Clinical trial results:
A Multicenter, Double-Blind, Fixed-Dose, Long-Term Extension Trial of the Safety of Asenapine using Olanzapine as an Active Control in Subjects Diagnosed with Schizophrenia who Completed Protocol P05688 (formerly 041038) (Phase 3B, Protocol P05689 [formerly 041039])

Summary

EudraCT number	2010-018408-96
Trial protocol	BG
Global end of trial date	06 March 2015

Results information

Result version number	v1 (current)
This version publication date	31 January 2019
First version publication date	31 January 2019

Trial information

Trial identification

Sponsor protocol code	P05689

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01617200
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Research Institute, Inc., an affiliate of Allergan, plc
Sponsor organisation address	185 Hudson Street, Jersey City, United States, NJ 07302
Public contact	Willie Earley, Forest Research Institute, Inc., an affiliate of Allergan, plc, Willie.Earley@Allergan.com
Scientific contact	Willie Earley, Forest Research Institute, Inc., an affiliate of Allergan, plc, Willie.Earley@Allergan.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2015
Global end of trial reached?	Yes
Global end of trial date	06 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to evaluate the long-term safety of 2.5 and 5 milligram (mg) twice daily (BID) asenapine in schizophrenia subjects.

Protection of trial subjects:

This trial was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

This was a long-term extension trial for subjects who had completed the 6-week short-term trial P05688. In the previous short-term trial, subjects had been randomly assigned to receive a fixed dose of asenapine (either 2.5 mg or 5 mg BID) or olanzapine 15 mg once daily (QD) or placebo (BID) for 6 weeks.

Evidence for comparator: -

Actual start date of recruitment	12 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Croatia: 7
Worldwide total number of subjects	120
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	120
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First participant enrolled: 12 March 2013; last participant completed: 6 Mar 2015. This study was performed at 39 sites across the United States, Bulgaria, Romania, Russian Federation, Croatia, and the Ukraine.

Pre-assignment

Screening details:

A total of 120 participants who had previously completed the short-term randomized trial P05688 continued in the current extension trial (P05689). Participants randomly assigned to asenapine or olanzapine in P05688 were assigned the same treatment regimen in P05689; participants randomly assigned to placebo were assigned to asenapine 2.5 mg BID.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo / Asenapine 2.5 mg

Arm description:

In the previous short-term trial PO5688, participants were administered placebo for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks.

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

Dosage and administration details:

2.5 mg fast-dissolving active asenapine tablets administered sublingually

Investigational medicinal product name	Placebo Olanzapine
Investigational medicinal product code	Placebo Olanzapine
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated placebo olanzapine tablets (to match 5 and 10 mg active olanzapine tablets) administered orally

Arm title	Asenapine 2.5 mg / Asenapine 2.5 mg

Arm description:

In the previous short-term trial PO5688, participants were administered one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 2.5 mg asenapine tablet BID) for 26 weeks.

Arm type	Experimental

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

Dosage and administration details:

2.5 mg fast-dissolving active asenapine tablets administered sublingually

Investigational medicinal product name	Placebo Olanzapine
Investigational medicinal product code	Placebo Olanzapine
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated placebo olanzapine tablets (to match 5 and 10 mg active olanzapine tablets) administered orally

Arm title	Asenapine 2.5 mg Overall

Arm description:

In the previous short-term trial PO5688, participants were administered either placebo or one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks. The 'asenapine 2.5 mg overall' arm represents the 'placebo / asenapine 2.5 mg' and 'asenapine 2.5 mg / asenapine 2.5 mg' arms combined.

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

Dosage and administration details:

2.5 mg fast-dissolving active asenapine tablets administered sublingually

Investigational medicinal product name	Placebo Olanzapine
Investigational medicinal product code	Placebo Olanzapine
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated placebo olanzapine tablets (to match 5 and 10 mg active olanzapine tablets) administered orally

Arm title	Asenapine 5 mg / Asenapine 5 mg

Arm description:

In the previous short-term trial PO5688, participants were administered one 5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 5 mg asenapine tablet BID) for 26 weeks.

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

Dosage and administration details:

5 mg fast-dissolving active asenapine tablets administered sublingually

Investigational medicinal product name	Placebo Olanzapine
Investigational medicinal product code	Placebo Olanzapine
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated placebo olanzapine tablets (to match 5 and 10 mg active olanzapine tablets) administered orally

Arm title	Olanzapine 15 mg / Olanzapine 15 mg

Arm description:

In the previous short-term trial PO5688, participants were administered 15 mg olanzapine (as one 10 mg and one 5 mg tablet) QD for 42 days (except during Week 1 when olanzapine 10 mg QD was administered); in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, 15 mg olanzapine) for 26 weeks.

Arm type	Active comparator
Investigational medicinal product name	Olanzapine
Investigational medicinal product code	Olanzapine
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 and 10 mg film-coated active olanzapine tablets administered orally QD. The time of the active olanzapine dose (either morning or evening) was not disclosed in order to preserve blinding

Investigational medicinal product name	Placebo Olanzapine
Investigational medicinal product code	Placebo Olanzapine
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated placebo olanzapine tablets (to match 5 and 10 mg active olanzapine tablets) administered orally

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

Dosage and administration details:

Fast dissolving placebo asenapine tablets (to match 2.5 mg and 5 mg active asenapine tablets) administered sublingually

Number of subjects in period 1	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 2.5 mg Overall
Started	31	31	62
Completed	31	28	59
Not completed	0	3	3
Consent withdrawn by subject	-	3	3
Adverse event, non-fatal	-	-	-
Lost to follow-up	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg

Started	42	16
Completed	32	12
Not completed	10	4
Consent withdrawn by subject	6	1
Adverse event, non-fatal	-	2
Lost to follow-up	1	1
Protocol deviation	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo / Asenapine 2.5 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered placebo for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks.	
Reporting group title	Asenapine 2.5 mg / Asenapine 2.5 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 2.5 mg asenapine tablet BID) for 26 weeks.	
Reporting group title	Asenapine 2.5 mg Overall
Reporting group description:	
In the previous short-term trial PO5688, participants were administered either placebo or one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks. The 'asenapine 2.5 mg overall' arm represents the 'placebo / asenapine 2.5 mg' and 'asenapine 2.5 mg / asenapine 2.5 mg' arms combined.	
Reporting group title	Asenapine 5 mg / Asenapine 5 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered one 5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 5 mg asenapine tablet BID) for 26 weeks.	
Reporting group title	Olanzapine 15 mg / Olanzapine 15 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered 15 mg olanzapine (as one 10 mg and one 5 mg tablet) QD for 42 days (except during Week 1 when olanzapine 10 mg QD was administered); in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, 15 mg olanzapine) for 26 weeks.	

Reporting group values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 2.5 mg Overall
Number of subjects	31	31	62
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	39.5	41.1	40.3
standard deviation	± 10.05	± 9.75	± 9.86
Gender Categorical Units: Subjects			
Male	18	18	36
Female	13	13	26
Weight Units: kilograms			
arithmetic mean	76.03	79.72	77.87
standard deviation	± 16.102	± 16.069	± 16.061

Reporting group values	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg	Total
Number of subjects	42	16	120

Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	39.5	37.4	
standard deviation	± 9.99	± 12.45	-
Gender Categorical Units: Subjects			
Male	25	10	71
Female	17	6	49
Weight Units: kilograms			
arithmetic mean	75.08	79.42	
standard deviation	± 18.889	± 16.481	-

End points reporting groups

Reporting group title	Placebo / Asenapine 2.5 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered placebo for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks.	
Reporting group title	Asenapine 2.5 mg / Asenapine 2.5 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 2.5 mg asenapine tablet BID) for 26 weeks.	
Reporting group title	Asenapine 2.5 mg Overall
Reporting group description:	
In the previous short-term trial PO5688, participants were administered either placebo or one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks. The 'asenapine 2.5 mg overall' arm represents the 'placebo / asenapine 2.5 mg' and 'asenapine 2.5 mg / asenapine 2.5 mg' arms combined.	
Reporting group title	Asenapine 5 mg / Asenapine 5 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered one 5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 5 mg asenapine tablet BID) for 26 weeks.	
Reporting group title	Olanzapine 15 mg / Olanzapine 15 mg
Reporting group description:	
In the previous short-term trial PO5688, participants were administered 15 mg olanzapine (as one 10 mg and one 5 mg tablet) QD for 42 days (except during Week 1 when olanzapine 10 mg QD was administered); in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, 15 mg olanzapine) for 26 weeks.	

Primary: Change From Trial P05688 Baseline in Body Weight at Day 182

End point title	Change From Trial P05688 Baseline in Body Weight at Day 182
End point description:	
Change from short-term trial (P05688) baseline in body weight at Day 182. Population for this analysis was the All Treated Set (ATS), defined as all randomized participants from the short-term trial who received ≥1 dose study drug in the current extension trial (P05689).	
End point type	Primary
End point timeframe:	
Baseline (P05688) to Day 182	

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 2.5 mg Overall	Asenapine 5 mg / Asenapine 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	62	42
Units: kilogram(s)				
least squares mean (standard error)	1.2 (± 0.88)	0.1 (± 0.9)	0.6 (± 0.63)	0.8 (± 0.82)

End point values	Olanzapine 15 mg / Olanzapine 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: kilogram(s)				
least squares mean (standard error)	1.2 (± 1.36)			

Statistical analyses

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Analysis was performed using a Mixed Model Repeated Measures (MMRM) for the ATS population. The model included change from short-term baseline (Trial P05688) score at each visit as the dependent variable, and terms for treatment, center, visit, treatment by visit interaction, and baseline weight as covariates. There was no multiple hypotheses testing for multiple comparisons.

Comparison groups	Asenapine 2.5 mg Overall v Olanzapine 15 mg / Olanzapine 15 mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS means difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	1.49

Statistical analysis title	Comparison by Treatment Group

Statistical analysis description:

Analysis was performed using MMRM for the ATS population. The model included change from short-term baseline (Trial P05688) score at each visit as the dependent variable, and terms for treatment, center, visit, treatment by visit interaction, and baseline weight as covariates. There was no multiple hypotheses testing for multiple comparisons.

Comparison groups	Asenapine 5 mg / Asenapine 5 mg v Olanzapine 15 mg / Olanzapine 15 mg

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS means difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	1.59

Secondary: Change From Trial P05688 Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	Change From Trial P05688 Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Days 7, 28, 84, 182, and Study Endpoint[1]

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 measure reports change from short-term trial baseline (P05688) at each specified visit, analysed using an analysis of covariance (ANCOVA) model adjusted for pooled investigative site and baseline values; improvement in symptoms is represented by negative values. Population for analysis was the Full Analysis Set (FAS), defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Baseline (P05688) and Days 7, 28, 84, 182, and Study Endpoint

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "Change From Trial P05688 Baseline in PANSS Total Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
least squares mean (standard error)				
Day 7 (n=28, 31, 40, 15)	-24.7 (± 2.61)	-25.3 (± 2.5)	-27.7 (± 2.17)	-29.9 (± 3.56)
Day 28 (n=26, 27, 35, 13)	-26.7 (± 2.55)	-28.3 (± 2.52)	-30.1 (± 2.2)	-28.8 (± 3.63)
Day 84 (n=24, 23, 30, 11)	-28.1 (± 2.6)	-29.9 (± 2.69)	-30 (± 2.39)	-29.9 (± 3.95)
Day 182 (n=21, 19, 22, 8)	-30.2 (± 2.51)	-28.5 (± 2.69)	-32.7 (± 2.53)	-36.4 (± 4.11)
Study Endpoint (n=31, 31, 42, 15)	-25.3 (± 3.03)	-28.5 (± 3.02)	-28.2 (± 2.57)	-30.6 (± 4.32)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Are PANSS Responders (≥30% Reduction From Trial P05688 Baseline in PANSS Total Score) at Days 7, 28, 84, 182, and Study Endpoint

End point title	Percentage of Participants Who Are PANSS Responders (≥30% Reduction From Trial P05688 Baseline in PANSS Total Score) at Days 7, 28, 84, 182, and Study Endpoint[2]

End point description:

A PANSS responder was defined as a participant who had a reduction from baseline of at least 30% in the PANSS Total Score at a post-baseline assessment. Responder status was assessed relative to the short-term trial baseline (P05688). 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 the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point "Percentage of Participants Who Are PANSS Responders" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: Percentage of responders				
number (not applicable)				
Day 7 (n=28, 31, 40, 15)	39.3	45.2	42.5	53.3
Day 28 (n=26, 27, 35, 13)	50	48.1	57.1	53.8
Day 84 (n=24, 23, 30, 11)	58.3	52.2	63.3	63.6
Day 182 (n=21, 19, 22, 8)	66.7	47.4	68.2	62.5
Study Endpoint (n=31, 31, 42, 15)	48.4	51.6	47.6	46.7

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Trial P05688 Baseline in Clinical Global Impression Scale-Severity (CGI-S) Score at Days 7, 14, 28, 56, 84, 112, 182, and Study Endpoint

End point title	Change From Trial P05688 Baseline in Clinical Global Impression Scale-Severity (CGI-S) Score at Days 7, 14, 28, 56, 84, 112, 182, and Study Endpoint[3]

End point description:

The 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 short-term trial baseline (P05688) at each specified visit, analysed using an ANCOVA model adjusted for pooled investigative site and baseline values; improvement in symptoms is represented by negative values. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Baseline (P05688) and Days 7, 14, 28, 56, 84, 112, 182, and Study Endpoint

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "Change From Trial P05688 Baseline in CGI-S Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
least squares mean (standard error)				
Day 7 (n=28, 31, 40, 15)	-1.6 (± 0.17)	-1.4 (± 0.16)	-1.5 (± 0.14)	-1.3 (± 0.23)
Day 14 (n=28, 30, 40, 14)	-1.4 (± 0.16)	-1.2 (± 0.15)	-1.5 (± 0.13)	-1 (± 0.22)
Day 28 (n=26, 27, 35, 13)	-1.6 (± 0.17)	-1.3 (± 0.17)	-1.4 (± 0.15)	-1.4 (± 0.24)
Day 56 (n=28, 28, 32, 11)	-1.6 (± 0.16)	-1.4 (± 0.16)	-1.3 (± 0.15)	-1.6 (± 0.26)
Day 84 (n=24, 23, 30, 11)	-1.6 (± 0.17)	-1.4 (± 0.18)	-1.5 (± 0.16)	-1.5 (± 0.26)
Day 112 (n=24, 22, 29, 10)	-1.8 (± 0.17)	-1.5 (± 0.19)	-1.5 (± 0.17)	-1.9 (± 0.28)
Day 182 (n=21, 19, 22, 8)	-1.9 (± 0.2)	-1.4 (± 0.22)	-1.5 (± 0.21)	-1.8 (± 0.33)
Study Endpoint (n=31, 31, 42, 15)	-1.5 (± 0.21)	-1.4 (± 0.21)	-1.3 (± 0.18)	-1.3 (± 0.29)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Are Clinical Global Impression Scale-Improvement (CGI-I) Responders at Days 7, 14, 28, 56, 84, 112, 182, and Study Endpoint

End point title	Percentage of Participants Who Are Clinical Global Impression Scale-Improvement (CGI-I) Responders at Days 7, 14, 28, 56, 84, 112, 182, and Study Endpoint[4]

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 a post-baseline assessment. Responder status was assessed relative to the short-term trial baseline (P05688). 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 the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 14, 28, 56, 84, 112, 182, and Study Endpoint

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "Percentage of Participants Who Are CGI-I Responders" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: Percentage of responders				
number (not applicable)				
Day 7 (n=28, 31, 40, 15)	71.4	77.4	70	80
Day 14 (n=28, 30, 40, 14)	64.3	76.7	80	71.4
Day 28 (n=26, 27, 35, 13)	76.9	85.2	82.9	84.6
Day 56 (n=28, 28, 32, 11)	78.6	92.9	75	81.8
Day 84 (n=24, 23, 30, 11)	79.2	87	80	90.9
Day 112 (n=24, 22, 29, 10)	83.3	86.4	86.2	90
Day 182 (n=21, 19, 22, 8)	85.7	94.7	86.4	87.5
Study Endpoint (n=31, 31, 42, 15)	64.5	90.3	69	80

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Negative Subscale Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS Negative Subscale Score at Days 7, 28, 84, 182, and Study Endpoint[5]

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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "PANSS Negative Subscale Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	19.8 (± 4.53)	18.5 (± 5.15)	18.7 (± 5.94)	18.2 (± 5.7)
Day 28 (n=26, 27, 35, 13)	19.3 (± 5)	17.8 (± 4.59)	18.2 (± 5.33)	18.2 (± 5.34)
Day 84 (n=24, 23, 30, 11)	19.1 (± 4.78)	19.2 (± 3.31)	18 (± 5.05)	18.5 (± 4.99)
Day 182 (n=21, 19, 22, 8)	18.1 (± 4.13)	18.9 (± 3.83)	16.6 (± 5.72)	18.6 (± 3.78)
Study Endpoint (n=31, 31, 42, 15)	18.6 (± 4.72)	19.1 (± 5.42)	18.2 (± 6.1)	18.4 (± 5.25)

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Positive Subscale Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS Positive Subscale Score at Days 7, 28, 84, 182, and Study Endpoint[6]

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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "PANSS Positive Subscale Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	15.5 (± 4.86)	15.8 (± 5.36)	15 (± 3.88)	14.9 (± 3.92)
Day 28 (n=26, 27, 35, 13)	15 (± 4.19)	14.5 (± 4.26)	14.7 (± 4.08)	14.8 (± 3.78)
Day 84 (n=24, 23, 30, 11)	14.3 (± 3.6)	13.3 (± 4.1)	14 (± 4.44)	13.5 (± 2.25)
Day 182 (n=21, 19, 22, 8)	13.9 (± 4.39)	13.9 (± 4.08)	13.6 (± 4.63)	11.1 (± 2.1)
Study Endpoint (n=31, 31, 42, 15)	16.2 (± 5.91)	14.5 (± 5.69)	15.5 (± 5)	14.2 (± 4.93)

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS General Psychopathology Subscale Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS General Psychopathology Subscale Score at Days 7, 28, 84, 182, and Study Endpoint[7]

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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point "PANSS General Psychopathology Subscale Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	32.5 (± 7.07)	34.4 (± 8.88)	32.8 (± 7.87)	28.7 (± 5.47)
Day 28 (n=26, 27, 35, 13)	31.5 (± 7.21)	31.8 (± 7.05)	31.3 (± 7.55)	29.3 (± 5.3)
Day 84 (n=24, 23, 30, 11)	31.3 (± 6.59)	31.1 (± 8.52)	31.8 (± 8.12)	28.8 (± 4.14)
Day 182 (n=21, 19, 22, 8)	29.9 (± 7.24)	31.4 (± 6.65)	30.7 (± 8.73)	25.6 (± 3.25)
Study Endpoint (n=31, 31, 42, 15)	32.9 (± 9.23)	31.7 (± 9.14)	32.8 (± 9.15)	28.3 (± 7.72)

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Marder Factor Positive Symptom Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS Marder Factor Positive Symptom Score at Days 7, 28, 84, 182, and Study Endpoint[8]

End point description:

This measure reports results for the 8 items of the Marder positive symptom 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 factor positive symptom 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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point "PANSS Marder Factor Positive Symptom Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	19.1 (± 5.43)	19.5 (± 6.31)	19 (± 5.29)	18.9 (± 4.81)
Day 28 (n=26, 27, 35, 13)	18.7 (± 5.31)	18 (± 5.18)	18.3 (± 5.27)	18.6 (± 5.06)
Day 84 (n=24, 23, 30, 11)	17.9 (± 5.08)	16.6 (± 5.44)	17.9 (± 5.93)	17.1 (± 2.84)
Day 182 (n=21, 19, 22, 8)	17.3 (± 5.62)	17.7 (± 4.78)	17.5 (± 6.22)	14 (± 2.56)
Study Endpoint (n=31, 31, 42, 15)	19.4 (± 6.52)	17.9 (± 6.12)	19.2 (± 6.13)	17.7 (± 6.07)

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Marder Factor Negative Symptom Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS Marder Factor Negative Symptom Score at Days 7, 28, 84, 182, and Study Endpoint[9]

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 factor negative symptom 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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point "PANSS Marder Factor Negative Symptom Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	18.6 (± 4.1)	17.4 (± 5.45)	17.2 (± 5.48)	16.4 (± 5.6)
Day 28 (n=26, 27, 35, 13)	17.9 (± 4.29)	16.7 (± 4.88)	16.7 (± 4.97)	16.6 (± 5.24)
Day 84 (n=24, 23, 30, 11)	17.5 (± 4.66)	18 (± 3.78)	16.4 (± 4.67)	16.5 (± 5.72)
Day 182 (n=21, 19, 22, 8)	16.5 (± 3.76)	17.3 (± 4.18)	15.5 (± 5.28)	17 (± 4.14)
Study Endpoint (n=31, 31, 42, 15)	17 (± 4.66)	17.7 (± 5.41)	16.6 (± 5.71)	16.8 (± 5.16)

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Marder Factor Disorganized Thought Symptom Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS Marder Factor Disorganized Thought Symptom Score at Days 7, 28, 84, 182, and Study Endpoint[10]

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 factor disorganized thought symptom 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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point "PANSS Marder Factor Disorganized Thought Symptom Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	17.2 (± 4.63)	17.4 (± 4.45)	16.6 (± 4.24)	16.1 (± 4.23)
Day 28 (n=26, 27, 35, 13)	16.4 (± 4.54)	16.3 (± 4.01)	16.3 (± 3.98)	16.1 (± 3.38)
Day 84 (n=24, 23, 30, 11)	16.8 (± 4.41)	16 (± 3.59)	16.3 (± 4.3)	15.7 (± 3.1)
Day 182 (n=21, 19, 22, 8)	15.7 (± 4.49)	16.1 (± 3.54)	15.5 (± 4.87)	14.6 (± 2.72)
Study Endpoint (n=31, 31, 42, 15)	16.7 (± 4.52)	16.4 (± 4.94)	16.5 (± 4.52)	15.1 (± 4.36)

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Marder Factor Hostility/Excitement Symptom Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS Marder Factor Hostility/Excitement Symptom Score at Days 7, 28, 84, 182, and Study Endpoint[11]

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 factor hostility/excitement symptom 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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point "PANSS Marder Factor Hostility/Excitement Symptom Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this

secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	6 (± 2.46)	6.9 (± 3.26)	6.9 (± 2.67)	5.3 (± 1.44)
Day 28 (n=26, 27, 35, 13)	6.2 (± 2.43)	6.3 (± 2.05)	6.6 (± 2.6)	5.5 (± 1.61)
Day 84 (n=24, 23, 30, 11)	6.2 (± 2.5)	5.9 (± 1.86)	6.2 (± 2.42)	5.8 (± 1.72)
Day 182 (n=21, 19, 22, 8)	5.9 (± 2.39)	5.8 (± 1.72)	6.5 (± 2.52)	4.9 (± 0.99)
Study Endpoint (n=31, 31, 42, 15)	6.8 (± 3.66)	6.1 (± 2.66)	7 (± 2.85)	5.4 (± 1.76)

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Marder Factor Anxiety/Depression Symptom Score at Days 7, 28, 84, 182, and Study Endpoint

End point title	PANSS Marder Factor Anxiety/Depression Symptom Score at Days 7, 28, 84, 182, and Study Endpoint[12]

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 factor anxiety/depression symptom 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. Population for analysis was the FAS, defined as all randomized participants from PO5688 who received ≥1 dose of study drug in PO5689 and had ≥1 post- PANSS Total Score measurement.

End point type	Secondary

End point timeframe:

Days 7, 28, 84, 182, and Study Endpoint

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point "PANSS Marder Factor Anxiety/Depression Symptom Score" was assessed in each of the individual treatment arms: "Placebo / Asenapine 2.5 mg"; "Asenapine 2.5 mg / Asenapine 2.5 mg"; "Asenapine 5 mg / Asenapine 5 mg" and "Olanzapine 15 mg / Olanzapine 15 mg". The 'Asenapine 2.5 mg Overall' arm represents the 'Placebo / Asenapine 2.5 mg' and 'Asenapine 2.5 mg / Asenapine 2.5 mg' arms combined and this combined arm was not included for analysis of this secondary end point.

End point values	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	42	15
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 7 (n=28, 31, 40, 15)	6.9 (± 2.38)	7.5 (± 3.35)	6.9 (± 2.94)	5.3 (± 1.53)
Day 28 (n=26, 27, 35, 13)	6.6 (± 2.71)	6.8 (± 3.15)	6.4 (± 2.95)	5.5 (± 1.85)
Day 84 (n=24, 23, 30, 11)	6.3 (± 2.22)	7 (± 3.4)	6.9 (± 3.27)	5.7 (± 1.56)
Day 182 (n=21, 19, 22, 8)	6.5 (± 2.75)	7.3 (± 3.58)	6.1 (± 2.62)	4.9 (± 1.36)
Study Endpoint (n=31, 31, 42, 15)	7.8 (± 3.57)	7.1 (± 3.6)	7.1 (± 3.62)	5.9 (± 2.55)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after last dose of study drug (up to approximately 30 weeks)

Adverse event reporting additional description:

Analysis population was the ATS which included all randomized subjects from the short-term trial (PO5688) who received ≥1 dose of study drug in the current extension trial (PO5689).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo / Asenapine 2.5 mg

Reporting group description:

In the previous short-term trial PO5688, participants were administered placebo for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks.

Reporting group title	Asenapine 2.5 mg / Asenapine 2.5 mg

Reporting group description:

In the previous short-term trial PO5688, participants were administered one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 2.5 mg asenapine tablet BID) for 26 weeks.

Reporting group title	Asenapine 2.5 mg Overall

Reporting group description:

In the previous short-term trial PO5688, participants were administered either placebo or one 2.5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were administered one 2.5 mg asenapine tablet BID for 26 weeks.

Reporting group title	Asenapine 5 mg / Asenapine 5 mg

Reporting group description:

In the previous short-term trial PO5688, participants were administered one 5 mg asenapine tablet BID for 42 days; in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, one 5 mg asenapine tablet BID) for 26 weeks.

Reporting group title	Olanzapine 15 mg / Olanzapine 15 mg

Reporting group description:

In the previous short-term trial PO5688, participants were administered 15 mg olanzapine (as one 10 mg and one 5 mg tablet) QD for 42 days (except during Week 1 when olanzapine 10 mg QD was administered); in the current extension trial (PO5689), participants were assigned to the same treatment regimen (ie, 15 mg olanzapine) for 26 weeks.

Serious adverse events	Placebo / Asenapine 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 2.5 mg Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 31 (16.13%)	3 / 31 (9.68%)	8 / 62 (12.90%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Psychomotor Hyperactivity			

subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	1 / 31 (3.23%)	3 / 31 (9.68%)	4 / 62 (6.45%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia,Paranoid Type			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 42 (14.29%)	2 / 16 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 42 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	5 / 42 (11.90%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia,Paranoid Type			
subjects affected / exposed	0 / 42 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	0 / 42 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
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 2.5 mg	Asenapine 2.5 mg / Asenapine 2.5 mg	Asenapine 2.5 mg Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 31 (54.84%)	9 / 31 (29.03%)	26 / 62 (41.94%)
Investigations			
Weight Increased			
subjects affected / exposed	4 / 31 (12.90%)	1 / 31 (3.23%)	5 / 62 (8.06%)
occurrences (all)	4	1	5
Weight Decreased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	2 / 62 (3.23%)
occurrences (all)	1	1	2
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
occurrences (all)	3	0	3
Blood Insulin Increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
occurrences (all)	2	0	2
Blood Pressure Increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	2 / 62 (3.23%)
occurrences (all)	1	1	2
Vascular disorders			

Hypertension			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
occurrences (all)	2	0	2
Nervous system disorders			
Somnolence			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	3 / 62 (4.84%)
occurrences (all)	3	1	4
Akathisia			
subjects affected / exposed	3 / 31 (9.68%)	0 / 31 (0.00%)	3 / 62 (4.84%)
occurrences (all)	3	0	3
Parkinsonism			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	3 / 62 (4.84%)
occurrences (all)	2	1	3
Dyskinesia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchitis Chronic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 31 (12.90%)	3 / 31 (9.68%)	7 / 62 (11.29%)
occurrences (all)	4	3	7
Anxiety			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 62 (1.61%)
occurrences (all)	1	0	1
Pulmonary Tuberculosis			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences (all)	0	0	0
Urinary Tract Infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 62 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Asenapine 5 mg / Asenapine 5 mg	Olanzapine 15 mg / Olanzapine 15 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 42 (28.57%)	6 / 16 (37.50%)	
Investigations			
Weight Increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Weight Decreased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Blood Insulin Increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Blood Pressure Increased			
subjects affected / exposed	1 / 42 (2.38%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	3 / 42 (7.14%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 42 (2.38%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Somnolence			

subjects affected / exposed	2 / 42 (4.76%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Akathisia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Parkinsonism			
subjects affected / exposed	1 / 42 (2.38%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dyskinesia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchitis Chronic			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 42 (4.76%)	0 / 16 (0.00%)	
occurrences (all)	5	0	
Anxiety			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Urinary Tract Infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2012	• In the list of medications prohibited prior to baseline and during trial, 'antiemetics containing dopamine agonist' was changed to 'antiemetics containing dopamine antagonists'. • The lists of urinalysis tests was updated to include urine pregnancy test, urine drug screen, nitrite, urobilinogen, and leukocyte esterase and deleted microscopic examination. • The Serious Adverse Event (SAE) section was updated to include 'cancer' as SAE outcome #6. • Text regarding drug induced liver injury was updated, including text on monitoring liver enzymes to align with Merck standards and latest guidance of the Food and Drug Administration. • Two additional closely monitored events were added: "suicidal ideation and/or behavior" and "drug hypersensitivity reactions". • Text regarding medication errors in three sections of the protocol was deleted. • "Incidents associated with the device" was deleted from the list of events requiring expedited reporting of safety observations by the investigator to the sponsor. • In the Tier 3 list of safety endpoints, "heart rate" was replaced with "pulse rate".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported