Clinical trial results:
A 26-Week, Multi-Center, Open-Label, Flexible Dose, Long-Term Safety Trial of Asenapine in Adolescent Subjects with Schizophrenia

Summary

EudraCT number	2009-018038-12
Trial protocol	RO Outside EU/EEA
Global end of trial date	07 October 2013

Results information

Result version number	v1 (current)
This version publication date	21 June 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	P05897

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01190267
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol number: MK-8274-021

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2013
Global end of trial reached?	Yes
Global end of trial date	07 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is designed to evaluate whether asenapine, which is approved by the United States Food and Drug Administration (US FDA) for acute treatment of schizophrenia in adults, is generally safe and well tolerated in adolescents with schizophrenia. This is an extension of base study P05896 (NCT01190254), which means participants must have completed participation in the 8-week base study in order to qualify for this extension study P05897. Participants in this extension study will receive open-label asenapine for 26 weeks. Throughout the study, observations will be made on each participant at various times to assess the long-term safety, tolerability and efficacy of the study treatment.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measure defined for this individual study was in place for the protection of trial subjects: For participants whose symptoms worsen or are not adequately controlled on assigned treatment, rescue medication may be administered during the trial in the following circumstances. For the control of agitation, anxiety, insomnia, restlessness, or akathisia and extrapyramidal symptoms (EPS) some benzodiazepines and EPS medications (i.e., anticholinergics) are allowed. Benadryl (diphenhydramine) and beta blockers are also permitted, provided that they are not taken within 8 hours of efficacy assessments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	India: 40
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Russian Federation: 88
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	South Africa: 3

Worldwide total number of subjects	204
EEA total number of subjects	8

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)	196
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

204 participants entered the study and received at least one dose of open-label trial medication.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Asenapine - Participants Who Were ≤17 Years Old

Arm description:

In this extension study all participants received open-label asenapine 2.5 mg twice daily (BID) on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were ≤17 years old at entry into the extension study.

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

Dosage and administration details:

asenapine 2.5 mg or 5.0 mg sublingual tablets, administered BID

Arm title	Asenapine - Participants Who Were 18 Years Old

Arm description:

In this extension study all participants received open-label asenapine 2.5 mg BID on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were 18 years old at entry into the extension study.

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Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

asenapine 2.5 mg or 5.0 mg sublingual tablets, administered BID

Number of subjects in period 1	Asenapine - Participants Who Were ≤17 Years Old	Asenapine - Participants Who Were 18 Years Old
Started	196	8
Completed	155	4
Not completed	41	4
Adverse event, serious fatal	1	-
Consent withdrawn by subject	13	1
Adverse event, non-fatal	9	-
Lost to follow-up	2	-
Lack of efficacy	8	2
Protocol deviation	8	1

Baseline characteristics

Reporting groups

Reporting group title	Asenapine - Participants Who Were ≤17 Years Old

Reporting group description:

In this extension study all participants received open-label asenapine 2.5 mg twice daily (BID) on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were ≤17 years old at entry into the extension study.

Reporting group title	Asenapine - Participants Who Were 18 Years Old

Reporting group description:

In this extension study all participants received open-label asenapine 2.5 mg BID on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were 18 years old at entry into the extension study.

Reporting group values	Asenapine - Participants Who Were ≤17 Years Old	Asenapine - Participants Who Were 18 Years Old	Total
Number of subjects	196	8	204
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	196	0	196
Adults (18-64 years)	0	8	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	15.3	18	
standard deviation	± 1.5	± 0	-
Gender categorical Units: Subjects			
Female	74	4	78
Male	122	4	126

End points

End points reporting groups

Reporting group title	Asenapine - Participants Who Were ≤17 Years Old

Reporting group description:

In this extension study all participants received open-label asenapine 2.5 mg twice daily (BID) on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were ≤17 years old at entry into the extension study.

Reporting group title	Asenapine - Participants Who Were 18 Years Old

Reporting group description:

In this extension study all participants received open-label asenapine 2.5 mg BID on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were 18 years old at entry into the extension study.

Primary: Number of Participants With a Treatment-Emergent Adverse Event (AE) During Extension Study

End point title	Number of Participants With a Treatment-Emergent Adverse Event (AE) During Extension Study[1]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An AE was defined as a "treatment-emergent" AE if it was not present at the extension study baseline, or if it was present at the extension study baseline but worsened in severity compared to baseline during the extension study treatment period. Population for analysis was all participants who received at least one dose of extension study medication.

End point type	Primary

End point timeframe:

Up to 30 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 hypothesis testing was planned for this endpoint.

End point values	Asenapine - Participants Who Were ≤17 Years Old	Asenapine - Participants Who Were 18 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	8		
Units: participants	114	3		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Study Drug During Extension Study Due to an AE

End point title	Number of Participants Who Discontinued Study Drug During Extension Study Due to an AE[2]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Population for analysis was all participants who received at least one dose of extension study medication.

End point type	Primary

End point timeframe:

Up to 26 weeks

Notes:

[2] - 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 hypothesis testing was planned for this endpoint.

End point values	Asenapine - Participants Who Were ≤17 Years Old	Asenapine - Participants Who Were 18 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	8		
Units: participants	10	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 weeks

Adverse event reporting additional description:

The serious adverse events (SAEs) table includes all SAEs that occurred during this extension study. The Other AEs table includes only AEs in study that were "treatment-emergent" (i.e., not present at the extension study baseline, or present at the extension study baseline but worsened in severity compared to baseline during the extension study).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Asenapine - Participants Who Were ≤17 Years Old

Reporting group description:

In this extension study all participants received open-label asenapine 2.5 mg BID on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were ≤17 years old at entry into the extension study.

Reporting group title	Asenapine - Participants Who Were 18 Years Old

Reporting group description:

In this extension study all participants received open-label asenapine 2.5 mg BID on Day 1-3, which was increased to 5.0 mg BID on Day 4 (dose could be increased earlier). Asenapine dosing was flexible for the remainder of the 26-week open-label drug administration period, and could be adjusted to either 2.5 mg or 5.0 mg BID. Participants in this reporting group were 18 years old at entry into the extension study.

Serious adverse events	Asenapine - Participants Who Were ≤17 Years Old	Asenapine - Participants Who Were 18 Years Old	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 196 (3.57%)	1 / 8 (12.50%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Multi-Organ Failure			
subjects affected / exposed	1 / 196 (0.51%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Aggression			

subjects affected / exposed	2 / 196 (1.02%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 196 (0.51%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 196 (0.51%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	3 / 196 (1.53%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 3	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	Asenapine - Participants Who Were ≤17 Years Old	Asenapine - Participants Who Were 18 Years Old	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 196 (30.10%)	3 / 8 (37.50%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	3 / 196 (1.53%)	1 / 8 (12.50%)	
occurrences (all)	4	3	
Injury			
subjects affected / exposed	0 / 196 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Akathisia			
subjects affected / exposed	4 / 196 (2.04%)	1 / 8 (12.50%)	
occurrences (all)	4	1	
Bradykinesia			

subjects affected / exposed	0 / 196 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cogwheel Rigidity			
subjects affected / exposed	0 / 196 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	13 / 196 (6.63%)	0 / 8 (0.00%)	
occurrences (all)	18	0	
Hypoaesthesia			
subjects affected / exposed	0 / 196 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Resting Tremor			
subjects affected / exposed	0 / 196 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Sedation			
subjects affected / exposed	10 / 196 (5.10%)	1 / 8 (12.50%)	
occurrences (all)	11	3	
Somnolence			
subjects affected / exposed	29 / 196 (14.80%)	0 / 8 (0.00%)	
occurrences (all)	36	0	
Tremor			
subjects affected / exposed	4 / 196 (2.04%)	1 / 8 (12.50%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 196 (2.55%)	1 / 8 (12.50%)	
occurrences (all)	5	1	
Feeling Cold			
subjects affected / exposed	0 / 196 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 196 (0.51%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Eye disorders			

Vision Blurred subjects affected / exposed occurrences (all)	1 / 196 (0.51%) 1	1 / 8 (12.50%) 1	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Upper Respiratory Tract Congestion subjects affected / exposed occurrences (all)	 1 / 196 (0.51%) 1 0 / 196 (0.00%) 0	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1	
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 1 / 196 (0.51%) 1	 1 / 8 (12.50%) 1	
Psychiatric disorders Suicidal Ideation subjects affected / exposed occurrences (all)	 3 / 196 (1.53%) 3	 1 / 8 (12.50%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 0 / 196 (0.00%) 0	 1 / 8 (12.50%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2011	Amendment 01: Primary reason for amendment was to incorporate revision to upper limit of age range for entry into study.
03 May 2012	Amendment 02: Primary reason for amendment was to incorporate revisions to requirements for final visit of preceding base study (P05896) and baseline visit of this extension study (P05897), list of efficacy endpoints, allowed concomitant medications/rescue therapy, list of closely monitored events, criteria for clinically important changes in safety measures and procedures for liver enzyme monitoring.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported