Clinical trial results:
Efficacy and Safety of 3-Week Fixed-Dose Asenapine Treatment in Pediatric Acute Manic or Mixed Episodes Associated with Bipolar I Disorder (Protocol No. P06107)

Summary

EudraCT number	2010-022647-38
Trial protocol	Outside EU/EEA
Global end of trial date	17 September 2013

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	24 June 2015

Trial information

Trial identification

Sponsor protocol code	P06107

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01244815
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration number: MK-8274-038

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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000228-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy and safety of asenapine for the treatment of bipolar I disorder (manic or mixed episodes) will be evaluated in participants between 10 and 17 years old, who are either hospitalized or non-hospitalized. In this 3-weeks, double-blind, parallel design trial, eligible participants will be randomized to receive one out of three fixed dose levels of asenapine, or placebo. Study primary hypothesis is that at least one asenapine dose is superior to placebo as measured by the change from baseline to Day 21 in Young Mania Rating Scale (Y-MRS) total score. Concurrent use of psychotropics is prohibited, except use of short-acting benzodiazepines and psychostimulants approved for treatment of attention deficit hyperactivity disorder (ADHD). Participants who complete the trial may be offered to continue treatment with asenapine for an extended period of time. Follow-up information on safety parameters will be collected in all participants within 30 days following treatment discontinuation.

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. The following additional measure defined for this individual study was in place for the protection of trial subjects: For participants whose symptoms worsen or are not adequately controlled on assigned treatment, rescue medication may be administered during the trial in the following circumstances. For the control of agitation, anxiety, insomnia, restlessness, or akathisia and extrapyramidal symptoms (EPS) some benzodiazepines and EPS medications (i.e., anticholinergics) are allowed. Benadryl (diphenhydramine) and beta blockers are also permitted, provided that they are not taken within 8 hours of efficacy assessments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	United States: 378
Worldwide total number of subjects	404
EEA total number of subjects	0

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)	69
Adolescents (12-17 years)	335
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 537 participants were screened to determine eligibility for entry into the trial, of which 133 were excluded and not randomized.

Period 1

Period 1 title	Randomization through Start Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants receive placebo twice daily (BID) for 21 days.

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

Dosage and administration details:

Placebo tablets to match asenapine tablets, administered sublingually BID

Arm title	Asenapine 2.5 mg BID

Arm description:

Participants receive asenapine 2.5 mg BID for 21 days.

Arm type	Experimental
Investigational medicinal product name	asenapine
Investigational medicinal product code	
Other name	SCH 900274, Saphris®
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine tablets, administered sublingually BID at one of three dose levels (2.5 mg, 5.0 mg, or 10.0 mg)

Arm title	Asenapine 5.0 mg BID

Arm description:

Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. Participants receive asenapine 5.0 mg BID for the remainder of the 21-day treatment period.

Arm type	Experimental

Investigational medicinal product name	asenapine
Investigational medicinal product code	
Other name	SCH 900274, Saphris®
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine tablets, administered sublingually BID at one of three dose levels (2.5 mg, 5.0 mg, or 10.0 mg)

Arm title	Asenapine 10.0 mg BID

Arm description:

Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. On Day 5 and 6 participants receive asenapine 5.0 mg BID. On Day 7 participants receive asenapine 5.0 mg in the morning and 10.0 mg in the evening. Participants receive asenapine 10.0 mg BID for the remainder of the 21-day treatment period.

Arm type	Experimental
Investigational medicinal product name	asenapine
Investigational medicinal product code	
Other name	SCH 900274, Saphris®
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine tablets, administered sublingually BID at one of three dose levels (2.5 mg, 5.0 mg, or 10.0 mg)

Number of subjects in period 1	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Started	101	105	99
Completed	101	104	99
Not completed	0	1	0
Not Treated	-	1	-

Number of subjects in period 1	Asenapine 10.0 mg BID
Started	99
Completed	99
Not completed	0
Not Treated	-

Period 2

Period 2 title	Treatment through Study Completion
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants receive placebo BID for 21 days.

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

Dosage and administration details:

Placebo tablets to match asenapine tablets, administered sublingually BID

Arm title	Asenapine 2.5 mg BID

Arm description:

Participants receive asenapine 2.5 mg BID for 21 days.

Arm type	Experimental
Investigational medicinal product name	asenapine
Investigational medicinal product code	
Other name	SCH 900274, Saphris®
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine tablets, administered sublingually BID at one of three dose levels (2.5 mg, 5.0 mg, or 10.0 mg)

Arm title	Asenapine 5.0 mg BID

Arm description:

Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. Participants receive asenapine 5.0 mg BID for the remainder of the 21-day treatment period.

Arm type	Experimental
Investigational medicinal product name	asenapine
Investigational medicinal product code	
Other name	SCH 900274, Saphris®
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine tablets, administered sublingually BID at one of three dose levels (2.5 mg, 5.0 mg, or 10.0 mg)

Arm title	Asenapine 10.0 mg BID

Arm description:

Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. On Day 5 and 6 participants receive asenapine 5.0 mg BID. On Day 7 participants receive asenapine 5.0 mg in the morning and 10.0 mg in the evening. Participants receive asenapine 10.0 mg BID for the remainder of the 21-day treatment period.

Arm type	Experimental
Investigational medicinal product name	asenapine
Investigational medicinal product code	
Other name	SCH 900274, Saphris®
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine tablets, administered sublingually BID at one of three dose levels (2.5 mg, 5.0 mg, or 10.0 mg)

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The participants who started Period 1 are those randomized, one of whom did not receive study drug. The participants who started Period 2 are those who received study drug. The baseline demographics table presents data for participants treated, therefore Period 2 was set as the baseline period.

Number of subjects in period 2[2]	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Started	101	104	99
Completed	87	88	88
Not completed	14	16	11
Consent withdrawn by subject	-	2	-
Adverse event, non-fatal	4	7	5
Did Not Meet Protocol Eligibility	-	1	-
Treatment Failure	-	-	-
Lost to follow-up	3	2	3
Protocol deviation	7	4	3

Number of subjects in period 2[2]	Asenapine 10.0 mg BID
Started	99
Completed	87
Not completed	12
Consent withdrawn by subject	3
Adverse event, non-fatal	5
Did Not Meet Protocol Eligibility	-
Treatment Failure	1
Lost to follow-up	2
Protocol deviation	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number enrolled in the trial presents participants randomized; one of these participants did not receive study drug. The participants who started Period 2 ("baseline period") are those who received study drug. The baseline demographics table presents data for participants treated, therefore Period 2 was set as the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants receive placebo BID for 21 days.	
Reporting group title	Asenapine 2.5 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID for 21 days.	
Reporting group title	Asenapine 5.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. Participants receive asenapine 5.0 mg BID for the remainder of the 21-day treatment period.	
Reporting group title	Asenapine 10.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. On Day 5 and 6 participants receive asenapine 5.0 mg BID. On Day 7 participants receive asenapine 5.0 mg in the morning and 10.0 mg in the evening. Participants receive asenapine 10.0 mg BID for the remainder of the 21-day treatment period.	

Reporting group values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Number of subjects	101	104	99
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	13.7	13.7	13.8
standard deviation	± 2	± 2.1	± 2
Gender categorical Units: Subjects			
Female	63	52	56
Male	38	52	43
Y-MRS total score			
Y-MRS is an 11-item instrument for assessing the severity of manic episodes. Seven of the 11 items are rated on a scale of 0-4 and 4 are rated on a scale of 0-8, with higher scores indicating greater severity of symptoms. The Y-MRS total score for each participant is the sum of the ratings for the 11 individual items, and can range from 0-60. Summary statistics presented are for efficacy population (Full Analysis Set [FAS]): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	29.9	29.5	30.3
standard deviation	± 5.5	± 5.7	± 5.9
Clinical Global Impression Scale for use in Bipolar Disorder (CGI-BP) overall score			
CGI-BP overall score is obtained using a 7-point scale assessing the severity of the participant's overall bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	4.3	4.5	4.4

standard deviation	± 0.5	± 0.6	± 0.6
CGI-BP mania score			
CGI-BP mania score is obtained using a 7-point scale assessing the severity of the mania component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	4.3	4.5	4.4
standard deviation	± 0.5	± 0.6	± 0.6
CGI-BP depression score			
CGI-BP depression score is obtained using a 7-point scale assessing the severity of the depression component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS) except as noted: N=97 (baseline value not available for 1 FAS participant in this group), 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	2.9	2.8	2.9
standard deviation	± 1.3	± 1.3	± 1.4
Children's Depression Rating Scale, Revised (CDRS-R) total score			
CDRS-R is a 17-item instrument for assessing depression in children. Items are rated on a scale of 1-7 (14 items) or 1-5 (3 items); higher scores indicate more severe symptoms. CDRS-R total score is sum of ratings for the 17 items (range: 17-113). Summary statistics presented are for efficacy population (FAS) except as noted: N=97 (baseline value not available for 1 FAS participant in this group), 99 (baseline value not available for 2 FAS participants in this group), 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	34.5	33.7	35.2
standard deviation	± 10.2	± 9	± 11.9
Children's Global Assessment Scale (CGAS) score - current functioning			
CGAS is a 100-point scale measuring psychological, social, and school functioning in children aged 6-17. Minimum scores ranged from 1-10, representing the need for constant supervision (worse result) to maximum scores of 91-100, representing superior functioning (better result). Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	49	49.6	48.4
standard deviation	± 7.9	± 7.4	± 7.4
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) total score			
PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant is asked to rate 15 items reflecting quality of life on a scale of 1=very poor to 5=very good. The PQ-LES-Q total score (sum of Items 1-14) ranged from 14 to 70 with a higher score indicating better quality of life. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	48.7	49.1	49.5
standard deviation	± 9.7	± 9.6	± 9.1
PQ-LES-Q overall score (i.e., item 15)			
PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant is asked to rate 15 items reflecting quality of life on a scale of 1=very poor to 5=very good. The PQ-LES-Q overall score (Item 15, a global assessment of quality of life) ranged from 1 to 5 with a higher score indicating better quality of life. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	3.7	3.8	3.8

standard deviation	± 1	± 1	± 0.9

Reporting group values	Asenapine 10.0 mg BID	Total	
Number of subjects	99	403	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	13.9		
standard deviation	± 2.1	-	
Gender categorical Units: Subjects			
Female	41	212	
Male	58	191	
Y-MRS total score			
Y-MRS is an 11-item instrument for assessing the severity of manic episodes. Seven of the 11 items are rated on a scale of 0-4 and 4 are rated on a scale of 0-8, with higher scores indicating greater severity of symptoms. The Y-MRS total score for each participant is the sum of the ratings for the 11 individual items, and can range from 0-60. Summary statistics presented are for efficacy population (Full Analysis Set [FAS]): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	30.2		
standard deviation	± 5.6	-	
Clinical Global Impression Scale for use in Bipolar Disorder (CGI-BP) overall score			
CGI-BP overall score is obtained using a 7-point scale assessing the severity of the participant's overall bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	4.4		
standard deviation	± 0.6	-	
CGI-BP mania score			
CGI-BP mania score is obtained using a 7-point scale assessing the severity of the mania component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	4.4		
standard deviation	± 0.6	-	
CGI-BP depression score			
CGI-BP depression score is obtained using a 7-point scale assessing the severity of the depression component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS) except as noted: N=97 (baseline value not available for 1 FAS participant in this group), 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	2.8		
standard deviation	± 1.2	-	
Children's Depression Rating Scale, Revised (CDRS-R) total score			

CDRS-R is a 17-item instrument for assessing depression in children. Items are rated on a scale of 1-7 (14 items) or 1-5 (3 items); higher scores indicate more severe symptoms. CDRS-R total score is sum of ratings for the 17 items (range: 17-113). Summary statistics presented are for efficacy population (FAS) except as noted: N=97 (baseline value not available for 1 FAS participant in this group), 99 (baseline value not available for 2 FAS participants in this group), 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale arithmetic mean standard deviation	 34.1 ± 9	 -	
Children's Global Assessment Scale (CGAS) score - current functioning			
CGAS is a 100-point scale measuring psychological, social, and school functioning in children aged 6-17. Minimum scores ranged from 1-10, representing the need for constant supervision (worse result) to maximum scores of 91-100, representing superior functioning (better result). Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale arithmetic mean standard deviation	 49.1 ± 6.7	 -	
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) total score			
PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant is asked to rate 15 items reflecting quality of life on a scale of 1=very poor to 5=very good. The PQ-LES-Q total score (sum of Items 1-14) ranged from 14 to 70 with a higher score indicating better quality of life. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale arithmetic mean standard deviation	 49.1 ± 10.5	 -	
PQ-LES-Q overall score (i.e., item 15)			
PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant is asked to rate 15 items reflecting quality of life on a scale of 1=very poor to 5=very good. The PQ-LES-Q overall score (Item 15, a global assessment of quality of life) ranged from 1 to 5 with a higher score indicating better quality of life. Summary statistics presented are for efficacy population (FAS): N=98, 101, 98 and 98 for Placebo, asenapine 2.5 mg BID, asenapine 5.0 mg BID and asenapine 10.0 mg BID groups, respectively.			
Units: score on a scale arithmetic mean standard deviation	 3.8 ± 1	 -	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants receive placebo twice daily (BID) for 21 days.	
Reporting group title	Asenapine 2.5 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID for 21 days.	
Reporting group title	Asenapine 5.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. Participants receive asenapine 5.0 mg BID for the remainder of the 21-day treatment period.	
Reporting group title	Asenapine 10.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. On Day 5 and 6 participants receive asenapine 5.0 mg BID. On Day 7 participants receive asenapine 5.0 mg in the morning and 10.0 mg in the evening. Participants receive asenapine 10.0 mg BID for the remainder of the 21-day treatment period.	
Reporting group title	Placebo
Reporting group description:	
Participants receive placebo BID for 21 days.	
Reporting group title	Asenapine 2.5 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID for 21 days.	
Reporting group title	Asenapine 5.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. Participants receive asenapine 5.0 mg BID for the remainder of the 21-day treatment period.	
Reporting group title	Asenapine 10.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. On Day 5 and 6 participants receive asenapine 5.0 mg BID. On Day 7 participants receive asenapine 5.0 mg in the morning and 10.0 mg in the evening. Participants receive asenapine 10.0 mg BID for the remainder of the 21-day treatment period.	

Primary: Change from Baseline in Y-MRS Total Score at Day 21

End point title	Change from Baseline in Y-MRS Total Score at Day 21
End point description:	
Y-MRS is an 11-item clinician-rated instrument for assessing severity of manic episodes. Severity of each item is rated based on the participant's assessment of his or her condition and clinician's observations during the interview. Seven of the 11 items are rated on a scale of 0-4 and 4 are rated on a scale of 0-8, with higher scores indicating greater severity of symptoms. The Y-MRS total score for each participant is the sum of the ratings for the 11 individual items, and can range from 0-60, with higher scores indicating greater severity of symptoms. The reported measure is the change from baseline at Day 21; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included an on-treatment Day 21 value of Y-MRS total score must be available for a participant.	
End point type	Primary
End point timeframe:	
Baseline and Day 21	

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	88	87	81
Units: score on a scale				
arithmetic mean (standard deviation)	-9.6 (± 7.8)	-12.3 (± 9)	-15.1 (± 9.5)	-15.9 (± 9.1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± standard deviation (SD) change from baseline is 79 for placebo and 88 for asenapine 2.5 mg (total – 167). Mixed model for repeated measures (MMRM) analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [1]
Method	MMRM
Parameter estimate	Difference in Least Squares (LS) Means
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	-0.8

Notes:

[1] - p-value is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 87 for asenapine 5.0 mg (total – 166). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-5.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	-2.9

Notes:

[2] - p-value is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 81 for asenapine 10.0 mg (total – 160). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	-3.8

Notes:

[3] - p-value is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.

Statistical analysis title	Analysis of Dose-response Relationship: Pattern 1

Statistical analysis description:

Analysis of dose-response relationship is a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 335 (total for 4 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 395) was used to evaluate 7 pre-defined dose-response patterns. Model includes terms of (pooled) site, treatment, visit, baseline, and interaction of visit by treatment and baseline by visit.

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID v Asenapine 10.0 mg BID
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [4]
Method	MMRM

Notes:

[4] - p-value (adjusted to control Type I error) for dose-response pattern 1 (Placebo<2.5 mg=5.0 mg=10.0 mg). Value of t-statistic associated with contrast of MMRM model for pattern 1 is -4.92. Lower value indicates pattern provides better fit to data.

Statistical analysis title	Analysis of Dose-response Relationship: Pattern 2

Statistical analysis description:

Analysis of dose-response relationship is a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 335 (total for 4 groups). Multiple contrast

testing using MMRM model (based on FAS population, total N = 395) was used to evaluate 7 pre-defined dose-response patterns. Model includes terms of (pooled) site, treatment, visit, baseline, and interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Asenapine 5.0 mg BID v Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [5]
Method	MMRM

Notes:

[5] - p-value (adjusted to control Type I error) for dose-response pattern 2 (Placebo=2.5 mg<5.0 mg=10.0 mg). Value of t-statistic associated with contrast of MMRM model for pattern 2 is -4.87. Lower value indicates pattern provides better fit to data.

Statistical analysis title	Analysis of Dose-response Relationship: Pattern 3

Statistical analysis description:

Analysis of dose-response relationship is a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 335 (total for 4 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 395) was used to evaluate 7 pre-defined dose-response patterns. Model includes terms of (pooled) site, treatment, visit, baseline, and interaction of visit by treatment and baseline by visit.

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID v Asenapine 10.0 mg BID
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0021 [6]
Method	MMRM

Notes:

[6] - p-value (adjusted to control Type I error) for dose-response pattern 3 (Placebo=2.5 mg=5.0 mg<10.0 mg). Value of t-statistic associated with contrast of MMRM model for pattern 3 is -3.40. Lower value indicates pattern provides better fit to data.

Statistical analysis title	Analysis of Dose-response Relationship: Pattern 4

Statistical analysis description:

Analysis of dose-response relationship is a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 335 (total for 4 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 395) was used to evaluate 7 pre-defined dose-response patterns. Model includes terms of (pooled) site, treatment, visit, baseline, and interaction of visit by treatment and baseline by visit.

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID v Asenapine 10.0 mg BID
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [7]
Method	MMRM

Notes:

[7] - p-value (adjusted to control Type I error) for dose-response pattern 4 (Placebo<2.5 mg<5.0 mg<10.0 mg). Value of t-statistic associated with contrast of MMRM model for pattern 4 is -5.28. Lower value indicates pattern provides better fit to data.

Statistical analysis title	Analysis of Dose-response Relationship: Pattern 5

Statistical analysis description:

Analysis of dose-response relationship is a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 335 (total for 4 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 395) was used to evaluate 7 pre-defined dose-response patterns. Model includes terms of (pooled) site, treatment, visit, baseline, and interaction

of visit by treatment and baseline by visit.

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID v Asenapine 10.0 mg BID
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [8]
Method	MMRM

Notes:

[8] - p-value (adjusted to control Type I error) for dose-response pattern 5 (Placebo=2.5 mg<5.0 mg<10.0 mg). Value of t-statistic associated with contrast of MMRM model for pattern 5 is -4.64. Lower value indicates pattern provides better fit to data.

Statistical analysis title	Analysis of Dose-response Relationship: Pattern 6

Statistical analysis description:

Analysis of dose-response relationship is a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 335 (total for 4 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 395) was used to evaluate 7 pre-defined dose-response patterns. Model includes terms of (pooled) site, treatment, visit, baseline, and interaction of visit by treatment and baseline by visit.

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID v Asenapine 10.0 mg BID
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [9]
Method	MMRM

Notes:

[9] - p-value (adjusted to control Type I error) for dose-response pattern 6 (Placebo<2.5 mg=5.0 mg<10.0 mg). Value of t-statistic associated with contrast of MMRM model for pattern 6 is -5.07. Lower value indicates pattern provides better fit to data.

Statistical analysis title	Analysis of Dose-response Relationship: Pattern 7

Statistical analysis description:

Analysis of dose-response relationship is a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 335 (total for 4 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 395) was used to evaluate 7 pre-defined dose-response patterns. Model includes terms of (pooled) site, treatment, visit, baseline, and interaction of visit by treatment and baseline by visit.

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID v Asenapine 10.0 mg BID
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [10]
Method	MMRM

Notes:

[10] - p-value (adjusted to control Type I error) for dose-response pattern 7 (Placebo<2.5 mg<5.0 mg=10.0 mg). Value of t-statistic associated with contrast of MMRM model for pattern 7 is -5.49. Lower value indicates pattern provides better fit to data.

Secondary: Change from Baseline in CGI-BP Overall Score at Day 21

End point title	Change from Baseline in CGI-BP Overall Score at Day 21

End point description:

Change from baseline in CGI-BP overall score at Day 21 is the Key Secondary Outcome Measure. The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the participant’s overall bipolar illness, with ratings from 1=normal, not ill to

7=very severely ill. The reported measure is the change from baseline at Day 21; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 21 value of CGI-BP overall score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	88	87	81
Units: score on a scale				
arithmetic mean (standard deviation)	-0.7 (± 0.9)	-1.3 (± 1.1)	-1.4 (± 1)	-1.4 (± 1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 88 for asenapine 2.5 mg (total – 167). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.3

Notes:

[11] - p-value is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 87 for asenapine 5.0 mg (total – 166). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.4

Notes:

[12] - p-value is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 81 for asenapine 10.0 mg (total – 160). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.4

Notes:

[13] - p-value is adjusted by Hochberg's method for testing three asenapine groups versus the placebo group.

Secondary: Total Y-MRS 50% Responders at Days 4, 7, 14 and 21

End point title	Total Y-MRS 50% Responders at Days 4, 7, 14 and 21

End point description:

Total Y-MRS 50% responder was defined as a participant with reduction from baseline to identified visit of ≥50% in Y-MRS total score. Y-MRS is an 11-item clinician-rated instrument for assessing the severity of manic episodes. The Y-MRS total score for each participant is sum of the ratings for the 11 individual items, and can range from 0-60 with higher scores indicating greater severity of symptoms. Last-Observation-Carried-Forward (LOCF) approach was used; if at a given visit no Y-MRS total score was available for determining whether a participant was a responder, the last available post-baseline on-treatment assessment prior to that visit was used. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included for a visit, a Y-MRS total score must be available for that visit or a prior post-baseline on-treatment visit.

End point type	Secondary

End point timeframe:

Baseline and Days 4, 7, 14 and 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	101	98	98
Units: participants				
Day 4 (n=95, 98, 93, 90)	7	19	20	13
Day 7 (n=98, 101, 98, 98)	14	33	31	37
Day 14 (n=98, 101, 98, 98)	20	36	50	50
Day 21 (n=98, 101, 98, 98)	27	42	53	51

Statistical analyses

Statistical analysis title	Comparison by Treatment Group: Day 4

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 4 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. Odds ratio (OR) was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response. Number in FAS for groups compared: placebo – 98, asenapine 2.5 mg – 101 (total – 199). Day 4 analysis includes only those in FAS with Day 4 data (LOCF): placebo – 95, asenapine 2.5 mg – 98 (total – 193).

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	7.6

Notes:

[14] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 4

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 4 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response. Number in FAS for groups compared: placebo – 98, asenapine 5.0 mg – 98 (total – 196). Day 4 analysis includes only those in FAS with Day 4 data (LOCF): placebo – 95, asenapine 5.0 mg – 93 (total – 188).

Comparison groups	Asenapine 5.0 mg BID v Placebo

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	8.6

Notes:

[15] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 4

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 4 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response. Number in FAS for groups compared: placebo – 98, asenapine 10.0 mg – 98 (total – 196). Day 4 analysis includes only those in FAS with Day 4 data (LOCF): placebo – 95, asenapine 10.0 mg – 90 (total – 185).

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.129 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	5.6

Notes:

[16] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 7

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 7 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	5.9

Notes:

[17] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 7

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 7 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	5.6

Notes:

[18] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 7

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 7 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	7.3

Notes:

[19] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 14

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 14 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	4.1

Notes:

[20] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 14

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 14 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [21]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	7.6

Notes:

[21] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 14

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 14 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 10.0 mg BID v Placebo

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [22]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	7.6

Notes:

[22] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 21

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 21 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.042 [23]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	3.4

Notes:

[23] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 21

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 21 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	5.8

Notes:

[24] - 95% Confidence Interval and p-value are based on Wald statistic.

Statistical analysis title	Comparison by Treatment Group: Day 21

Statistical analysis description:

Analysis is for asenapine versus placebo on Day 21 (LOCF). Logistic regression model included terms of treatment and baseline Y-MRS total score. OR was adjusted for baseline. An OR of >1 means that asenapine has a higher probability of achieving Total Y-MRS 50% response.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [25]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	5.3

Notes:

[25] - 95% Confidence Interval and p-value are based on Wald statistic.

Secondary: Change from Baseline in CGI-BP Mania Score at Day 4

End point title	Change from Baseline in CGI-BP Mania Score at Day 4

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the mania component of the participant’s bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 4; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 4 value of CGI-BP mania score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 4

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	97	93	90
Units: score on a scale				
arithmetic mean (standard deviation)	-0.3 (± 0.6)	-0.6 (± 0.8)	-0.5 (± 0.7)	-0.5 (± 0.8)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 93 for placebo and 97 for asenapine 2.5 mg (total – 190). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.014
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.05

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 93 for placebo and 93 for asenapine 5.0 mg (total – 186). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.107
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.04

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 93 for placebo and 90 for asenapine 10.0 mg (total – 183). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.01

Secondary: Change from Baseline in CGI-BP Mania Score at Day 7

End point title	Change from Baseline in CGI-BP Mania Score at Day 7

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the mania component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 7; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 7 value of CGI-BP mania score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 7

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	95	98	95	97
Units: score on a scale				
arithmetic mean (standard deviation)	-0.5 (± 0.7)	-0.9 (± 0.9)	-0.9 (± 1)	-0.9 (± 0.9)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 95 for placebo and 98 for asenapine 2.5 mg (total – 193). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.1

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 95 for placebo and 95 for asenapine 5.0 mg (total – 190). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.12

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 95 for placebo and 97 for asenapine 10.0 mg (total – 192). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.21

Secondary: Change from Baseline in CGI-BP Mania Score at Day 14

End point title	Change from Baseline in CGI-BP Mania Score at Day 14

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the mania component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 14; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 14 value of CGI-BP mania score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 14

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	91	90	91
Units: score on a scale				
arithmetic mean (standard deviation)	-0.6 (± 1)	-1.1 (± 1)	-1.4 (± 1)	-1.3 (± 1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 89 for placebo and 91 for asenapine 2.5 mg (total – 180). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.011
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.08

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 89 for placebo and 90 for asenapine 5.0 mg (total – 179). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	-0.36

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 89 for placebo and 91 for asenapine 10.0 mg (total – 180). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.35

Secondary: Change from Baseline in CGI-BP Mania Score at Day 21

End point title	Change from Baseline in CGI-BP Mania Score at Day 21

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the mania component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 21; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 21 value of CGI-BP mania score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	88	87	81
Units: score on a scale				
arithmetic mean (standard deviation)	-0.7 (± 0.9)	-1.3 (± 1.1)	-1.5 (± 1.1)	-1.4 (± 1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 88 for asenapine 2.5 mg (total – 167). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.32

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 87 for asenapine 5.0 mg (total – 166). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	-0.46

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 79 for placebo and 81 for asenapine 10.0 mg (total – 160). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	-0.45

Secondary: Change from Baseline in CGI-BP Depression Score at Day 4

End point title	Change from Baseline in CGI-BP Depression Score at Day 4

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the depression component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 4; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 4 value of CGI-BP depression score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 4

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92	97	93	90
Units: score on a scale				
arithmetic mean (standard deviation)	-0.2 (± 0.7)	-0.3 (± 0.8)	-0.2 (± 1)	-0.1 (± 1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 92 for placebo and 97 for asenapine 2.5 mg (total – 189). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.536
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.15

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 92 for placebo and 93 for asenapine 5.0 mg (total – 185). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.811
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.19

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 92 for placebo and 90 for asenapine 10.0 mg (total – 182). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.556
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.28

Secondary: Change from Baseline in CGI-BP Depression Score at Day 7

End point title	Change from Baseline in CGI-BP Depression Score at Day 7

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the depression component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 7; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 7 value of CGI-BP depression score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 7

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	98	95	97
Units: score on a scale				
arithmetic mean (standard deviation)	-0.4 (± 0.9)	-0.5 (± 0.8)	-0.5 (± 1.1)	-0.5 (± 0.9)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 94 for placebo and 98 for asenapine 2.5 mg (total – 192). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.053
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 94 for placebo and 95 for asenapine 5.0 mg (total – 189). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.094
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.03

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 94 for placebo and 97 for asenapine 10.0 mg (total – 191). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.178
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.07

Secondary: Change from Baseline in CGI-BP Depression Score at Day 14

End point title	Change from Baseline in CGI-BP Depression Score at Day 14

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the depression component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 14; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 14 value of CGI-BP depression score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 14

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	91	90	91
Units: score on a scale				
arithmetic mean (standard deviation)	-0.5 (± 1.1)	-0.5 (± 1)	-0.7 (± 1)	-0.6 (± 1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 88 for placebo and 91 for asenapine 2.5 mg (total – 179). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.506
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.16

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 88 for placebo and 90 for asenapine 5.0 mg (total – 178). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.131
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.06

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 88 for placebo and 91 for asenapine 10.0 mg (total – 179). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.211
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.09

Secondary: Change from Baseline in CGI-BP Depression Score at Day 21

End point title	Change from Baseline in CGI-BP Depression Score at Day 21

End point description:

The CGI-BP is a clinician-rated instrument for assessing bipolar illness that includes subscales assessing mania and depression. This measure reports one item within the CGI-BP, which is a 7-point scale assessing the severity of the depression component of the participant's bipolar illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 21; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 21 value of CGI-BP depression score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	88	87	81
Units: score on a scale				
arithmetic mean (standard deviation)	-0.4 (± 1)	-0.6 (± 1.1)	-0.8 (± 1.1)	-0.6 (± 1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 78 for placebo and 88 for asenapine 2.5 mg (total – 166). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.079
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.03

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 78 for placebo and 87 for asenapine 5.0 mg (total – 165). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.08

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 78 for placebo and 81 for asenapine 10.0 mg (total – 159). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.139
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.06

Secondary: Change from Baseline in CDRS-R Total Score at Day 7

End point title	Change from Baseline in CDRS-R Total Score at Day 7

End point description:

The CDRS-R is a 17-item clinician-rated instrument for assessing the presence and severity of depressive symptoms in children. Fourteen of the 17 items are rated on a scale of 1-7 and 3 of the items are rated on a scale of 1-5, with higher scores indicating greater severity of symptoms. The CDRS-R total score for each participant is the sum of the ratings for the 17 individual items, and can range from 17-113, with higher scores indicating greater severity of symptoms. The reported measure is the change from baseline at Day 7; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 7 value of CDRS-R total score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 7

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	95	91	95
Units: score on a scale				
arithmetic mean (standard deviation)	-4.1 (± 8.1)	-6.1 (± 7.1)	-6.1 (± 8)	-5.9 (± 8.5)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 94 for placebo and 95 for asenapine 2.5 mg (total – 189). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.38
upper limit	-0.83

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 94 for placebo and 91 for asenapine 5.0 mg (total – 185). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.95
upper limit	-0.39

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 94 for placebo and 95 for asenapine 10.0 mg (total – 189). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.93
upper limit	-0.38

Secondary: Change from Baseline in CDRS-R Total Score at Day 14

End point title	Change from Baseline in CDRS-R Total Score at Day 14

End point description:

The CDRS-R is a 17-item clinician-rated instrument for assessing the presence and severity of depressive symptoms in children. Fourteen of the 17 items are rated on a scale of 1-7 and 3 of the items are rated on a scale of 1-5, with higher scores indicating greater severity of symptoms. The CDRS-R total score for each participant is the sum of the ratings for the 17 individual items, and can range from 17-113, with higher scores indicating greater severity of symptoms. The reported measure is the change from baseline at Day 14; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 14 value of CDRS-R total score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 14

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	89	90	90
Units: score on a scale				
arithmetic mean (standard deviation)	-5.5 (± 8.1)	-5.8 (± 6.5)	-8.7 (± 10.5)	-6.6 (± 8.8)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 88 for placebo and 89 for asenapine 2.5 mg (total – 177). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.395
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	1.04

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 88 for placebo and 90 for asenapine 5.0 mg (total – 178). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.26
upper limit	-0.63

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 88 for placebo and 90 for asenapine 10.0 mg (total – 178). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.121
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	0.38

Secondary: Change from Baseline in CDRS-R Total Score at Day 21

End point title	Change from Baseline in CDRS-R Total Score at Day 21

End point description:

The CDRS-R is a 17-item clinician-rated instrument for assessing the presence and severity of depressive symptoms in children. Fourteen of the 17 items are rated on a scale of 1-7 and 3 of the items are rated on a scale of 1-5, with higher scores indicating greater severity of symptoms. The CDRS-R total score for each participant is the sum of the ratings for the 17 individual items, and can range from 17-113, with higher scores indicating greater severity of symptoms. The reported measure is the change from baseline at Day 21; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 21 value of CDRS-R total score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	87	87	81
Units: score on a scale				
arithmetic mean (standard deviation)	-6.1 (± 8.8)	-6.9 (± 7.3)	-8.7 (± 11.4)	-6.8 (± 8.9)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 78 for placebo and 87 for asenapine 2.5 mg (total – 165). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.135
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	0.45

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 78 for placebo and 87 for asenapine 5.0 mg (total – 165). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.023
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.08
upper limit	-0.3

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 78 for placebo and 81 for asenapine 10.0 mg (total – 159). MMRM analysis uses FAS population (Number of participants: placebo – 98, asenapine 2.5 mg – 101, asenapine 5.0 mg – 98, asenapine 10.0 mg – 98, total – 395). Model includes terms of (pooled) site, treatment, visit, baseline, and the interaction of visit by treatment and baseline by visit.

Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.189
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	0.63

Secondary: Change from Baseline in CGAS Score at Day 21

End point title	Change from Baseline in CGAS Score at Day 21

End point description:

CGAS is a 100-point scale measuring psychological, social, and school functioning in children aged 6-17. Minimum scores ranged from 1-10, representing the need for constant supervision (worse result) to maximum scores of 91-100, representing superior functioning (better result). The reported measure is the change from baseline at Day 21; improvement in functioning is represented by positive values. This analysis used an LOCF approach; if no Day 21 value was available for a participant, the last available post-baseline on-treatment assessment prior to the Day 21 assessment was used. Population for analysis was randomized participants who received ≥1 dose of study drug and had both a baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included a baseline and at least 1 post-baseline on-treatment value of CGAS score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	93	91	85
Units: score on a scale				
arithmetic mean (standard deviation)	6 (± 8.1)	9.4 (± 9.5)	13 (± 11.6)	10.8 (± 9.7)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description: Analysis of covariance (ANCOVA) model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	4.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	7.02

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description: ANCOVA model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	6.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.22
upper limit	9.68

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:	
ANCOVA model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	5.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.31
upper limit	7.91

Secondary: Change from Baseline in PQ-LES-Q Total Score at Day 21

End point title	Change from Baseline in PQ-LES-Q Total Score at Day 21

End point description:

PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. Participant rates 15 items on scale of 1=very poor to 5=very good. Items 1-14 assess specific areas; Item 15 is a global assessment. PQ-LES-Q total score for each participant was sum of rating assigned to first 14 items, and ranged from 14 to 70 with higher score indicating better quality of life. Positive values of measure represent improvement in quality of life versus baseline. LOCF approach was used; if no Day 21 value was available for participant, last available post-baseline on-treatment assessment prior to Day 21 assessment was used. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included baseline and at least 1 post-baseline on-treatment value of PQ-LES-Q total score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	92	90	84
Units: score on a scale				
arithmetic mean (standard deviation)	1.5 (± 8.2)	3.7 (± 8.6)	2.5 (± 10.8)	4 (± 9.8)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description:	
ANCOVA model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 2.5 mg BID v Placebo

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	4.48

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description: ANCOVA model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.239
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	3.59

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description: ANCOVA model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	5.08

Secondary: Change from Baseline in PQ-LES-Q Overall Score (i.e., Item 15) at Day 21

End point title	Change from Baseline in PQ-LES-Q Overall Score (i.e., Item 15) at Day 21

End point description:

PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. Participant rates 15 items on scale of 1=very poor to 5=very good. Items 1-14 assess specific areas; Item 15 is a global assessment of quality of life. The Item 15 result is defined to be the PQ-LES-Q overall score, and ranged from 1 to 5 with a higher score indicating better quality of life. Positive values of measure represent improvement in quality of life versus baseline. LOCF approach was used; if no Day 21 value was available for participant, last available post-baseline on-treatment assessment prior to Day 21 assessment was used. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment Y-MRS total score (this group is termed the efficacy FAS); also, to be included baseline and at least 1 post-baseline on-treatment value of PQ-LES-Q total score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	Asenapine 10.0 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	92	90	84
Units: score on a scale				
arithmetic mean (standard deviation)	0 (± 0.9)	0.4 (± 1)	0.1 (± 1)	0.2 (± 1.1)

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

ANCOVA model includes terms of (pooled) site, treatment and baseline.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.62

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description: ANCOVA model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.135
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.41

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description: ANCOVA model includes terms of (pooled) site, treatment and baseline.	
Comparison groups	Asenapine 10.0 mg BID v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.044
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.49

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 30 days after the last dose of study drug (Up to 51 days)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants receive placebo BID for 21 days.	
Reporting group title	Asenapine 2.5 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID for 21 days.	
Reporting group title	Asenapine 5.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. Participants receive asenapine 5.0 mg BID for the remainder of the 21-day treatment period.	
Reporting group title	Asenapine 10.0 mg BID
Reporting group description:	
Participants receive asenapine 2.5 mg BID through Day 3. On Day 4 participants receive asenapine 2.5 mg in the morning and 5.0 mg in the evening. On Day 5 and 6 participants receive asenapine 5.0 mg BID. On Day 7 participants receive asenapine 5.0 mg in the morning and 10.0 mg in the evening. Participants receive asenapine 10.0 mg BID for the remainder of the 21-day treatment period.	

Serious adverse events	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 101 (2.97%)	0 / 104 (0.00%)	2 / 99 (2.02%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Bipolar Disorder			
subjects affected / exposed	1 / 101 (0.99%)	0 / 104 (0.00%)	0 / 99 (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
Bipolar I Disorder			
subjects affected / exposed	1 / 101 (0.99%)	0 / 104 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			

subjects affected / exposed	0 / 101 (0.00%)	0 / 104 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Behaviour			
subjects affected / exposed	1 / 101 (0.99%)	0 / 104 (0.00%)	0 / 99 (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
Suicidal Ideation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 104 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 101 (0.00%)	0 / 104 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Asenapine 10.0 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 99 (2.02%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Bipolar Disorder			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bipolar I Disorder			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Suicidal Behaviour			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal Ideation			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 101 (29.70%)	68 / 104 (65.38%)	70 / 99 (70.71%)
Investigations			
Weight Increased			
subjects affected / exposed	0 / 101 (0.00%)	6 / 104 (5.77%)	2 / 99 (2.02%)
occurrences (all)	0	6	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 101 (2.97%)	6 / 104 (5.77%)	10 / 99 (10.10%)
occurrences (all)	4	6	11
Dysgeusia			
subjects affected / exposed	2 / 101 (1.98%)	4 / 104 (3.85%)	5 / 99 (5.05%)
occurrences (all)	2	4	5
Headache			
subjects affected / exposed	6 / 101 (5.94%)	8 / 104 (7.69%)	11 / 99 (11.11%)
occurrences (all)	6	11	12
Sedation			
subjects affected / exposed	5 / 101 (4.95%)	16 / 104 (15.38%)	19 / 99 (19.19%)
occurrences (all)	5	16	19

Somnolence			
subjects affected / exposed	6 / 101 (5.94%)	34 / 104 (32.69%)	34 / 99 (34.34%)
occurrences (all)	6	39	36
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 101 (4.95%)	4 / 104 (3.85%)	8 / 99 (8.08%)
occurrences (all)	5	4	8
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	6 / 101 (5.94%)	5 / 104 (4.81%)	2 / 99 (2.02%)
occurrences (all)	6	5	2
Hypoaesthesia Oral			
subjects affected / exposed	2 / 101 (1.98%)	18 / 104 (17.31%)	18 / 99 (18.18%)
occurrences (all)	2	18	19
Nausea			
subjects affected / exposed	3 / 101 (2.97%)	6 / 104 (5.77%)	6 / 99 (6.06%)
occurrences (all)	3	6	6
Paraesthesia Oral			
subjects affected / exposed	2 / 101 (1.98%)	9 / 104 (8.65%)	9 / 99 (9.09%)
occurrences (all)	2	9	9
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	2 / 101 (1.98%)	10 / 104 (9.62%)	9 / 99 (9.09%)
occurrences (all)	2	10	10

Non-serious adverse events	Asenapine 10.0 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 99 (72.73%)		
Investigations			
Weight Increased			
subjects affected / exposed	2 / 99 (2.02%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 99 (5.05%)		
occurrences (all)	5		
Dysgeusia			

subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Sedation subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	9 / 99 (9.09%) 9 9 / 99 (9.09%) 10 18 / 99 (18.18%) 20 31 / 99 (31.31%) 34		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 13 / 99 (13.13%) 13		
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all) Hypoaesthesia Oral subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Paraesthesia Oral subjects affected / exposed occurrences (all)	 3 / 99 (3.03%) 3 20 / 99 (20.20%) 21 6 / 99 (6.06%) 7 11 / 99 (11.11%) 11		
Metabolism and nutrition disorders Increased Appetite subjects affected / exposed occurrences (all)	 6 / 99 (6.06%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2013	Amendment 01: Primary reason for amendment was to incorporate revisions to age range for study entry (lower limit), exclusion criteria and list of closely monitored events. Original base protocol and Amendments 01, 02 and 03 were submitted together to country authority (Russia health ministry) that provided approval.
16 January 2013	Amendment 02: Primary reason for amendment was to incorporate revisions to age range for study entry (lower limit), list of treatments allowed as rescue therapy, list of closely monitored events and testing to monitor liver enzymes. Original base protocol and Amendments 01, 02 and 03 were submitted together to country authority (Russia health ministry) that provided approval.
16 January 2013	Amendment 03: Primary reason for amendment was to add cognitive testing and additional laboratory tests for hormone levels. Original base protocol and Amendments 01, 02 and 03 were submitted together to country authority (Russia health ministry) that provided approval.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported