EU Clinical Trials Register

Clinical trial results:
An 8-week, Placebo-Controlled, Double-Blind, Randomized, Fixed-Dose Efficacy and Safety Trial of Asenapine in Adolescent Subjects with Schizophrenia

Summary

EudraCT number	2009-017971-10
Trial protocol	RO Outside EU/EEA
Global end of trial date	01 April 2013

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	P05896

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01190254
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol number: MK-8274-020

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 April 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is designed to evaluate whether asenapine, which is approved by the United States Food and Drug Administration (US FDA) for acute treatment of schizophrenia in adults, is also effective in adolescents with schizophrenia. Participants who qualify for the study will be randomly assigned to receive a fixed dose of asenapine (either 2.5 mg or 5 mg twice daily [BID]) or placebo for 8 weeks. Throughout the study, observations will be made on each participant at various times to assess the efficacy and safety of the study treatment. The primary objective of the trial is to demonstrate significant superiority of at least one asenapine dose to placebo, as measured by the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at Day 56.

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	28 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	India: 100
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Philippines: 1
Country: Number of subjects enrolled	Russian Federation: 101

Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	South Africa: 3
Worldwide total number of subjects	306
EEA total number of subjects	12

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)	1
Adolescents (12-17 years)	304
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 306 subjects were randomized to treatment with placebo (N=102), asenapine 2.5 mg BID (N=98) or asenapine 5.0 mg BID (N=106).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants receive placebo asenapine tablets sublingually BID for 8 weeks

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

Dosage and administration details:

Asenapine-matched placebo tablets for sublingual administration

Arm title	Asenapine 2.5 mg BID

Arm description:

Participants receive active asenapine 2.5 mg tablets sublingually BID for 8 weeks

Arm type	Experimental
Investigational medicinal product name	asenapine 2.5 mg
Investigational medicinal product code	
Other name	Saphris®, SCH 900274, Org 5222
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine 2.5 mg tablets for sublingual administration

Arm title	Asenapine 5.0 mg BID

Arm description:

Participants receive active asenapine 2.5 mg tablets sublingually 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 active asenapine 5.0 mg tablets sublingually BID for the remainder of the 8-week treatment period

Arm type	Experimental

Investigational medicinal product name	asenapine 2.5 mg
Investigational medicinal product code	
Other name	Saphris®, SCH 900274, Org 5222
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine 2.5 mg tablets for sublingual administration

Investigational medicinal product name	asenapine 5.0 mg
Investigational medicinal product code	
Other name	Saphris®, SCH 900274, Org 5222
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Asenapine 5.0 mg tablets for sublingual administration

Number of subjects in period 1	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Started	102	98	106
Treated	102	98	106
Completed	81	81	84
Not completed	21	17	22
Did not meet protocol eligibility	1	-	-
Consent withdrawn by subject	4	5	7
Adverse event, non-fatal	3	6	8
Lost to follow-up	4	2	-
Lack of efficacy	7	4	5
Protocol deviation	2	-	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants receive placebo asenapine tablets sublingually BID for 8 weeks	
Reporting group title	Asenapine 2.5 mg BID
Reporting group description:	
Participants receive active asenapine 2.5 mg tablets sublingually BID for 8 weeks	
Reporting group title	Asenapine 5.0 mg BID
Reporting group description:	
Participants receive active asenapine 2.5 mg tablets sublingually 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 active asenapine 5.0 mg tablets sublingually BID for the remainder of the 8-week treatment period	

Reporting group values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Number of subjects	102	98	106
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	1
Adolescents (12-17 years)	102	98	104
Adults (18-64 years)	0	0	1
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	15.4	15.2	15.4
standard deviation	± 1.4	± 1.5	± 1.5
Gender categorical			
Units: Subjects			
Female	40	36	39
Male	62	62	67
Positive and Negative Syndrome Scale (PANSS) total score			
The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS total score (30 items) ranged from 30 to 210 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (Full Analysis Set [FAS]): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	97.5	97.4	98.6
standard deviation	± 10.3	± 10.2	± 13.4
Clinical Global Impression of Severity (CGI-S) score			
CGI-S is a 7-point scale for assessing the global severity of the participant's illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS):			

N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.		
Units: score on a scale			
arithmetic mean	4.6	4.6	4.7
standard deviation	± 0.6	± 0.6	± 0.6
PANSS positive subscale score			
The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS positive subscale score (7 PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	25.5	25.4	26.2
standard deviation	± 3.8	± 4.2	± 4.5
PANSS negative subscale score			
The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS negative subscale score (7 PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	25	24.9	24.5
standard deviation	± 4.5	± 4.8	± 5.4
PANSS positive and negative subscale scores combined			
The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS positive and negative subscale scores combined (14 PANSS items) ranged from 14 to 98 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	50.5	50.2	50.7
standard deviation	± 5.7	± 5.9	± 7.3
PANSS general psychopathology subscale score			
The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS general psychopathology subscale score (16 PANSS items) ranged from 16 to 112 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	47.1	47.2	47.9
standard deviation	± 6.4	± 6	± 7.7
PANSS Marder positive symptoms factor score			
The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder positive symptoms factor score (calculated from value of 8 identified PANSS items) ranged from 8 to 56 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.			
Units: score on a scale			
arithmetic mean	28.4	28.7	28.9
standard deviation	± 4	± 3.6	± 4.3
PANSS Marder negative symptoms factor score			
The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder negative symptoms factor score (calculated from value of 7 identified PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg			

BID groups, respectively.			
Units: score on a scale			
arithmetic mean	24.2	23.9	23.8
standard deviation	± 4.8	± 5.4	± 5.9
PANSS Marder disorganized thoughts factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder disorganized thoughts factor score (calculated from value of 7 identified PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean	22.4	22.3	22.5
standard deviation	± 3.7	± 3.4	± 4.6
PANSS Marder hostility/excitement factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder hostility/excitement factor score (calculated from value of 4 identified PANSS items) ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean	12.9	12.8	13.1
standard deviation	± 3.5	± 3.6	± 4.3
PANSS Marder anxiety/depression factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder anxiety/depression factor score (calculated from value of 4 identified PANSS items) ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean	9.6	9.8	10.3
standard deviation	± 3.1	± 3.1	± 3.1
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) except as noted: N=99 (baseline value not available for 1 FAS participant in this group), 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean	43	41.6	42.9
standard deviation	± 8.4	± 9.1	± 8.5
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 with respect to the previous week on a scale of 1=very poor to 5=very good. The PQ-LES-Q total score (sum of Items 1-14) for each participant ranged from 14 to 70 with a higher score indicating better quality of life. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean	41.6	41.2	40.7
standard deviation	± 10.7	± 10	± 9.5
PQ-LES-Q overall 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 with respect to the previous week 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=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean	3.1	3.1	3
standard deviation	± 1	± 0.9	± 1

Reporting group values	Total		
Number of subjects	306		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	1		
Adolescents (12-17 years)	304		
Adults (18-64 years)	1		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	115		
Male	191		
Positive and Negative Syndrome Scale (PANSS) total score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS total score (30 items) ranged from 30 to 210 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (Full Analysis Set [FAS]): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
Clinical Global Impression of Severity (CGI-S) score			

CGI-S is a 7-point scale for assessing the global severity of the participant's illness, with ratings from 1=normal, not ill to 7=very severely ill. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS positive subscale score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS positive subscale score (7 PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS negative subscale score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS negative subscale score (7 PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS positive and negative subscale scores combined			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS positive and negative subscale scores combined (14 PANSS items) ranged from 14 to 98 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS general psychopathology subscale score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS general psychopathology subscale score (16 PANSS items) ranged from 16 to 112 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS Marder positive symptoms factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder positive symptoms factor score (calculated from value of 8 identified PANSS items) ranged from 8 to 56 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS Marder negative symptoms factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder negative symptoms factor score (calculated from value of 7 identified PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS Marder disorganized thoughts factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder disorganized thoughts factor score (calculated from value of 7 identified PANSS items) ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg

BID groups, respectively.			
Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS Marder hostility/excitement factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder hostility/excitement factor score (calculated from value of 4 identified PANSS items) ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PANSS Marder anxiety/depression factor score			

The PANSS is a 30-item scale for assessing the symptoms of schizophrenia. For each PANSS item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Marder anxiety/depression factor score (calculated from value of 4 identified PANSS items) ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
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) except as noted: N=99 (baseline value not available for 1 FAS participant in this group), 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
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 with respect to the previous week on a scale of 1=very poor to 5=very good. The PQ-LES-Q total score (sum of Items 1-14) for each participant ranged from 14 to 70 with a higher score indicating better quality of life. Summary statistics presented are for efficacy population (FAS): N=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		
PQ-LES-Q overall 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 with respect to the previous week 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=100, 96 and 104 for placebo, asenapine 2.5 mg BID and asenapine 5.0 mg BID groups, respectively.

Units: score on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants receive placebo asenapine tablets sublingually BID for 8 weeks	
Reporting group title	Asenapine 2.5 mg BID
Reporting group description:	
Participants receive active asenapine 2.5 mg tablets sublingually BID for 8 weeks	
Reporting group title	Asenapine 5.0 mg BID
Reporting group description:	
Participants receive active asenapine 2.5 mg tablets sublingually 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 active asenapine 5.0 mg tablets sublingually BID for the remainder of the 8-week treatment period	

Primary: Change From Baseline in PANSS Total Score at Day 56

End point title	Change From Baseline in PANSS Total Score at Day 56
End point description:	

The PANSS is a 30-item clinician-rated instrument for assessing schizophrenia symptoms. It consists of 3 subscales: positive subscale (7 items), negative subscale (7 items), and general psychopathology subscale (16 items). For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS total score for each participant was sum of the rating assigned to each of the 30 PANSS items, and ranged from 30 to 210 with a higher score indicating greater severity of symptoms. The reported measure is the change from baseline at Day 56; 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 PANSS Total Score (this group is termed the efficacy FAS); also, to be included an on-treatment Day 56 value of PANSS Total Score must be available for a participant.

End point type	Primary
End point timeframe:	
Baseline and Day 56	

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-17.8 (± 17.8)	-23.7 (± 18.6)	-25.5 (± 16.9)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). Mixed model for repeated measures (MMRM) analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07 [1]
Method	MMRM
Parameter estimate	Difference in Least Squares (LS) Means
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	0.4

Notes:

[1] - p-value is adjusted by Hochberg's method for testing two 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 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064 [2]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	-0.5

Notes:

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

Statistical analysis title	Analysis of Dose-response: Linear Pattern

Statistical analysis description:

Investigation of dose-response relationship of change from baseline to Day 56 in PANSS Total Score was a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 228 (total for 3 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 300) was used to evaluate 3 pre-defined dose-response patterns (Linear, Convex, Concave).

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID

Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.064 [3]
Method	MMRM

Notes:

[3] - p-value (adjusted to control Type I error in multiple testing) for Linear dose-response pattern (Placebo<2.5 mg<5.0 mg)

Statistical analysis title	Analysis of Dose-response: Convex Pattern

Statistical analysis description:

Investigation of dose-response relationship of change from baseline to Day 56 in PANSS Total Score was a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 228 (total for 3 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 300) was used to evaluate 3 pre-defined dose-response patterns (Linear, Convex, Concave).

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.046 [4]
Method	MMRM

Notes:

[4] - p-value (adjusted to control Type I error in multiple testing) for Convex dose-response pattern (Placebo<2.5 mg=5.0 mg)

Statistical analysis title	Analysis of Dose-response: Concave Pattern

Statistical analysis description:

Investigation of dose-response relationship of change from baseline to Day 56 in PANSS Total Score was a Secondary study endpoint. Number of participants for calculation of reported mean ± SD changes from baseline is 228 (total for 3 groups). Multiple contrast testing using MMRM model (based on FAS population, total N = 300) was used to evaluate 3 pre-defined dose-response patterns (Linear, Convex, Concave).

Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.273 [5]
Method	MMRM

Notes:

[5] - p-value (adjusted to control Type I error in multiple testing) for Concave dose-response pattern (Placebo=2.5 mg<5.0 mg)

Secondary: Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Day 56

End point title	Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Day 56

End point description:

Change from baseline in CGI-S score at Day 56 is the Key Secondary Outcome Measure. CGI-S is a 7-point scale for assessing the global severity of the participant's illness, with ratings from 1=normal, not ill to 7=very severely ill. The reported measure is the change from baseline at Day 56; 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 PANSS Total Score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 56 value of the CGI-S score must be available for a participant.

End point type	Secondary

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-0.8 (± 1.1)	-1.1 (± 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 76 for placebo and 72 for asenapine 2.5 mg (total – 148). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	148
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.218 [6]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.1

Notes:

[6] - Confirmative testing for key secondary endpoint was to be performed only if both asenapine doses were superior to placebo in change from baseline in PANSS total score at Day 56. If this did not occur, multiplicity unadjusted p-values are provided.

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 76 for placebo and 79 for asenapine 5.0 mg (total – 155). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	155
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.024 [7]
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0

Notes:

[7] - Confirmative testing for key secondary endpoint was to be performed only if both asenapine doses were superior to placebo in change from baseline in PANSS total score at Day 56. If this did not occur, multiplicity unadjusted p-values are provided.

Secondary: Change From Baseline in PANSS Positive Subscale Score at Day 56

End point title	Change From Baseline in PANSS Positive Subscale Score at Day 56

End point description:

This measure reports results for the 7 items of the positive subscale of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. Positive symptoms refer to an excess or distortion of normal mental status (e.g., delusions). For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. PANSS positive subscale score for each participant was sum of the rating assigned to each of the 7 subscale items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Measure reports change from baseline; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (this group is termed the efficacy FAS); also, to be included baseline and an on-treatment Day 56 value of PANSS positive subscale score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-6 (± 6.1)	-7.9 (± 5.8)	-9.1 (± 5.6)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.067
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.6
Confidence interval	

level	95 %
sides	2-sided
lower limit	-3.3
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 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.012
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.1
Confidence interval	

level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-0.5

Secondary: Change From Baseline in PANSS Negative Subscale Score at Day 56

End point title	Change From Baseline in PANSS Negative Subscale Score at Day 56

End point description:

This measure reports results for the 7 items of the negative subscale of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. Negative symptoms represent a diminution or loss of normal functions (e.g., emotional withdrawal). For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. PANSS negative subscale score for each participant was sum of the rating assigned to each of the 7 subscale items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Measure reports change from baseline; 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 PANSS Total Score (this group is termed the efficacy FAS); also, to be included baseline and an on-treatment Day 56 value of PANSS negative subscale score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-3.4 (± 5.2)	-4.8 (± 5.6)	-4.9 (± 4.5)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.097
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.2

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description:	

Number of participants for calculation of reported mean ± SD change from baseline is 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.099
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.2

Secondary: Change From Baseline in PANSS Positive and Negative Subscale Scores Combined at Day 56

End point title	Change From Baseline in PANSS Positive and Negative Subscale Scores Combined at Day 56

End point description:

This measure reports results for combined positive (7 items) and negative (7 items) subscales of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. For each of the total 14 items in the combined positive and negative subscales, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS positive and negative subscale scores combined for each participant was sum of rating assigned to the 14 subscale items, and ranged from 14 to 98 with a higher score indicating greater severity of symptoms. Measure reports change from baseline; 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 PANSS Total Score (efficacy FAS); also, to be included a baseline and an on-treatment Day 56 value of PANSS positive/negative subscale scores combined must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-9.4 (± 10.1)	-12.7 (± 10.2)	-14 (± 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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.062
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
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 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-0.4

Secondary: Change From Baseline in PANSS General Psychopathology Subscale Score at Day 56

End point title	Change From Baseline in PANSS General Psychopathology Subscale Score at Day 56

End point description:

This measure reports results for the 16 items of the general psychopathology subscale of the PANSS, which is a 30-item clinician-rated instrument used to assess the symptoms of schizophrenia. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS general psychopathology subscale score for each participant was calculated as the sum of the rating assigned to each of the 16 subscale items, and ranged from 16 to 112 with a higher score indicating greater severity of symptoms. The reported measure is the change from baseline at Day 56; 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 PANSS Total Score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 56 value of the PANSS general psychopathology subscale score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-8.5 (± 8.6)	-10.9 (± 9.5)	-11.5 (± 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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.098
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	0.4

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.071
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	0.2

Secondary: Change From Baseline in PANSS Marder Positive Symptoms Factor Score at Day 56

End point title	Change From Baseline in PANSS Marder Positive Symptoms Factor Score at Day 56

End point description:

This measure reports results for the 8 items of the Marder positive symptoms factor of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. Marder factors are a modified grouping of the 30 PANSS items. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. PANSS Marder positive symptoms factor score for each participant was sum of rating assigned to each of the 8 applicable Marder factor items, and ranged from 8 to 56 with a higher score indicating greater severity of symptoms. Measure reports change from baseline; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (efficacy FAS); also, to be included baseline and an on-treatment Day 56 value of the PANSS Marder positive symptoms factor score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-6.1 (± 6.1)	-7.9 (± 6.1)	-8.9 (± 5.5)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
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 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	-0.2

Secondary: Change From Baseline in PANSS Marder Negative Symptoms Factor Score at Day 56

End point title	Change From Baseline in PANSS Marder Negative Symptoms Factor Score at Day 56

End point description:

This measure reports results for the 7 items of the Marder negative symptoms factor of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. Marder factors are a modified grouping of the 30 PANSS items. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. PANSS Marder negative symptoms factor score for each participant was sum of the rating assigned to each of the 7 applicable Marder factor items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Measure reports change from baseline; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (efficacy FAS); also, to be included baseline and an on-treatment Day 56 value of the PANSS Marder negative symptoms factor score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-3.7 (± 5.3)	-5.2 (± 5.5)	-5.3 (± 4.5)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.083
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.2

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Number of participants for calculation of reported mean ± SD change from baseline is 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.067
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	0.1

Secondary: Change From Baseline in PANSS Marder Disorganized Thoughts Factor Score at Day 56

End point title	Change From Baseline in PANSS Marder Disorganized Thoughts Factor Score at Day 56

End point description:

This measure reports results for the 7 items of the Marder disorganized thoughts factor of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. Marder factors are a modified grouping of the 30 PANSS items. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. PANSS Marder disorganized thoughts factor score for each participant was sum of rating assigned to each of the 7 applicable Marder factor items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Measure is change from baseline; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (efficacy FAS); also, to be included baseline and an on-treatment Day 56 value of PANSS Marder disorganized thoughts factor score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-3.4 (± 4.1)	-4.3 (± 4.3)	-4.8 (± 4.3)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.131
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
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 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.135
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	0.3

Secondary: Change From Baseline in PANSS Marder Hostility/Excitement Factor Score at Day 56

End point title	Change From Baseline in PANSS Marder Hostility/Excitement Factor Score at Day 56

End point description:

This measure reports results for the 4 items of the Marder hostility/excitement factor of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. Marder factors are a modified grouping of the 30 PANSS items. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. PANSS Marder hostility/excitement factor score for each participant was sum of rating assigned to each of the 4 applicable Marder factor items, and ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Measure is change from baseline; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (efficacy FAS); also, to be included baseline and an on-treatment Day 56 value of PANSS Marder hostility/excitement factor score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-2.8 (± 4)	-3.8 (± 3.6)	-3.8 (± 4.3)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.071
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
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 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.12
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.2

Secondary: Change From Baseline in PANSS Marder Anxiety/Depression Factor Score at Day 56

End point title	Change From Baseline in PANSS Marder Anxiety/Depression Factor Score at Day 56

End point description:

This measure reports results for the 4 items of the Marder anxiety/depression factor of the PANSS, which is a 30-item clinician-rated instrument used to assess schizophrenia symptoms. Marder factors are a modified grouping of the 30 PANSS items. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. PANSS Marder anxiety/depression factor score for each participant

was sum of rating assigned to each of the 4 applicable Marder factor items, and ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Measure is change from baseline; improvement in symptoms is represented by negative values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (efficacy FAS); also, to be included baseline and an on-treatment Day 56 value of the PANSS Marder anxiety/depression factor score must be available for a participant.

End point type	Secondary
End point timeframe: Baseline and Day 56	

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	-1.8 (± 2.4)	-2.4 (± 2.9)	-2.7 (± 2.9)	

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 77 for placebo and 72 for asenapine 2.5 mg (total – 149). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.263
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
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 77 for placebo and 79 for asenapine 5.0 mg (total – 156). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.146
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.2

Secondary: Total PANSS 30% Responders

End point title	Total PANSS 30% Responders

End point description:

A Total PANSS 30% responder was defined as a participant who had a reduction from baseline of at least 30% in the PANSS Total score at the last available assessment of the study for that participant (i.e., endpoint). The PANSS is a 30-item clinician-rated instrument for assessing schizophrenia symptoms. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The Total score is the sum of the ratings for the individual items, and ranged from 30 to 210 with a higher score indicating greater severity of symptoms. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (this group is termed the efficacy FAS).

End point type	Secondary

End point timeframe:

Baseline up to Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	96	104	
Units: participants	36	48	51	

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Model included terms of (pooled) site, treatment, and baseline PANSS Total Score. Odds ratio (OR) was adjusted for baseline and (pooled) site. An OR of >1 is considered to mean that asenapine has a higher probability of achieving Total PANSS 30% response.

Comparison groups	Asenapine 2.5 mg BID v Placebo

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.028 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.6

Notes:

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

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Model included terms of (pooled) site, treatment, and baseline PANSS Total Score. OR was adjusted for baseline and (pooled) site. An OR of >1 is considered to mean that asenapine has a higher probability of achieving Total PANSS 30% response.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.048 [9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	3.3

Notes:

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

Secondary: Kaplan-Meier Estimate of Cumulative Percentage of Participants With Total PANSS 30% Response at End of Study

End point title	Kaplan-Meier Estimate of Cumulative Percentage of Participants With Total PANSS 30% Response at End of Study

End point description:

A total PANSS 30% response was defined as a reduction from baseline of at least 30% in the PANSS Total score. The PANSS is a 30-item clinician-rated instrument for assessing schizophrenia symptoms. For each item, symptom severity was rated on a 7-point scale, from 1=absent to 7=extreme. The Total score is the sum of the ratings for the individual items, and ranged from 30 to 210 with a higher score indicating greater severity of symptoms. The Kaplan-Meier estimate reports the cumulative percentage of participants with total PANSS 30% response from first drug intake up to approximately Day 59. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (this group is termed the efficacy FAS).

End point type	Secondary

End point timeframe:

Baseline up to approximately Day 59

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	96	104	
Units: cumulative % of participants w/ Response				
number (not applicable)	62	64.2	72.1	

Statistical analyses

Statistical analysis title	Test of Difference in Time to Event Curves
Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.576 [10]
Method	Logrank

Notes:

[10] - p-value is for Log Rank test of difference in time to event (PANSS 30% response) curves between the three treatment groups

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Model included factors for (pooled) site, treatment and baseline PANSS Total Score. A Hazard ratio (HR) of >1 is considered to mean that asenapine has a higher likelihood of being a Total PANSS 30% Responder than placebo.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.171
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Model included factors for (pooled) site, treatment and baseline PANSS Total Score. A Hazard ratio (HR) of >1 is considered to mean that asenapine has a higher likelihood of being a Total PANSS 30% Responder than placebo.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.368
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.8

Secondary: Clinical Global Impression of Improvement (CGI-I) Score at Day 56

End point title	Clinical Global Impression of Improvement (CGI-I) Score at Day 56

End point description:

CGI-I is a 7-point scale for assessing the global improvement of the participant's illness relative to baseline, with ratings from 1=very much improved to 7=very much worse. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (this group is termed the efficacy FAS); also, to be included an on-treatment Day 56 value of the CGI-I score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	3.1 (± 1.1)	2.8 (± 1.1)	2.5 (± 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 76 for placebo and 72 for asenapine 2.5 mg (total – 148). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). Model includes terms of (pooled) site, treatment, visit and the interaction of visit by treatment.

Comparison groups	Asenapine 2.5 mg BID v Placebo

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.094
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
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 76 for placebo and 79 for asenapine 5.0 mg (total – 155). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). Model includes terms of (pooled) site, treatment, visit and the interaction of visit by treatment.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.2

Secondary: CGI-I Responders

End point title	CGI-I Responders

End point description:

A CGI-I responder was defined as a participant who had a CGI-I score of 1 (very much improved) or 2 (much improved) at the last available assessment of the study for that participant (i.e., endpoint). CGI-I is a 7-point scale for assessing the global improvement of the participant's illness relative to baseline, with ratings from 1=very much improved to 7=very much worse. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (this group is termed the efficacy FAS).

End point type	Secondary

End point timeframe:

Baseline up to Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	96	104	
Units: participants	28	36	41	

Statistical analyses

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description:	
Model included terms of region (Asia-Pacific, North America, Eastern Europe [Africa/Latin America sites assigned to this region]) and treatment. OR was adjusted for region. An OR of >1 is considered to mean that asenapine has a higher probability of achieving CGI-I response.	
Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.177 [11]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.8

Notes:

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

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description:	
Model included terms of region (Asia-Pacific, North America, Eastern Europe [Africa/Latin America sites assigned to this region]) and treatment. OR was adjusted for region. An OR of >1 is considered to mean that asenapine has a higher probability of achieving CGI-I response.	
Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.114 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.9

Notes:

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

Secondary: Kaplan-Meier Estimate of Cumulative Percentage of Participants With CGI-I Response at End of Study

End point title	Kaplan-Meier Estimate of Cumulative Percentage of Participants With CGI-I Response at End of Study

End point description:

CGI-I response was defined as the occurrence of a CGI-I score of 1 (very much improved) or 2 (much improved). CGI-I is a 7-point scale for assessing the global improvement of the participant's illness relative to baseline, with ratings from 1=very much improved to 7=very much worse. The Kaplan-Meier estimate reports the cumulative percentage of participants with CGI-I response from first drug intake up to approximately Day 58. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (this group is termed the efficacy FAS).

End point type	Secondary

End point timeframe:

Baseline up to approximately Day 58

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	96	104	
Units: cumulative % of participants w/ Response				
number (not applicable)	54.7	47.1	60.1	

Statistical analyses

Statistical analysis title	Test of Difference in Time to Event Curves
Comparison groups	Placebo v Asenapine 2.5 mg BID v Asenapine 5.0 mg BID
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.057 [13]
Method	Logrank

Notes:

[13] - p-value is for Log Rank test of difference in time to event (CGI-I response) curves between the three treatment groups

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Model included factors for (pooled) site and treatment. An HR of >1 is considered to mean that asenapine has a higher likelihood of being a CGI-I Responder than placebo.

Comparison groups	Asenapine 2.5 mg BID v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.135
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.3

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Model included factors for (pooled) site and treatment. An HR of >1 is considered to mean that asenapine has a higher likelihood of being a CGI-I Responder than placebo.

Comparison groups	Asenapine 5.0 mg BID v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	2.9

Secondary: Change From Baseline in Children's Global Assessment Scale (CGAS) Score at Day 56

End point title	Change From Baseline in Children's Global Assessment Scale (CGAS) Score at Day 56

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 56; improvement in functioning is represented by positive values. Population for analysis was randomized participants who received ≥1 dose of study drug and had both baseline and ≥1 post-baseline on-treatment PANSS Total Score (this group is termed the efficacy FAS); also, to be included a baseline and an on-treatment Day 56 value of the CGAS score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	72	79	
Units: score on a scale				
arithmetic mean (standard deviation)	10.2 (± 12.9)	12.8 (± 12.1)	15 (± 10.8)	

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 76 for placebo and 72 for asenapine 2.5 mg (total – 148). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	148
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.417
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	4.8

Statistical analysis title	Comparison by Treatment Group
Statistical analysis description:	

Number of participants for calculation of reported mean ± SD change from baseline is 76 for placebo and 79 for asenapine 5.0 mg (total – 155). MMRM analysis uses FAS population (Number of participants: placebo – 100, asenapine 2.5 mg – 96, asenapine 5.0 mg – 104). 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	155
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017
Method	MMRM
Parameter estimate	Difference in LS Means
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	7.6

Secondary: Change From Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) Total Score at Day 56

End point title	Change From Baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) Total Score at Day 56

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 a 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 a higher score indicating better quality of life. Measure reports change from baseline; improvement in quality of life is represented by positive values. Last-observation-carried-forward (LOCF) approach was used; if no Day 56 value was available, the last available assessment prior to Day 56 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 PANSS Total Score (efficacy FAS); also, to be included baseline and ≥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 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	83	82	
Units: score on a scale				
arithmetic mean (standard deviation)	3.1 (± 8.9)	3.9 (± 9.3)	6.1 (± 8.7)	

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	168
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2.8

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	167
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.064
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	4.3

Secondary: Change From Baseline in PQ-LES-Q Overall Score (i.e., Item 15) at Day 56

End point title	Change From Baseline in PQ-LES-Q Overall Score (i.e., Item 15) at Day 56

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 a scale of 1=very poor to 5=very good. Items 1-14 assess specific areas; Item 15 is a global assessment. 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. Measure reports change from baseline; improvement in quality of life is represented by positive values. LOCF approach was used; if no Day 56 value was available, the last available assessment prior to Day 56 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 PANSS Total Score (this group is termed the efficacy FAS); also, to be included a baseline and ≥1 post-baseline on-treatment value of the PQ-LES-Q overall score must be available for a participant.

End point type	Secondary

End point timeframe:

Baseline and Day 56

End point values	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	83	82	
Units: score on a scale				
arithmetic mean (standard deviation)	0.2 (± 1)	0.3 (± 1.1)	0.5 (± 0.9)	

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	168
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.407
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.33

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	167
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.111
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.42

Adverse events

Adverse events information

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants receive placebo asenapine tablets sublingually BID for 8 weeks	
Reporting group title	Asenapine 2.5 mg BID
Reporting group description:	
Participants receive active asenapine 2.5 mg tablets sublingually BID for 8 weeks	
Reporting group title	Asenapine 5.0 mg BID
Reporting group description:	
Participants receive active asenapine 2.5 mg tablets sublingually 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 active asenapine 5.0 mg tablets sublingually BID for the remainder of the 8-week 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 / 102 (2.94%)	3 / 98 (3.06%)	3 / 106 (2.83%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Psychiatric disorders			
Hallucination, Auditory			
subjects affected / exposed	0 / 102 (0.00%)	1 / 98 (1.02%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	3 / 102 (2.94%)	1 / 98 (1.02%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	2 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 102 (0.00%)	1 / 98 (1.02%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Typhoid Fever			
subjects affected / exposed	0 / 102 (0.00%)	0 / 98 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Asenapine 2.5 mg BID	Asenapine 5.0 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 102 (22.55%)	39 / 98 (39.80%)	46 / 106 (43.40%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 102 (5.88%)	7 / 98 (7.14%)	8 / 106 (7.55%)
occurrences (all)	7	12	11
Sedation			
subjects affected / exposed	2 / 102 (1.96%)	4 / 98 (4.08%)	12 / 106 (11.32%)
occurrences (all)	2	4	14
Somnolence			
subjects affected / exposed	7 / 102 (6.86%)	20 / 98 (20.41%)	18 / 106 (16.98%)
occurrences (all)	7	22	21
Akathisia			
subjects affected / exposed	1 / 102 (0.98%)	4 / 98 (4.08%)	7 / 106 (6.60%)
occurrences (all)	1	5	9
Dizziness			
subjects affected / exposed	1 / 102 (0.98%)	7 / 98 (7.14%)	2 / 106 (1.89%)
occurrences (all)	1	7	5
Gastrointestinal disorders			
Hypoaesthesia Oral			
subjects affected / exposed	1 / 102 (0.98%)	5 / 98 (5.10%)	5 / 106 (4.72%)
occurrences (all)	1	6	5
Nausea			

subjects affected / exposed	8 / 102 (7.84%)	2 / 98 (2.04%)	2 / 106 (1.89%)
occurrences (all)	9	2	2
Psychiatric disorders Insomnia			
subjects affected / exposed	6 / 102 (5.88%)	5 / 98 (5.10%)	10 / 106 (9.43%)
occurrences (all)	8	6	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2011	Amendment 01: Primary reason for amendment was to incorporate revisions to text presenting tapering periods for discontinuation of prohibited medications prior to study and upper limit of age range for entry into extension trial (Protocol P05897).
03 May 2012	Amendment 02: Primary reason for amendment was to incorporate revisions to requirements for final visit for subjects enrolling in extension trial (Protocol P05897), measures included in key secondary objectives, identification of staff qualified to administer an efficacy assessment, allowed concomitant medications/rescue therapy, list of closely monitored events, statistical analysis and procedures for liver enzyme monitoring.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported