Clinical trial results:
A 50-Week Open-Label, Flexible-Dose Trial of Asenapine Extension Treatment to P06107 in Pediatric Subjects with Acute Manic or Mixed Episodes Associated With Bipolar I Disorder

Summary

EudraCT number	2010-022648-19
Trial protocol	Outside EU/EEA
Global end of trial date	05 September 2014

Results information

Result version number	v1
This version publication date	05 April 2016
First version publication date	11 March 2015

Trial information

Trial identification

Sponsor protocol code	P05898

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01349907
WHO universal trial number (UTN)	-

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	05 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2014
Global end of trial reached?	Yes
Global end of trial date	05 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will investigate the safety and tolerability of a flexible dosing regimen of asenapine for the long term treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents who completed the 3-week treatment base trial P06107 (NCT01244815).

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 measures defined for this individual study were 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 (i.e. lorazepam up to 4 mg/day or an equivalent dose of short-acting benzodiazepines) and EPS medications (i.e. anticholinergics) are allowed. Benadryl (dipenhydramine) 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	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	United States: 303
Worldwide total number of subjects	322
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)	53
Adolescents (12-17 years)	268
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:

Participants were chosen from children and adolescents with a manic or mixed episode associated with bipolar I disorder who completed the 3-week efficacy and safety base trial P06107.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Asenapine

Arm description:

Participants treated with placebo in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg twice per day (BID), then up-titrated to 5 mg BID at Day 4, then up-titrated to 10 mg BID at Day 7. After Day 7, flexible dosing of asenapine was continued for up to 50 weeks.

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

Dosage and administration details:

One flavored asenapine sublingual tablet BID (either 2.5, 5 or 10 mg) starting at 2.5 mg on Day 1 for three consecutive days. Normally on Day 4, the dose will increase to 5 mg BID beginning with the evening dose. Normally on Day 7, the dose will increase to 10 mg BID beginning with the evening dose. The dose may be up-titrated earlier than Days 4 and 7 at the investigator's discretion. Beginning on Day 8 (or after at least 1 day on 10 mg asenapine BID) dosing will be flexible (2.5, 5, or 10 mg BID) until up to Week 50.

Investigational medicinal product name	Rescue medication
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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 (i.e. lorazepam up to 4 mg/day or an equivalent dose of short-acting benzodiazepines) and EPS medications (i.e. anticholinergics) are allowed. Benadryl (dipenhydramine) and beta blockers are also permitted, provided that they are not taken within 8 hours of efficacy assessments.

Arm title	Asenapine/Asenapine

Arm description:

Participants treated with asenapine in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg BID, then up-titrated to 5 mg BID at Day 4, then up-titrated to 10 mg BID at Day 7. After Day 7, flexible dosing of asenapine was continued for up to 50 weeks.

Arm type	Experimental

Investigational medicinal product name	Asenapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Oral use

Dosage and administration details:

One flavored asenapine sublingual tablet BID (either 2.5, 5 or 10 mg) starting at 2.5 mg on Day 1 for three consecutive days. Normally on Day 4, the dose will increase to 5 mg BID beginning with the evening dose. Normally on Day 7, the dose will increase to 10 mg BID beginning with the evening dose. The dose may be up-titrated earlier than Days 4 and 7 at the investigator's discretion. Beginning on Day 8 (or after at least 1 day on 10 mg asenapine BID) dosing will be flexible (2.5, 5, or 10 mg BID) until up to Week 50.

Investigational medicinal product name	Rescue medication
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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 (i.e. lorazepam up to 4 mg/day or an equivalent dose of short-acting benzodiazepines) and EPS medications (i.e. anticholinergics) are allowed. Benadryl (dipenhydramine) and beta blockers are also permitted, provided that they are not taken within 8 hours of efficacy assessments.

Number of subjects in period 1	Placebo/Asenapine	Asenapine/Asenapine
Started	81	241
Completed	38	102
Not completed	43	139
Consent withdrawn by subject	8	30
Treatment failure	4	13
Administrative	1	1
Adverse event, non-fatal	11	37
Lost to follow-up	6	25
Protocol deviation	13	33

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/Asenapine
Reporting group description:	
Participants treated with placebo in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg twice per day (BID), then up-titrated to 5 mg BID at Day 4, then up-titrated to 10 mg BID at Day 7. After Day 7, flexible dosing of asenapine was continued for up to 50 weeks.	
Reporting group title	Asenapine/Asenapine
Reporting group description:	
Participants treated with asenapine in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg BID, then up-titrated to 5 mg BID at Day 4, then up-titrated to 10 mg BID at Day 7. After Day 7, flexible dosing of asenapine was continued for up to 50 weeks.	

Reporting group values	Placebo/Asenapine	Asenapine/Asenapine	Total
Number of subjects	81	241	322
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)	13	40	53
Adolescents (12-17 years)	67	201	268
Adults (18-64 years)	1	0	1
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	13.7	13.8	
standard deviation	± 2	± 2	-
Gender categorical Units: Subjects			
Female	48	113	161
Male	33	128	161

End points

End points reporting groups

Reporting group title	Placebo/Asenapine

Reporting group description:

Participants treated with placebo in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg twice per day (BID), then up-titrated to 5 mg BID at Day 4, then up-titrated to 10 mg BID at Day 7. After Day 7, flexible dosing of asenapine was continued for up to 50 weeks.

Reporting group title	Asenapine/Asenapine

Reporting group description:

Participants treated with asenapine in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg BID, then up-titrated to 5 mg BID at Day 4, then up-titrated to 10 mg BID at Day 7. After Day 7, flexible dosing of asenapine was continued for up to 50 weeks.

Primary: Number of participants who experienced clinical or laboratory adverse events

End point title	Number of participants who experienced clinical or laboratory adverse events[1]

End point description:

A clinical or laboratory adverse event is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Participants analyzed received at least one dose of trial medication, and were 17 years old or younger. One treated participant from the Placebo/Asenapine group, who was 18 years old, was excluded from this analysis.

End point type	Primary

End point timeframe:

Day 1 of treatment to 30 days after the last dose of study drug (up to approximately 54 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned or performed for this primary endpoint; or for any other endpoint in this study.

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[2]	241		
Units: Participants				
number (not applicable)	74	197		

Notes:

[2] - One participant who was 18 years old was excluded from this analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Young Mania Rating Scale (Y-MRS) total score at Day 182

End point title	Change from baseline in Young Mania Rating Scale (Y-MRS) total score at Day 182

End point description:

The Y-MRS assesses the severity of manic episodes by assigning a severity rating to each of 11 items (Elevated mood, Increased motor activity-energy, Sexual interest, Sleep, Irritability, Speech, Language-

thought disorder, Thought content, Disruptive-aggressive behavior, Appearance, Insight). Seven of the 11 items are rated on a scale of 0-4, and 4 of the items are rated on a scale of 0-8. The Y-MRS total score, observed cases (OC), the assessment closest to the scheduled assessment day within the allowed window, 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. Improvement in symptoms is represented by change from baseline values that are negative. The Full Analysis Set (FAS) is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[3]	112[4]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-13 (± 8.3)	-4.9 (± 7.8)		

Notes:

[3] - Full Analysis Set (FAS)

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Y-MRS total score at Day 350

End point title	Change from baseline in Y-MRS total score at Day 350

End point description:

The Y-MRS assesses the severity of manic episodes by assigning a severity rating to each of 11 items (Elevated mood, Increased motor activity-energy, Sexual interest, Sleep, Irritability, Speech, Language-thought disorder, Thought content, Disruptive-aggressive behavior, Appearance, Insight). Seven of the 11 items are rated on a scale of 0-4, and 4 of the items are rated on a scale of 0-8. The Y-MRS total score, OC, 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. Improvement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[5]	45[6]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-15.2 (± 5.8)	-6.5 (± 10.5)		

Notes:

[5] - FAS at Day 350

[6] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were Y-MRS total score remitters (Y-MRS =<12) at Day 182

End point title	Percentage of participants who were Y-MRS total score remitters (Y-MRS =<12) at Day 182

End point description:

The Y-MRS is an 11-item clinician-rated instrument for assessing the severity of manic episodes. The Y-MRS total score, OC 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. A remitter is a participant with a Y-MRS total score of 12 or lower. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[7]	112[8]		
Units: Percentage of participants				
number (not applicable)	83.8	63.4		

Notes:

[7] - FAS at Day 182

[8] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were Y-MRS total score remitters (Y-MRS =<12) at Day 350

End point title	Percentage of participants who were Y-MRS total score remitters (Y-MRS =<12) at Day 350

End point description:

The Y-MRS is an 11-item clinician-rated instrument for assessing the severity of manic episodes. The Y-MRS total score, OC 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. A remitter is a participant with a Y-MRS total score of 12 or lower. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[9]	45[10]		
Units: Percentage of participants				
number (not applicable)	90	75.6		

Notes:

[9] - FAS at Day 350

[10] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were Y-MRS total score responders at Day 182

End point title	Percentage of participants who were Y-MRS total score responders at Day 182

End point description:

The Y-MRS is an 11-item clinician-rated instrument for assessing the severity of manic episodes.The Y-MRS total score, OC 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. A Y-MRS responder experiences a 50% or more decrease from baseline in Y-MRS total score. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[11]	111[12]		
Units: Percentage of participants				
number (not applicable)	64.9	37.8		

Notes:

[11] - FAS at Day 182

[12] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who were Y-MRS total score responders at Day 350

End point title	Percentage of participants who were Y-MRS total score responders at Day 350

End point description:

The Y-MRS is an 11-item clinician-rated instrument for assessing the severity of manic episodes.The Y-MRS total score, OC 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. A Y-MRS responder experiences a 50% or more decrease from baseline in Y-MRS total score. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[13]	43[14]		
Units: Percentage of participants				
number (not applicable)	80	53.5		

Notes:

[13] - FAS at Day 350

[14] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first total Y-MRS 50% response

End point title	Time to first total Y-MRS 50% response

End point description:

The Y-MRS is an 11-item clinician-rated instrument for assessing the severity of manic episodes. The Y-MRS total score, OC for each participant is the sum of the ratings for the 11 individual items, ranging from 0-60, with higher scores indicating more severe symptoms. The time to 50% response is the number of days on treatment to achieve a 50% decrease from baseline in Y-MRS total score. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Up to Week 50

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[15]	227[16]		
Units: Days				
median (confidence interval 95%)	49 (44 to 50)	15 (14 to 21)		

Notes:

[15] - FAS population

[16] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to failure to maintain response in Y-MRS total score

End point title	Time to failure to maintain response in Y-MRS total score

End point description:

The Y-MRS is an 11-item clinician-rated instrument for assessing the severity of manic episodes. The Y-MRS total score, OC for each participant is the sum of the ratings for the 11 individual items, ranging from 0-60, with higher scores indicating more severe symptoms. The time to failure is the number of days from first achieving a 50% or more decrease from baseline in Y-MRS total score to the first subsequent day of a less than 50% decrease from baseline in Y-MRS total score. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment. Results were shown as "0" because either time to failure or the 95% Confidence Interval (CI) were unable to be determined even after 362 days of follow-up (NA). For the Asenapine/Asenapine arm: Median - NA, 95% CI - 268.0 to NA. For the Placebo/Asenapine arm: Median -194.0, 95% CI - 78.0 to NA.

End point type	Secondary

End point timeframe:

Up to Week 50

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[17]	120[18]		
Units: Days				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Notes:

[17] - Y-MRS 50% responders in base trial P06107, who were also FAS population in P05898

[18] - Y-MRS 50% responders in base trial P06107, who were also FAS population in P05898

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Clinical Global Impression Scale for assessing overall Bipolar Illness (CGI-BP overall) at Day 182

End point title	Change from baseline in Clinical Global Impression Scale for assessing overall Bipolar Illness (CGI-BP overall) at Day 182

End point description:

The CGI-BP overall OC is a single value score for assessing overall bipolar illness, recorded on a 7-point scale ranging from 1 for normal/not ill, to 7 for very severely ill. An improvement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[19]	113[20]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.8 (± 1.1)	-0.9 (± 1)		

Notes:

[19] - FAS at Day 182

[20] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Clinical Global Impression Scale for assessing overall Bipolar Illness (CGI-BP overall) at Day 350

End point title	Change from baseline in Clinical Global Impression Scale for assessing overall Bipolar Illness (CGI-BP overall) at Day 350

End point description:

The CGI-BP overall OC is a single value score for assessing overall bipolar illness, recorded on a 7-point scale ranging from 1 for normal/not ill, to 7 for very severely ill. An improvement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[21]	46[22]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.4 (± 1.2)	-1.2 (± 1.3)		

Notes:

[21] - FAS at Day 350

[22] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Clinical Global Impression Scale for assessing

depression (CGI-BP depression) at Day 182

End point title	Change from baseline in Clinical Global Impression Scale for assessing depression (CGI-BP depression) at Day 182

End point description:

The CGI-BP depression OC is a single value score for assessing depression, recorded on a 7-point scale ranging from 1 for normal/not ill, to 7 for very severely ill. An improvement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[23]	113[24]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.8 (± 1.2)	-0.5 (± 0.9)		

Notes:

[23] - FAS at Day 182

[24] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Clinical Global Impression Scale for assessing depression (CGI-BP depression) at Day 350

End point title	Change from baseline in Clinical Global Impression Scale for assessing depression (CGI-BP depression) at Day 350

End point description:

The CGI-BP depression OC is a single value score for assessing depression, recorded on a 7-point scale ranging from 1 for normal/not ill, to 7 for very severely ill. An improvement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[25]	46[26]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.2 (± 1.3)	-0.4 (± 1)		

Notes:

[25] - FAS at day 350

[26] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Clinical Global Impression Scale for assessing mania (CGI-BP mania) at Day 182

End point title	Change from baseline in Clinical Global Impression Scale for assessing mania (CGI-BP mania) at Day 182

End point description:

The CGI-BP mania OC is a single value score for assessing mania, recorded on a 7-point scale ranging from 1 for normal/not ill, to 7 for very severely ill. An improvement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[27]	113[28]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.9 (± 1.1)	-1 (± 1)		

Notes:

[27] - FAS at Day 182

[28] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Clinical Global Impression Scale for assessing mania (CGI-BP mania) at Day 350

End point title	Change from baseline in Clinical Global Impression Scale for assessing mania (CGI-BP mania) at Day 350

End point description:

The CGI-BP mania OC is a single value score for assessing mania, recorded on a 7-point scale ranging from 1 for normal/not ill, to 7 for very severely ill. An improvement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary
End point timeframe: Baseline and Day 350	

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[29]	46[30]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.3 (± 1.2)	-1.2 (± 1.3)		

Notes:

[29] - FAS at Day 350

[30] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Children's Depression Rating Scale, Revised (CDRS-R) total score at Day 182

End point title	Change from baseline in Children's Depression Rating Scale, Revised (CDRS-R) total score at Day 182

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, OC 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. Iimprovement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary
End point timeframe: Baseline and Day 182	

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[31]	112[32]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-5.4 (± 7.5)	-1.4 (± 6.4)		

Notes:

[31] - FAS at Day 182

[32] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Children's Depression Rating Scale, Revised (CDRS-R) total score at Day 350

End point title	Change from baseline in Children's Depression Rating Scale, Revised (CDRS-R) total score at Day 350

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, OC 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. Iimprovement in symptoms is represented by change from baseline values that are negative. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[33]	44[34]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-4.3 (± 6.6)	-1.1 (± 5.5)		

Notes:

[33] - FAS at Day 350

[34] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of CDRS-R responders at Day 182

End point title	Percentage of CDRS-R responders at Day 182

End point description:

The CDRS-R is a 17-item clinician-rated instrument for assessing the presence and severity of depressive symptoms in children. The CDRS-R total score, OC 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. A CDRS-R responder experiences a 50% or more decrease from baseline in CDRS-R total score. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[35]	111[36]		
Units: Percentage of participants				
number (not applicable)	56.8	36		

Notes:

[35] - FAS at Day 182

[36] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of CDRS-R responders at Day 350

End point title	Percentage of CDRS-R responders at Day 350

End point description:

The CDRS-R is a 17-item clinician-rated instrument for assessing the presence and severity of depressive symptoms in children. The CDRS-R total score, OC 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. A CDRS-R responder experiences a 50% or more decrease from baseline in CDRS-R total score. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[37]	43[38]		
Units: Percentage of participants				
number (not applicable)	65	32.6		

Notes:

[37] - FAS at Day 350

[38] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with emergent depression based on CDRS-R at Day 182

End point title	Percentage of participants with emergent depression based on CDRS-R at Day 182

End point description:

The CDRS-R is a 17-item clinician-rated instrument for assessing the presence and severity of depressive symptoms in children. The CDRS-R total score, OC 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. Participants with a CDRS-R score of 40 or greater (whose baseline CDRS-R less than 40) are defined as exhibiting emergent depression which is a strong indicator of the presence or

potential for a major depressive disorder. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[39]	112[40]		
Units: Percentage of participants				
number (not applicable)	0	2.7		

Notes:

[39] - FAS at Day 182

[40] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with emergent depression based on CDRS-R at Day 350

End point title	Percentage of participants with emergent depression based on CDRS-R at Day 350

End point description:

The CDRS-R is a 17-item clinician-rated instrument for assessing the presence and severity of depressive symptoms in children. The CDRS-R total score, OC 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. Participants with a CDRS-R score of 40 or greater (whose baseline CDRS-R less than 40) are defined as exhibiting emergent depression which is a strong indicator of the presence or potential for a major depressive disorder. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[41]	44[42]		
Units: Percentage of participants				
number (not applicable)	5	2.3		

Notes:

[41] - FAS at Day 350

[42] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Children's Global Assessment Scale (CGAS) at Day 182

End point title	Change from baseline in Children's Global Assessment Scale (CGAS) at Day 182

End point description:

CGAS is a scale with a possible range of 1 to 100, measuring psychological, social, and school functioning in children. Minimum scores, OC range from 1-10, representing the need for constant supervision (worse result) to maximum scores of 91-100, representing superior functioning (better result). An improvement in function is represented by a change from baseline value that is positive. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[43]	114[44]		
Units: Score on a scale				
arithmetic mean (standard deviation)	17.4 (± 9.9)	9.7 (± 10.1)		

Notes:

[43] - FAS at Day 182

[44] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Children's Global Assessment Scale (CGAS) at Day 350

End point title	Change from baseline in Children's Global Assessment Scale (CGAS) at Day 350

End point description:

CGAS is a scale with a possible range of 1 to 100, measuring psychological, social, and school functioning in children. Minimum scores, OC range from 1-10, representing the need for constant supervision (worse result) to maximum scores of 91-100, representing superior functioning (better result). An improvement in function is represented by a change from baseline value that is positive. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[45]	46[46]		
Units: Score on a scale				
arithmetic mean (standard deviation)	22.5 (± 8)	13.1 (± 13.6)		

Notes:

[45] - FAS at Day 350

[46] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a CGAS score of equal or greater than 70 at Day 182

End point title	Percentage of participants with a CGAS score of equal or greater than 70 at Day 182

End point description:

CGAS is a scale with a possible range of 1 to 100, measuring psychological, social, and school functioning in children. Minimum scores, OC range from 1-10, representing the need for constant supervision (worse result) to maximum scores of 91-100, representing superior functioning (better result). The percentage of participants with a score of 70 or greater, represent those with normal to superior social functioning. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[47]	114[48]		
Units: Percentage of participants				
number (not applicable)	73	55.3		

Notes:

[47] - FAS at Day 182

[48] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a CGAS score of equal or greater than 70 at Day 350

End point title	Percentage of participants with a CGAS score of equal or greater than 70 at Day 350

End point description:

CGAS is a scale with a possible range of 1 to 100, measuring psychological, social, and school functioning in children. Minimum scores, OC range from 1-10, representing the need for constant supervision (worse result) to maximum scores of 91-100, representing superior functioning (better result). The percentage of participants with a score of 70 or greater, represent those with normal or superior social functioning. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[49]	46[50]		
Units: Percentage of participants				
number (not applicable)	85	73.9		

Notes:

[49] - FAS at Day 350

[50] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaires (PQ-LES-Q) total score at Day 182

End point title	Change from baseline in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaires (PQ-LES-Q) total score at Day 182

End point description:

PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant rates 15 items reflecting quality of life from the previous week on a scale of 1=very poor to 5=very good. Items 1-14 assess specific areas (e.g., health, mood or feelings); item 15 is a global assessment of overall quality of life. The PQ-LES-Q total score for each participant, OC is the sum of the rating assigned to each of the first 14 items, and ranges from 14 to 70, with a higher score indicating better quality of life. An improvement in quality of life is represented by change from baseline values that are positive. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 182

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[51]	111[52]		
Units: Score on a scale				
arithmetic mean (standard deviation)	4.4 (± 8.3)	1 (± 7.1)		

Notes:

[51] - FAS at Day 182

[52] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in PQ-LES-Q total score at Day 350

End point title	Change from baseline in PQ-LES-Q total score at Day 350

End point description:

PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant rates 15 items reflecting quality of life from the previous week on a scale of 1=very poor to 5=very good. Items 1-14 assess specific areas (e.g., health, mood or feelings); item 15 is a global assessment of overall quality of life. The PQ-LES-Q total score for each participant, OC is the sum of the rating assigned to each of the first 14 items, and ranges from 14 to 70, with a higher score indicating better quality of life. An improvement in quality of life is represented by change from baseline values that are positive. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary

End point timeframe:

Baseline and Day 350

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[53]	45[54]		
Units: Score on a scale				
arithmetic mean (standard deviation)	3.4 (± 10.9)	0.5 (± 7.3)		

Notes:

[53] - FAS at Day 350

[54] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in PQ-LES-Q overall score at Day 182

End point title	Change from baseline in PQ-LES-Q overall score at Day 182

End point description:

PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant rates 15 items reflecting quality of life from the previous week. Item 15, the PQ-LES-Q overall score, OC is a global assessment of overall quality of life, and ranges from 1 to 5, with a higher score indicating better quality of life. An improvement in quality of life is represented by change from baseline values that are positive. The FAS is analyzed consisting of participants 17 years

old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary
End point timeframe:	
Baseline and Day 182	

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[55]	111[56]		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.3 (± 0.8)	0.1 (± 0.8)		

Notes:

[55] - FAS at Day 182

[56] - FAS at Day 182

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in PQ-LES-Q overall score at Day 350

End point title	Change from baseline in PQ-LES-Q overall score at Day 350

End point description:

PQ-LES-Q is a questionnaire to assess quality of life enjoyment and satisfaction in children and adolescents. The participant rates 15 items reflecting quality of life from the previous week. Item 15, the PQ-LES-Q overall score, OC is a global assessment of overall quality of life, and ranges from 1 to 5, with a higher score indicating better quality of life. An improvement in quality of life is represented by change from baseline values that are positive. The FAS is analyzed consisting of participants 17 years old or younger, who have taken at least one dose of trial medication, and have a baseline and at least one post-baseline Y-MRS assessment.

End point type	Secondary
End point timeframe:	
Baseline and Day 350	

End point values	Placebo/Asenapine	Asenapine/Asenapine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[57]	45[58]		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.3 (± 0.9)	0.4 (± 1)		

Notes:

[57] - FAS at Day 350

[58] - FAS at Day 350

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
30 days after the last dose of study drug (up to approximately 54 weeks)	
Adverse event reporting additional description:	
All enrolled and treated participants	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo/Asenapine
Reporting group description:	
Participants treated with placebo in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg twice per day (BID), then up-titrated to 5 mg BID at day 4, then up-titrated to 10 mg BID at day 7. After day 7, flexible dosing of asenapine was continied for 1 year.	
Reporting group title	Asenapine/Asenapine
Reporting group description:	
Participants treated with asenapine in base trial P06107 were first treated with open-label flavored asenapine 2.5 mg twice per day (BID), then up-titrated to 5 mg BID at day 4, then up-titrated to 10 mg BID at day 7. After day 7, flexible dosing of asenapine was continied for 1 year.	

Serious adverse events	Placebo/Asenapine	Asenapine/Asenapine	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 81 (7.41%)	17 / 241 (7.05%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dystonia			

subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	16 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 81 (1.23%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	16 / 32	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Swollen tongue			
subjects affected / exposed	1 / 81 (1.23%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	16 / 32	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 81 (1.23%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 32	0 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 81 (1.23%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 16	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bipolar disorder			
subjects affected / exposed	2 / 81 (2.47%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 37	0 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 81 (0.00%)	3 / 241 (1.24%)	
occurrences causally related to treatment / all	0 / 0	16 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in social behaviour			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exhibitionism			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impulsive behaviour			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self-injurious ideation			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	0 / 81 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 81 (1.23%)	7 / 241 (2.90%)	
occurrences causally related to treatment / all	0 / 16	16 / 128	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo/Asenapine	Asenapine/Asenapine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 81 (80.25%)	135 / 241 (56.02%)	
Investigations			
Weight increased			
subjects affected / exposed	16 / 81 (19.75%)	42 / 241 (17.43%)	
occurrences (all)	128	343	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 81 (9.88%)	5 / 241 (2.07%)	
occurrences (all)	83	48	
Dysgeusia			
subjects affected / exposed	5 / 81 (6.17%)	4 / 241 (1.66%)	
occurrences (all)	40	32	
Headache			
subjects affected / exposed	11 / 81 (13.58%)	21 / 241 (8.71%)	
occurrences (all)	168	240	
Sedation			
subjects affected / exposed	19 / 81 (23.46%)	23 / 241 (9.54%)	
occurrences (all)	216	232	
Somnolence			
subjects affected / exposed	29 / 81 (35.80%)	44 / 241 (18.26%)	
occurrences (all)	288	403	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 81 (7.41%)	15 / 241 (6.22%)	
occurrences (all)	56	136	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	6 / 81 (7.41%)	10 / 241 (4.15%)	
occurrences (all)	48	120	
Hypoaesthesia oral			
subjects affected / exposed	11 / 81 (13.58%)	2 / 241 (0.83%)	
occurrences (all)	88	16	
Nausea			
subjects affected / exposed	9 / 81 (11.11%)	15 / 241 (6.22%)	
occurrences (all)	72	136	
Paraesthesia oral			
subjects affected / exposed	8 / 81 (9.88%)	3 / 241 (1.24%)	
occurrences (all)	80	24	
Vomiting			
subjects affected / exposed	4 / 81 (4.94%)	16 / 241 (6.64%)	
occurrences (all)	32	144	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	5 / 81 (6.17%)	4 / 241 (1.66%)	
occurrences (all)	40	32	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	6 / 81 (7.41%)	16 / 241 (6.64%)	
occurrences (all)	48	144	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2011	Amendment 1: Raised the lower age limit to greater than or equal to 12 years of age, and allowed participants who turned 18 years of age during acute trial (P06107) to continue into extension trial (P05898).
02 December 2011	Amendment 2: Addition of new investigators, and revised information for one investigator
12 January 2012	Amendment 3: Inclusion of 10 and 11 year olds; revision of options for conducting visits; updated text on non-sexually active females; updating of allowed rescue therapy; updated to clarify safety follow-up visit; added drug hypersensitivity reactions as a closely monitored event; updated monitoring of liver enzymes; clarified definition of "clinically important at any time"; updated reference section.
28 June 2012	Amendment 4:Extended length of trial to 50 weeks of treatment; added Cognition Battery and laboratory tests at Days 182 and 350; updated sponsor in title page; updated text for monitoring participants; updated footnote for date of informed consent; added text to clarify visit windows; deleted subgroup analysis; deleted efficacy parameter "sustained Y-MRS remitter".
15 May 2013	Amendment 5: Added clarification about growth analysis for Russia; added subgroup analysis by geographic region; provided guidance for interim analysis, and interim CSR

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported