Clinical trial results:
26-week open-label extension study evaluating the safety and tolerability of flexible doses of oral ziprasidone in adolescent subjects with schizophrenia.

Summary

EudraCT number	2005-005502-23
Trial protocol	SE DE
Global end of trial date	16 April 2009

Results information

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

Trial information

Trial identification

Sponsor protocol code	A1281135

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00265382
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 00 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 00 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	30 November 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2009
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of oral ziprasidone (40-80 milligram [mg] twice a day [BID]) during long-term, open-label administration in adolescent subjects with schizophrenia.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2006
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	Singapore: 2
Country: Number of subjects enrolled	United States: 44
Country: Number of subjects enrolled	India: 28
Country: Number of subjects enrolled	Russian Federation: 66
Country: Number of subjects enrolled	Malaysia: 14
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Costa Rica: 3
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	Colombia: 8
Worldwide total number of subjects	221
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)	0
Adolescents (12-17 years)	221
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study enrolled adolescent subjects with schizophrenia, ages 13-17 years, who participated in the double-blind placebo controlled Study A1281134 (Eudract Number: 2005-005502-23) (NCT00257192) who met qualification criteria and wished to receive treatment with open-label ziprasidone.

Pre-assignment

Screening details:

The study was conducted at 60 centers in 9 countries between 15 June 2006 to 16 April 2009.

Period 1

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

Arms

Arm title	Ziprasidone

Arm description:

Ziprasidone capsules administered BID with meals.

Arm type	Experimental
Investigational medicinal product name	Ziprasidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Titrated over a 2-week period, starting with an evening dose of 20 mg/day, and subsequent dose increases of 20 mg/day every second day up to a target dose of 80 to 160 mg/day for subjects weighing >=45 kilograms (kg). For subjects with a body weight <45 kg, the maximum permitted dose was 80 mg/day (40 mg BID). Doses could have been reduced to a minimum of 40 mg/day (20 mg BID).

Number of subjects in period 1	Ziprasidone
Started	221
Completed	76
Not completed	145
Consent withdrawn by subject	13
Adverse Event	21
Death	1
Miscellaneous	6
Study terminated by sponsor	94
Lost to follow-up	3
Laboratory Abnormality	1
Lack of efficacy	6

Baseline characteristics

Reporting groups	
Reporting group title	Ziprasidone
Reporting group description:	
Ziprasidone capsules administered BID with meals.	

Reporting group values	Ziprasidone	Total	
Number of subjects	221	221	
Age categorical			
Baseline data are from the preceding Study A1281134 (Eudract Number: 2005-005502-23) (NCT00265382).			
Units: Subjects			
>12 years and <13 years at start of treatment	3	3	
13 to 17 years	218	218	
Gender categorical			
Units: Subjects			
Female	90	90	
Male	131	131	

End points

End points reporting groups

Reporting group title	Ziprasidone

Reporting group description:

Ziprasidone capsules administered BID with meals.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

All observed or volunteered treatment-emergent AEs and SAEs regardless of treatment group or suspected causal relationship to the investigational product(s) were reported. Safety Analysis Set = all subjects who took at least one dose of study medication. In this table, the number of subjects with AEs is based on a 0 percent (%) AE threshold whereas the number of subjects with AEs reported in the AE section are based on a 5% AE threshold.

End point type	Primary

End point timeframe:

26 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: Only descriptive data was planned to be reported for this outcome measure.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	221			
Units: subjects				
AEs	137			
SAEs	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change From Baseline to Each Pubertal Stage of Development as Assessed by the Tanner Adolescent Pubertal Self Assessment

End point title	Number of Subjects With Change From Baseline to Each Pubertal Stage of Development as Assessed by the Tanner Adolescent Pubertal Self Assessment

End point description:

Tanner Adolescent Pubertal Staging Questionnaire: used to document the stage of development of secondary sexual characteristics. Female pubertal development staged by pubic hair development and breast size; males pubertal development staged by size of the genitalia and development of pubic hair. Rated in 5 stages: stage 1 (no development) to 5 (adult-like development in quantity and size). Safety Analysis Set. Baseline data from Study A1281134 (Eudract Number: 2005-005502-23) (NCT00257192) served as the baseline for A1281135.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Early Termination (ET)

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	73[2]			
Units: subjects				
Pubic Hair, Week 26 (Stage 1)	1			
Pubic Hair, Week 26 (Stage 2)	1			
Pubic Hair, Week 26 (Stage 3)	11			
Pubic Hair, Week 26 (Stage 4)	39			
Pubic Hair, Week 26 (Stage 5)	21			
Pubic Hair, ET (Stage 1)	0			
Pubic Hair, ET (Stage 2)	10			
Pubic Hair, ET (Stage 3)	22			
Pubic Hair, ET (Stage 4)	59			
Pubic Hair, ET (Stage 5)	30			

Notes:

[2] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Problem Behavior and Aggression Questionnaire (CPBAQ) Total Score

End point title	Change From Baseline in Children's Problem Behavior and Aggression Questionnaire (CPBAQ) Total Score

End point description:

CPBAQ: 19-item parent or legal guardian completed questionnaire to rate the child's verbal (such as yelling or cursing) and physical aggression (such a fighting with peers or being cruel to an animal) during the past week. Behavior was rated on a 4-point scale; range 0 (behavior did not occur or was not a problem) to 3 (behavior occurred a lot or was severe problem). Total score range 0 to 57; higher scores indicate a greater frequency and severity of aggression. Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). Last Observation Carried Forward (LOCF) imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 6, 18, 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	208[3]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=178)	-0.3 (± 4.8)			

Week 6 (n=153)	-0.8 (± 6.1)			
Week 18 (n=93)	-0.5 (± 6.5)			
Week 26 (n=68)	0.7 (± 7.7)			
ET (n=113)	0.5 (± 7.1)			
Week 26 LOCF (n=177)	-0.5 (± 7)			

Notes:

[3] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child Depression Rating Scale - Revised (CDRS-R): Total Score

End point title	Change From Baseline in Child Depression Rating Scale - Revised (CDRS-R): Total Score

End point description:

CDRS-R: clinician-rated interview-based scale (with both child and parent or guardian) to assess 17 distinct symptom areas to derive an index of depression severity. Discrepancies between informants' responses were resolved by using most impaired rating given by valid informant. Rated on a 7-point scale; range from 1 (no impairment) to 7 (indicates greater impairment). Total score calculated as sum of the 17 items (range 1 to 119); higher score indicates greater impairment. Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 6, 10, 14, 18, 22, 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	214[4]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=198)	-1.4 (± 4.8)			
Week 2 (n=188)	-2.2 (± 6.1)			
Week 6 (n=160)	-3.5 (± 6.3)			
Week 10 (n=129)	-4.6 (± 7.3)			
Week 14 (n=105)	-5 (± 7.4)			
Week 18 (n=94)	-4.9 (± 8.1)			
Week 22 (n=78)	-5.1 (± 7.9)			
Week 26 (n=72)	-5.3 (± 7.8)			
ET (n=122)	-2.7 (± 7.3)			
Week 26 LOCF (n=197)	-4.5 (± 7)			

Notes:

[4] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Central Nervous System (CNS) Vital Signs Cognitive Test Battery (Includes Sedation Item): Subscales

End point title	Change From Baseline in Central Nervous System (CNS) Vital Signs Cognitive Test Battery (Includes Sedation Item): Subscales

End point description:

Computerized subject-administered test battery with subtests for verbal and visual memory, processing speed, nonverbal reasoning, executive functioning, working memory, sustained attention. Computerized 7- point sedation item (0 [not sleepy] to 10 [very sleepy]) was completed prior to test battery. Neurocognitive index score was derived from subtest scores per an algorithm. Index score and subtest scores assessed the subject's changes in cognition. Scores were rated as above average (score >109), average (90 to 109), below average (80 to 89), or well below average (70 to 79). Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	212[5]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Sedation: Week 6 (n=149)	0.1 (± 1.7)			
Sedation: Week 26 (n=70)	-0.2 (± 1.5)			
Sedation: ET (n=102)	-0.1 (± 2)			
Sedation: Week 26 LOCF (n=153)	-0.2 (± 1.7)			
Verbal Memory: Week 6 (n=150)	-1.3 (± 13.7)			
Verbal Memory: Week 26 (n=71)	0.6 (± 14)			
Verbal Memory: ET (n=103)	-0.7 (± 14.6)			
Verbal Memory: Week 26 LOCF (n=155)	0.3 (± 14.5)			
Visual Memory: Week 6 (n=148)	-3.6 (± 13.7)			
Visual Memory: Week 26 (n=71)	-2.1 (± 15.5)			
Visual Memory: ET (n=103)	-1.9 (± 12.7)			
Visual Memory: Week 26 LOCF (n=154)	-1.5 (± 14.4)			
Processing Speed: Week 6 (n=148)	-1.2 (± 11.4)			
Processing Speed: Week 26 (n=71)	2.1 (± 10.2)			
Processing Speed: ET (n=103)	-1.4 (± 19)			
Processing Speed: Week 26 LOCF (n=153)	0.5 (± 12)			
Reasoning: Week 6 (n=145)	-0.3 (± 14.1)			
Reasoning: Week 26 (n=71)	3 (± 11.3)			
Reasoning: ET (n=100)	1.9 (± 14.9)			
Reasoning: Week 26 LOCF (n=151)	1.5 (± 14.3)			
Executive Functioning: Week 6 (n=145)	2 (± 16.7)			
Executive Functioning: Week 26 (n=71)	2 (± 16.8)			
Executive Functioning: ET (n=100)	2.4 (± 15.7)			
Executive Functioning: Week 26 LOCF (n=151)	2.4 (± 16.9)			

Working Memory: Week 6 (n=145)	-0.5 (± 12.6)			
Working Memory: Week 26 (n=68)	0.8 (± 16.4)			
Working Memory: ET (n=99)	0.3 (± 12.1)			
Working Memory: Week 26 LOCF (n=150)	0.7 (± 14.2)			
Sustained Attention: Week 6 (n=145)	0.2 (± 12)			
Sustained Attention: Week 26 (n=68)	1.9 (± 14)			
Sustained Attention: ET (n=99)	-0.6 (± 12.2)			
Sustained Attention: Week 26 LOCF (n=150)	1.2 (± 12.7)			

Notes:

[5] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CNS Vital Signs Cognitive Test Battery: Neurocognitive Index

End point title	Change From Baseline in CNS Vital Signs Cognitive Test Battery: Neurocognitive Index

End point description:

Computerized subject-administered test battery with subtests for verbal and visual memory, processing speed, nonverbal reasoning, executive functioning, working memory, sustained attention. Computerized 7- point sedation item (0 [not sleepy] to 10 [very sleepy]) was completed prior to test battery. Neurocognitive index score was derived from subtest scores per an algorithm. Index score and subtest scores assessed the subject's changes in cognition. Scores were rated as above average (score >109), average (90 to 109), below average (80 to 89), or well below average (70 to 79). Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	208[6]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Neurocognitive Index: Week 6 (n=144)	-0.6 (± 7.2)			
Neurocognitive Index: Week 26 (n=68)	1.3 (± 7.3)			
Neurocognitive Index: ET (n=99)	0.5 (± 6.3)			
Neurocognitive Index: Week 26 LOCF (n=150)	0.7 (± 7.7)			

Notes:

[6] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simpson-Angus Rating Scale (SARS)

End point title	Change From Baseline in Simpson-Angus Rating Scale (SARS)

End point description:

SARS: 10-item clinician rated instrument to assess parkinsonian symptoms (7 items) and related extrapyramidal side effects (3 items): gait, arm dropping, shoulder shaking, elbow rigidity, leg pendulousness, glabellar tap, tremor, and salivation. Head dropping (modified SARS item 7) substituted for head rotation. Anchored 5-point scale: range 0 (absence of condition, normal) to 4 (most extreme form of condition). Total score is sum of individual item scores (range 0 to 40); higher score indicates more affected. Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 6, 10, 14, 18, 22, 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	221[7]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=206)	-0.05 (± 1.4)			
Week 2 (n=197)	-0.11 (± 1.3)			
Week 6 (n=168)	-0.04 (± 1.7)			
Week 10 (n=135)	-0.1 (± 1.6)			
Week 14 (n=110)	-0.02 (± 1.9)			
Week 18 (n=99)	0.02 (± 1.4)			
Week 22 (n=82)	-0.04 (± 1.7)			
Week 26 (n=76)	-0.32 (± 1.4)			
ET (n=127)	-0.31 (± 2)			
Week 26 LOCF (n=206)	-0.15 (± 1.5)			

Notes:

[7] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Barnes Akathisia Rating Scale (BAS) Global Clinical Assessment Item

End point title	Change From Baseline in Barnes Akathisia Rating Scale (BAS) Global Clinical Assessment Item

End point description:

BAS: clinician rated scale to assess akathisia to determine the degree of subjective restlessness and distress associated with restlessness. First 3 items (Objective, Subjective, and Distress related to restlessness) rated on a 4-point scale with range 0 (no symptoms) to 3 (increased severity of symptoms). Item 4 Global Clinical Assessment of Akathisia rated on a 6-point scale range 0 (no symptoms) to 5 (increased severity of symptoms); higher score indicates increased severity. All rating are anchored. Only the Global Clinical Assessment of Akathisia was to be analyzed.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 6, 10, 14, 18, 22, 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	221			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=206)	0 (± 0.4)			
Week 2 (n=197)	0 (± 0.4)			
Week 6 (n=168)	0 (± 0.4)			
Week 10 (n=135)	0 (± 0.5)			
Week 14 (n=110)	0.1 (± 0.6)			
Week 18 (n=99)	0 (± 0.4)			
Week 22 (n=82)	0 (± 0.6)			
Week 26 (n=76)	0 (± 0.6)			
ET (n=127)	0 (± 0.5)			
Week 26 LOCF (n=206)	0.1 (± 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Movement Cluster Score

End point title	Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Movement Cluster Score

End point description:

AIMS: clinician rated 12-item scale to rate 7 body areas and global judgments on the severity of abnormal movements, incapacitation and subject's awareness of abnormal movements. Items 1 to 10 scored 0 (none) to 4 (severe) (total possible score 0 to 40; higher score indicates greater severity); items 11 to 14 are No or Yes response to dental status and sleep movements. Only the sum of the first 7 items to be analyzed (AIMS Movement Cluster score). Total score 0 to 28; higher score indicates greater severity. Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 2, 6, 10, 14, 18, 22, 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	221[8]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=206)	0.06 (± 1.3)			
Week 2 (n=197)	-0.05 (± 0.7)			
Week 6 (n=168)	-0.04 (± 0.9)			
Week 10 (n=135)	0.02 (± 1.4)			
Week 14 (n=110)	0.01 (± 0.9)			
Week 18 (n=99)	0.01 (± 0.6)			
Week 22 (n=82)	0.1 (± 1.2)			
Week 26 (n=76)	0.08 (± 1.2)			
ET (n=127)	-0.12 (± 1.5)			
Week 26 LOCF (n=206)	0 (± 1)			

Notes:

[8] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brief Psychiatric Rating Scale - Anchored (BPRS-A) Total Score

End point title	Change From Baseline in Brief Psychiatric Rating Scale - Anchored (BPRS-A) Total Score

End point description:

BPRS-A: 18-item clinician rated scale to assess somatic concern, anxiety, emotional withdrawal, disorganization, hallucinatory behavior, guilt feelings, suspiciousness, disorientation, tension, mannerisms, posturing, grandiosity, depressive mood, hostility, motor retardation, uncooperativeness, unusual thought content, blunted affect, excitement. Ratings anchored to improve consistency for single rater over time or between raters. Items rated on 7-point scale 0 (not present) to 6 (extremely severe). Total score=sum of items (range 0 to 108); higher scores indicate increased pathology. Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 6, 18, 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	220[9]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=196)	-3.8 (± 7.8)			
Week 6 (n=167)	-6.1 (± 8.8)			
Week 18 (n=98)	-7.8 (± 11)			
Week 26 (n=75)	-8.5 (± 9.9)			
ET (n=127)	-4 (± 9.1)			

Week 26 LOCF (n=196)	-6.9 (± 8.9)			

Notes:

[9] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Global Assessment Scale (CGAS)

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

End point description:

CGAS: clinician-rated global assessment item for children based on symptoms and social functioning in home, school, and community settings. Scores on this single item range from 1 to 100 (higher levels indicate greater health) with descriptive anchors for every 10-point interval. Scores above 70 on this scale are considered within the "normal" range; lower score indicates need for increased supervision. Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 6, 18, 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	221[10]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=197)	55.5 (± 12.9)			
Week 6 (n=168)	59.2 (± 12.5)			
Week 18 (n=99)	62.3 (± 11.4)			
Week 26 (n=76)	65.6 (± 12.4)			
ET (n=127)	56.6 (± 15.1)			
Week 26 LOCF (n=197)	60.5 (± 14.2)			

Notes:

[10] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child Health Questionnaire (CHQ)

End point title	Change From Baseline in Child Health Questionnaire (CHQ)

End point description:

CHQ: 50-item, 15 subscale parent or legal guardian assessed instrument of child's physical, emotional, social well-being, and relative burden of disease on the parents; rated on Likert-type scale: range 0 to 100; higher scores indicate a more positive health status. Global indicators for Physical Health and Psychosocial Health are weighted composites derived from subscale items using scoring algorithms

(transformed scores); range 0 to 100: higher scores indicate more positive health status. Safety Analysis Set. n=number of subjects with analyzable data at post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	220[11]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Global Health: Week 6 (n=163)	44.2 (± 23.9)			
Global Health: Week 26 (n=75)	50.3 (± 22.1)			
Global Health: ET (n=124)	40.5 (± 25.8)			
Global Health: Week 26 LOCF (n=164)	44.9 (± 22.9)			
Global Behavior: Week 6 (n=163)	44.9 (± 23.6)			
Global Behavior: Week 26 (n=75)	47 (± 24.2)			
Global Behavior: ET (n=124)	38.7 (± 25.8)			
Global Behavior: Week 26 LOCF (n=164)	43.8 (± 24.4)			
Family Cohesion: Week 6 (n=163)	53 (± 23.9)			
Family Cohesion: Week 26 (n=75)	54.4 (± 24.7)			
Family Cohesion: ET (n=124)	50 (± 23.9)			
Family Cohesion: Week 26 LOCF (n=164)	53.4 (± 23.7)			
Physical Health: Week 6 (n=163)	76.4 (± 30.8)			
Physical Health: Week 26 (n=74)	80.2 (± 28.8)			
Physical Health: ET (n=123)	75.5 (± 32.8)			
Physical Health: Week 26 LOCF (n=163)	77.8 (± 31.2)			
Bodily Pain: Week 6 (n=163)	80.8 (± 21.6)			
Bodily Pain: Week 26 (n=75)	84.4 (± 21.5)			
Bodily Pain: ET (n=124)	81 (± 22.7)			
Bodily Pain: Week 26 LOCF (n=164)	82.5 (± 21.3)			
Emotion, Behavior: Week 6 (n=163)	53.3 (± 32.6)			
Emotion, Behavior: Week 26 (n=74)	60.1 (± 31.2)			
Emotion, Behavior: ET (n=123)	49.5 (± 34.5)			
Emotion, Behavior: Week 26 LOCF (n=163)	54.8 (± 32.2)			
Time Impact on Parent: Week 6 (n=163)	62 (± 26.6)			
Time Impact on Parent: Week 26 (n=75)	69.9 (± 23.5)			
Time Impact on Parent: ET (n=124)	59.9 (± 28.6)			
Time Impact on Parent: Week 26 LOCF (n=164)	65.1 (± 26.3)			
Emotional Impact on Parent: Week 6 (n=163)	49.5 (± 24.6)			
Emotional Impact on Parent: Week 26 (n=75)	57.2 (± 24.7)			

Emotional Impact on Parent: ET (n=124)	43.4 (± 25.9)			
Emotional Impact on Parent: Week 26 LOCF (n=164)	52.2 (± 26)			
Mental Health: Week 6 (n=163)	63.6 (± 16.1)			
Mental Health: Week 26 (n=75)	66.7 (± 16.5)			
Mental Health: ET (n=124)	60.8 (± 18.3)			
Mental Health: Week 26 LOCF (n=164)	65.1 (± 16.1)			
Physical Function: Week 6 (n=163)	80.4 (± 22.3)			
Physical Function: Week 26 (n=75)	84.9 (± 19)			
Physical Function: ET (n=124)	79.5 (± 23.4)			
Physical Function: Week 26 LOCF (n=164)	81.4 (± 21.9)			
Behavior Scale: Week 6 (n=163)	62.7 (± 16.8)			
Behavior Scale: Week 26 (n=75)	64.5 (± 20)			
Behavior Scale: ET (n=124)	60.2 (± 18.7)			
Behavior Scale: Week 26 LOCF (n=164)	63 (± 18.4)			
Self-Esteem: Week 6 (n=163)	52.7 (± 20.3)			
Self-Esteem: Week 26 (n=74)	55.3 (± 21)			
Self-Esteem: ET (n=124)	52.6 (± 21.7)			
Self-Esteem: Week 26 LOCF (n=163)	54.5 (± 20.6)			
General Health Perception: Week 6 (n=163)	50.3 (± 15.3)			
General Health Perception: Week 26 (n=75)	51.8 (± 16.4)			
General Health Perception: ET (n=124)	49.7 (± 15.1)			
General Health Perception: Week 26 LOCF (n=164)	50.3 (± 15.4)			
Family Activities: Week 6 (n=163)	60.1 (± 24.9)			
Family Activities: Week 26 (n=75)	63.9 (± 24.1)			
Family Activities: ET (n=124)	56.3 (± 27.6)			
Family Activities: Week 26 LOCF (n=164)	61.6 (± 26.1)			
Physical Health Global Subscale: Week 6 (n=163)	44.1 (± 11.7)			
Physical Health Global Subscale: Week 26 (n=74)	46.6 (± 10.9)			
Physical Health Global: ET (n=123)	43.8 (± 12.9)			
Physical Health Global: Week 26 LOCF (n=163)	44.8 (± 12.2)			
Psychosocial Health Global: Week 6 (n=163)	35.7 (± 10.4)			
Psychosocial Health Global: Week 26 (n=74)	38.5 (± 10.9)			
Psychosocial Health Global: ET (n=123)	33.7 (± 11.9)			
Psychosocial Health Global: Week 26 LOCF (n=163)	36.8 (± 10.7)			

Notes:

[11] - N=number of subjects with analyzable data at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Per Response on the School Placement Questionnaire: School Situation

End point title	Number of Subjects Per Response on the School Placement Questionnaire: School Situation

End point description:

School placement questionnaire: parent or legal guardian assessed questionnaire to determine whether the child is currently enrolled in school (or planned to be enrolled if on school holiday like summer break), whether attending regularly if enrolled, and how well the child is doing overall in school. Questions were modified from those used in the National Institute of Mental Health (NIMH) funded Treatment of Early Onset Schizophrenia Spectrum (TEOSS) study. Results determine whether subjects are currently attending school and qualitatively describe how well they are doing in school. Safety Analysis Set. n=number of subjects with analyzable data at baseline and post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	221[12]			
Units: subjects				
Baseline: Enrolled or Attend (n=221)	63			
Baseline: Not Attend or Mental Illness (n=221)	59			
Baseline: Not Attend or Other (n=221)	4			
Baseline: Enrolled or Vacation (n=221)	26			
Baseline: Not Enrolled or Mental Illness (n=221)	42			
Baseline: Not Enrolled or Other (n=221)	27			
Week 6: Enrolled or Attend (n=166)	68			
Week 6: Not Attend or Mental Illness (n=166)	32			
Week 6: Not Attend or Other (n=166)	1			
Week 6: Enrolled or Vacation (n=166)	14			
Week 6: Not Enrolled or Mental Illness (n=166)	29			
Week 6: Not Enrolled or Other (n=166)	22			
Week 26: Enrolled or Attend (n=75)	35			
Week 26: Not Attend or Mental Illness (n=75)	9			
Week 26: Not Attend or Other (n=75)	0			
Week 26: Enrolled or Vacation (n=75)	5			
Week 26: Not Enrolled or Mental Illness (n=75)	13			
Week 26: Not Enrolled or Other (n=75)	13			
ET: Enrolled or Attend (n=125)	42			
ET: Not Attend or Mental Illness (n=125)	35			
ET: Not Attend or Other (n=125)	1			
ET: Enrolled or Vacation (n=125)	9			
ET: Not Enrolled or Mental Illness (n=125)	21			
ET: Not Enrolled or Other (n=125)	17			
Week 26 LOCF: Enrolled or Attend (n=166)	75			

Week 26 LOCF: Not Attend or Mental Illness (n=166)	30			
Week 26 LOCF: Not Attend or Other (n=166)	1			
Week 26 LOCF: Enrolled or Vacation (n=166)	8			
Week 26 LOCF: Not Enrolled/Mental Illness (n=166)	28			
Week 26 LOCF: Not Enrolled or Other (n=166)	24			

Notes:

[12] - N=number of subjects analyzable for School Placement Questionnaire.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Per Response on the School Placement Questionnaire: School Attendance

End point title	Number of Subjects Per Response on the School Placement Questionnaire: School Attendance

End point description:

School placement questionnaire: parent or legal guardian assessed questionnaire to determine whether the child is currently enrolled in school (or planned to be enrolled if on school holiday like summer break), whether attending regularly if enrolled, and how well the child is doing overall in school. Questions were modified from those used in the National Institute of Mental Health (NIMH) funded Treatment of Early Onset Schizophrenia Spectrum (TEOSS) study. Results determine whether subjects are currently attending school and qualitatively describe how well they are doing in school. Safety Analysis Set. n=number of subjects with analyzable data at baseline and post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	133[13]			
Units: subjects				
Baseline: No Absences (n=133)	25			
Baseline: Only a Few Absences (n=133)	37			
Baseline: Frequent Absences (n=133)	12			
Baseline: Did Not Attend (n=133)	36			
Baseline: Not Applicable or Vacation (n=133)	23			
Week 6: No Absences (n=95)	31			
Week 6: Only a Few Absences (n=95)	29			
Week 6: Frequent Absences (n=95)	11			
Week 6: Did Not Attend (n=95)	10			
Week 6: Not Applicable or Vacation (n=95)	14			
Week 26: No Absences (n=42)	14			
Week 26: Only a Few Absences (n=42)	16			

Week 26: Frequent Absences (n=42)	7			
Week 26: Did Not Attend (n=42)	0			
Week 26: Not Applicable or Vacation (n=42)	5			
ET: No Absences (n=62)	16			
ET: Only a Few Absences (n=62)	23			
ET: Frequent Absences (n=62)	5			
ET: Did Not Attend (n=62)	11			
ET: Not Applicable or Vacation (n=62)	7			
Week 26 LOCF: No Absences (n=93)	32			
Week 26 LOCF: Only a Few Absences (n=93)	32			
Week 26 LOCF: Frequent Absences (n=93)	14			
Week 26 LOCF: Did Not Attend (n=93)	7			
Week 26 LOCF: Not Applicable or Vacation (n=93)	8			

Notes:

[13] - N=number of subjects analyzable for School Placement Questionnaire.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Per Response on the School Placement Questionnaire: Overall School Performance

End point title	Number of Subjects Per Response on the School Placement Questionnaire: Overall School Performance

End point description:

School placement questionnaire: parent or legal guardian assessed questionnaire to determine whether the child is currently enrolled in school (or planned to be enrolled if on school holiday like summer break), whether attending regularly if enrolled, and how well the child is doing overall in school. Questions were modified from those used in the National Institute of Mental Health (NIMH) funded Treatment of Early Onset Schizophrenia Spectrum (TEOSS) study. Results determine whether subjects are currently attending school and qualitatively describe how well they are doing in school. Safety Analysis Set. n=number of subjects with analyzable data at baseline and post-baseline observation. Baseline was the last available observation from Study A1281134 (EudraCT Number: 2005-005502-23) (NCT00257192). LOCF imputation used for Week 26 LOCF time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 6 and 26, ET

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	103[14]			
Units: subjects				
Baseline: Excellent (n=103)	5			
Baseline: Good (n=103)	25			
Baseline: Fair (n=103)	40			
Baseline: Poor (n=103)	23			
Baseline: Very Poor (n=103)	10			
Week 6: Excellent (n=73)	2			

Week 6: Good (n=73)	23			
Week 6: Fair (n=73)	34			
Week 6: Poor (n=73)	14			
Week 6: Very Poor (n=73)	0			
Week 26: Excellent (n=37)	1			
Week 26: Good (n=37)	10			
Week 26: Fair (n=37)	18			
Week 26: Poor (n=37)	5			
Week 26: Very Poor (n=37)	3			
ET: Excellent (n=48)	0			
ET: Good (n=48)	15			
ET: Fair (n=48)	23			
ET: Poor (n=48)	6			
ET: Very Poor (n=48)	4			
Week 26 LOCF: Excellent (n=80)	1			
Week 26 LOCF: Good (n=80)	22			
Week 26 LOCF: Fair (n=80)	39			
Week 26 LOCF: Poor (n=80)	15			
Week 26 LOCF: Very Poor (n=80)	3			

Notes:

[14] - N=number of subjects analyzable for School Placement Questionnaire.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events are reported from time of first dose of study treatment up to 6 days after last dose of study treatment.

Adverse event reporting additional description:

Safety population= all randomized subjects with at least 1 dose of study treatment. An Adverse Event (AE) term may be reported as both a serious and non-serious AE, but are distinct events. AE may= serious for 1 subject and= non-serious for another subject or subject may have experienced both serious and non-serious episode of the same event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0.0

Reporting groups

Reporting group title	Ziprasidone

Reporting group description:

Titrated over a 2-week period, starting with an evening dose of 20 mg/day, and subsequent dose increases of 20 mg/day every second day up to a target dose of 80 to 160 mg/day for subjects weighing >=45 kg. For subjects with a body weight <45 kg, the maximum permitted dose was 80 mg/day (40 mg BID). Doses could have been reduced to a minimum of 40 mg/day (20 mg BID).

Serious adverse events	Ziprasidone		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 221 (7.24%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Nervous system disorders			
Dystonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Drug ineffective			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			

Sexual activity increased				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Victim of sexual abuse				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Aggression				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Agitation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Delusional perception				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination, auditory				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 221 (0.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intentional self-injury				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Major depression				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obsessive-compulsive disorder				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 221 (0.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Persecutory delusion				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Schizophrenia alternative assessment type: Non-systematic				
subjects affected / exposed	4 / 221 (1.81%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Schizophrenia, paranoid type alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Self injurious behaviour alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 221 (0.90%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Suicidal behaviour alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 221 (1.36%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Thinking abnormal alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 221 (0.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Ziprasidone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 221 (24.89%)		
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 221 (9.05%)		
occurrences (all)	35		
Somnolence			
alternative assessment type: Non-systematic			
subjects affected / exposed	33 / 221 (14.93%)		
occurrences (all)	38		
Tremor			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 221 (6.33%)		
occurrences (all)	21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2006	1. Electrocardiograms (ECGs) showing a Fridericia corrected QT (QTcF) of >=460 milliseconds (msec) or a suspected increase from baseline of 60 msec or greater was to be repeated within the same visit. If the QTcF value persisted at >=460 msec and/or the change from baseline. persisted at >=60 msec, the study drug was to be discontinued immediately and a pediatric cardiologist or a pediatric intensive care specialist should be contacted to discuss the ECG result. 2. Waist Circumference evaluation, fasting glucose and Glycosylated hemoglobin (HbA1c) as clinical laboratory testing and Possibly Suicide-Related Adverse Events (PSRAEs) monitoring were included. 4. Benzhexol, other anticholinergics and Steroids (except inhaled, if taken at least 2 months before study with stable dose and clinical condition) were included in concomitant medications. 5. It was recommended that subjects should complete the Central nervous system (CNS) Vital Signs battery before any intrusive assessments such as blood draws, if at all possible. 6. Exposure In utero definition was amended to include paternal exposure. 7. 8. For safety, for those subjects who were randomized to placebo in the double-blind study, baseline values was to be the observation prior to dosing for ECG and blood pressure/pulse only, initiating dosing in the open-label extension study.
17 January 2007	1. To assess risks related to the possible prolongation of the QT interval, subjects with QTcF ≥440 460 msec or with risk factors for QT prolongation were to be excluded. Extensive ECG monitoring was to be performed throughout the study, including triplicate ECGs at baseline (3 timepoints). 2. Concomitant medication section amended to include trihexyphenidyl hydrochloride (HCl) and exclude Benzhexol.
13 November 2007	1. Trial treatment section was amended to include drug blister card design to decrease the chance for dosing errors (usually overdosing).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The AE tables were amended to incorporate previously unreported AEs that were found during an independent audit and verified by the investigators.

Notes: