Closely Monitored Event to include Drug Hyperesensitivity Reactions; updated Monitoring Liver Enzymes to be consistent with guidance; updated Pharmacogenetic Specimen Handling and Shipping Instructions; Antiemetics containing dopamine agonist was changed to : Antiemetics containing dopamine antagonists.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported