Clinical trial results:
Six week, double-blind, placebo controlled Phase III trial evaluating the efficacy, safety and pharmacokinetics of flexible doses of oral ziprasidone in adolescent subjects with schizophrenia.

Summary

EudraCT number	2005-005501-28
Trial protocol	SE DE
Global end of trial date	26 March 2009

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	A1281134

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00257192
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., ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 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	29 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2009
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To establish efficacy of oral ziprasidone compared to placebo in the treatment of adolescent subjects with schizophrenia, as measured by the change from baseline to Week 6 in Brief Psychiatric Rating Scale - Anchored (BPRS-A) total score.
2. To evaluate the safety and tolerability of oral ziprasidone over 6 weeks in the treatment of 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	25 April 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	Colombia: 8
Country: Number of subjects enrolled	Costa Rica: 5
Country: Number of subjects enrolled	India: 38
Country: Number of subjects enrolled	Malaysia: 14
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Russian Federation: 81
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Ukraine: 56
Country: Number of subjects enrolled	United States: 69
Worldwide total number of subjects	283
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	283
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Data Safety Monitoring Board (DSMB) recommended to terminate study due to futility per interim analysis charter (p-value=0.9840). Only 1 active subject was affected by this decision. A total of 284 subjects randomized to study. Of these,193 took ziprasidone and 90 took placebo,while 1 subject assigned to placebo did not receive treatment.

Pre-assignment

Screening details:

Screening visit followed by a 1 to 10 day period to allow for wash-out of exclusionary medications.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ziprasidone

Arm description:

Ziprasidone capsules administered twice daily (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:

Oral (PO) capsules administered twice daily (BID); titrated from a starting dose of 20 milligrams per day (mg/day) over 2 weeks with dose increase of 20 mg/day every second day up to a target dose range of 120 to 160 mg/day for subjects with body weight greater than or equal to (>=) 45 kilograms (kg); target dose for subjects with body weight less than (<) 45 kg is 60 to 80 mg/day. After titration dose was attained, flexible dosing range of 80 to 160 (if body weight >=45 kg) or 40 to 80 mg/day (if body weight <45 kg) for duration of the study.

Arm title	Placebo

Arm description:

Placebo capsules matched to ziprasidone twice daily (BID) with meals.

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

Dosage and administration details:

Placebo matching ziprasidone administration; titrated from a starting dose of 20 mg/day over 2 weeks with dose increases of 20 mg/day every second day up to a target dose range of 120 to 160 mg/day for subjects with body weight >=45 kg; target dose for subjects with body weight <45 kg is 60 to 80 mg/day. After titration dose is attained, flexible dosing range of 80 to 160 (if body weight >=45 kg) or 40 to 80 mg/day (if body weight <45 kg) for duration of the study.

Number of subjects in period 1	Ziprasidone	Placebo
Started	193	90
Completed	135	52
Not completed	58	38
Consent withdrawn by subject	14	2
Adverse Event	21	10
Miscellaneous	-	4
Study terminated by sponsor	1	-
Laboratory abnormality	1	1
Lost to follow-up	3	3
Insufficient clinical response	18	18

Baseline characteristics

Reporting groups	
Reporting group title	Ziprasidone
Reporting group description:	
Ziprasidone capsules administered twice daily (BID) with meals.	
Reporting group title	Placebo
Reporting group description:	
Placebo capsules matched to ziprasidone twice daily (BID) with meals.	

Reporting group values	Ziprasidone	Placebo	Total
Number of subjects	193	90	283
Age categorical			
Units: Subjects			
>12 years and <13 years at start of treatment	4	0	4
Between 13 and 17 years	189	90	279
Age continuous			
Units: years			
arithmetic mean	15.3	15.4	
standard deviation	± 1.4	± 1.4	-
Gender categorical			
Units: Subjects			
Female	84	28	112
Male	109	62	171
Ethnicity			
Units: Subjects			
Hispanic / Latino	21	9	30
Not Hispanic / Latino	172	81	253
Race			
Units: Subjects			
White	116	60	176
Black	17	2	19
Asian	38	17	55
Hispanic	9	3	12
Other	13	8	21
Tanner adolescent pubertal self-assessment: Breast (females)			
At baseline, subjects self-administer a gender appropriate Tanner Adolescent Pubertal Staging Questionnaire 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).			
Units: Subjects			
Stage 1	0	1	1
Stage 2	6	3	9
Stage 3	16	4	20
Stage 4	35	11	46
Stage 5	25	9	34
Not applicable	109	62	171

Missing (not answered)	2	0	2
Tanner adolescent pubertal self-assessment: Genitalia (males)			
At baseline, subjects self-administer a gender appropriate Tanner Adolescent Pubertal Staging Questionnaire 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).			
Units: Subjects			
Stage 1	0	1	1
Stage 2	9	3	12
Stage 3	25	16	41
Stage 4	57	26	83
Stage 5	18	16	34
Not applicable	82	28	110
Missing (not answered)	2	0	2
Tanner adolescent pubertal self-assessment: Pubic hair (females and males)			
At baseline, subjects self-administer a gender appropriate Tanner Adolescent Pubertal Staging Questionnaire 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).			
Units: Subjects			
Stage 1	0	3	3
Stage 2	13	7	20
Stage 3	36	13	49
Stage 4	90	43	133
Stage 5	52	24	76
Missing (not answered)	2	0	2
Height			
Units: centimeters (cm)			
arithmetic mean	164.9	167.8	
standard deviation	± 10.1	± 10	-
Weight			
Units: kilograms (kg)			
arithmetic mean	61.2	64.3	
standard deviation	± 15.5	± 15.7	-

End points

End points reporting groups

Reporting group title	Ziprasidone
Reporting group description:	
Ziprasidone capsules administered twice daily (BID) with meals.	
Reporting group title	Placebo
Reporting group description:	
Placebo capsules matched to ziprasidone twice daily (BID) with meals.	

Primary: Change From Baseline in Brief Psychiatric Rating Scale - Anchored (BPRS-A) Total Score at Week 6

End point title	Change From Baseline in Brief Psychiatric Rating Scale - Anchored (BPRS-A) Total Score at Week 6

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, and excitement. Ratings anchored to improve consistency for a 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. Intent to treat (ITT): all randomized subjects who had baseline measurements, took at least 1 dose of study medication, and had at least 1 post-baseline visit.

End point type	Primary

End point timeframe:

Baseline, Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189[1]	87[2]		
Units: scores on a scale				
least squares mean (standard error)	-14.16 (± 0.78)	-12.35 (± 1.05)		

Notes:

[1] - N= number of subjects with analyzable data at post-baseline observation.

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

Statistical analyses

Statistical analysis title	Analysis of Change in BPRS-A at Week 6

Statistical analysis description:

Sample size for 85 percent (%) power 2-tailed 0.05 significance level based on expected difference of -5 with average within-group standard deviation=13 was 276 subjects (2 to 1 ratio of enrollment: 184 ziprasidone, 92 placebo). Interim analysis at 60% enrollment (ITT population): may stop trial early for efficacy (2-sided p-value less than (<) 0.0124) or for futility (2-sided p-value greater than (>) 0.4772); The final analysis is to employ a 2-sided p-value <0.0462.

Comparison groups	Ziprasidone v Placebo

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.153 [4]
Method	ANCOVA
Parameter estimate	Least squares mean
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.28
upper limit	0.67
Variability estimate	Standard error of the mean
Dispersion value	1.26

Notes:

[3] - P-value for final analysis is to be adjusted due to planned interim analysis (0.0462).

[4] - Mixed effects repeated measures (MMRM) analysis of covariance model with subject as random effect, treatment, region, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

Secondary: Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Week 6

End point title	Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Week 6

End point description:

CGI-S: single-item clinician rated scale to rate the severity of a subject's illness over time. Scores range from 1 (normal, not at all ill) to 7 (among the most severely ill subjects); higher score indicates more affected. ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190[5]	87[6]		
Units: scores on a scale				
least squares mean (standard error)	-1.05 (± 0.08)	-0.84 (± 0.12)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Analysis of Change in CGI-S Score at Week 6

Statistical analysis description:

Difference from placebo. Hochberg procedure was applied to p-value to preserve type I error in the analysis of key secondary endpoints (Positive and Negative Syndrome Scale (PANSS) total score and CGI-S).

Comparison groups	Ziprasidone v Placebo

Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1289 [7]
Method	ANCOVA
Parameter estimate	Least squares mean
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[7] - Mixed effects repeated measures (MMRM) analysis of covariance model with subject as random effect, treatment, region, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

Secondary: Change From Baseline in Positive and Negative Syndrome Scale (PANSS) - Total Score at Week 6

End point title	Change From Baseline in Positive and Negative Syndrome Scale (PANSS) - Total Score at Week 6

End point description:

PANSS: 30-item clinician-rated scale to measure severity of psychopathology (16 items); positive scale (7 items); negative scale (7 items); summarized as positive score, negative score, and total score. Items scored on anchored Likert scale rated 1 (absent symptoms) to 7 (extreme); scores above 1 indicate clinical symptom is present; scores from 2 to 7 indicate increased severity. Total score range 30 to 210: higher score indicates greater severity. ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183[8]	86[9]		
Units: scores on a scale				
least squares mean (standard error)	-23.58 (± 1.42)	-21.01 (± 1.73)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Analysis of Change in PANSS Total Score at Week 6

Statistical analysis description:

Total score: difference from placebo. Hochberg procedure was applied to p-value to preserve type I error in the analysis of key secondary endpoints (PANSS total score and CGI-S).

Comparison groups	Ziprasidone v Placebo

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1987 [10]
Method	ANCOVA
Parameter estimate	Least squares mean
Point estimate	-2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	1.36
Variability estimate	Standard error of the mean
Dispersion value	2

Notes:

[10] - Mixed effects repeated measures (MMRM) analysis of covariance model with subject as random effect, treatment, region, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

Secondary: Change From Baseline in PANSS: Positive and Negative Subscales at Week 6

End point title	Change From Baseline in PANSS: Positive and Negative Subscales at Week 6

End point description:

PANSS: 30-item clinician-rated scale to measure severity of psychopathology (16 items); positive scale (7 items); negative scale (7 items); summarized as positive score, negative score, and total score. Items scored on anchored Likert scale rated 1 (absent symptoms) to 7 (extreme); scores above 1 indicate clinical symptom is present; scores from 2 to 7 indicate increased severity. Total score range 30 to 210: higher score indicates greater severity. ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183[11]	86[12]		
Units: scores on a scale				
least squares mean (standard error)				
Positive score	-7.22 (± 0.44)	-5.88 (± 0.56)		
Negative score	-5.51 (± 0.43)	-5.09 (± 0.51)		

Notes:

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

[12] - N=number of subjects with analyzable data at post-baseline observation.

Statistical analyses

Statistical analysis title	Change in Positive Subscale

Statistical analysis description:

Positive Score: Difference From Placebo.

Comparison groups	Ziprasidone v Placebo

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0412 [13]
Method	ANCOVA
Parameter estimate	Least squares mean
Point estimate	-1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.65

Notes:

[13] - Mixed effects repeated measures (MMRM) analysis of covariance model with subject as random effect, treatment, region, visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

Statistical analysis title	Change in Negative Subscales

Statistical analysis description:

Negative Score: Difference From Placebo.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4661 [14]
Method	ANCOVA
Parameter estimate	Least squares mean
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	0.72
Variability estimate	Standard error of the mean
Dispersion value	0.58

Notes:

[14] - Mixed effects repeated measures (MMRM) analysis of covariance model with subject as random effect, treatment, region, visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

Secondary: Clinical Global Impression of Improvement (CGI-I) Score at Week 6

End point title	Clinical Global Impression of Improvement (CGI-I) Score at Week 6

End point description:

CGI-I: single-item clinician rated scale used to assess the subject's improvement or worsening from baseline. Scores range from 1 (very much improved) to 4 (no change) to 7 (very much worse); higher score indicates more affected. ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190[15]	87[16]		
Units: scores on a scale				
least squares mean (standard error)	2.66 (± 0.09)	2.85 (± 0.12)		

Notes:

[15] - N=number of subjects with analyzable data at post-baseline observation.

[16] - N=number of subjects with analyzable data at post-baseline observation.

Statistical analyses

Statistical analysis title	Analysis of CGI-I Score at Week 6
Statistical analysis description: Difference from placebo.	
Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182 [17]
Method	ANOVA
Parameter estimate	Least squares mean
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[17] - Mixed effects MMRM with subject as random effect, treatment, region, visit and visit-by-treatment interaction as fixed effects.

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. ITT population. Here, (n)=number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. ET (Early Termination) includes observations from visits not within windowing criteria. Last observation carried forward [LOCF] imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 6, ET

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	90		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=183, 86)	4.7 (± 8.7)	2.6 (± 5.8)		
Week 4 (n=155, 63)	7.9 (± 10.4)	6.2 (± 8.9)		
Week 6 (n=135, 52)	10.9 (± 11.8)	10.8 (± 9.9)		
ET (n=20, 15)	1.3 (± 10.1)	1.7 (± 8.9)		
Week 6 [LOCF] (n=185, 87)	8.4 (± 11.8)	6.4 (± 10.6)		

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. ITT. ET includes observations from visits not within windowing criteria. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 6, ET

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	90		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Global health: Week 6	5 (± 18.2)	8.5 (± 24.7)		
Global health: ET	-5.4 (± 24)	-9.1 (± 17.4)		
Global health: Week 6 [LOCF]	2.8 (± 19.9)	1.4 (± 23.7)		
Global behavior: Week 6	9.4 (± 23.6)	10.9 (± 22.1)		
Global behavior: ET	6.4 (± 21.4)	-0.5 (± 23)		
Global behavior: Week 6 [LOCF]	8.8 (± 23.1)	6.5 (± 23.1)		
Family cohesion: Week 6	1.9 (± 21.3)	-0.8 (± 19.7)		
Family cohesion: ET	-1.8 (± 18.4)	-2.6 (± 16.1)		
Family cohesion: Week 6 [LOCF]	1.2 (± 20.8)	-1.1 (± 18.1)		

Physical health: Week 6	3.5 (± 33.9)	5 (± 28)		
Physical health: ET	-6.5 (± 32.9)	3.2 (± 23.3)		
Physical health: Week 6 [LOCF]	1.4 (± 33.8)	4.8 (± 26)		
Bodily pain: Week 6	4.4 (± 21.6)	8 (± 19.4)		
Bodily pain: ET	4.7 (± 23)	0 (± 14.6)		
Bodily pain: Week 6 [LOCF]	4.5 (± 21.9)	4.9 (± 18.1)		
Emotion, behavior: Week 6	16.2 (± 29.8)	13.8 (± 31.1)		
Emotion, behavior: ET	4 (± 43.1)	-2.5 (± 22.7)		
Emotion, behavior: Week 6 [LOCF]	13.6 (± 33.4)	7.8 (± 29.2)		
Time impact on parent: Week 6	8.8 (± 25.4)	11.8 (± 23.1)		
Time impact on parent: ET	2 (± 25.8)	1.8 (± 21.7)		
Time impact on parent: Week 6 [LOCF]	7.4 (± 25.5)	8 (± 23.1)		
Emotional impact on parent: Week 6	8.9 (± 21.6)	10 (± 22.3)		
Emotional impact on parent: ET	3.5 (± 21.2)	2.7 (± 12.6)		
Emotional impact on parent: Week 6 [LOCF]	7.7 (± 21.6)	7.4 (± 19.4)		
Mental health: Week 6	8.1 (± 15.3)	12.6 (± 18.2)		
Mental health: ET	1.3 (± 17.9)	-0.8 (± 12)		
Mental health: Week 6 [LOCF]	6.7 (± 16.1)	7.5 (± 17.4)		
Physical function: Week 6	5.6 (± 19.7)	5.9 (± 25.2)		
Physical function: ET	-5.4 (± 22.5)	-0.2 (± 17.7)		
Physical function: Week 6 [LOCF]	3.3 (± 20.8)	3.7 (± 22.8)		
Behavior scale: Week 6	9 (± 17.1)	9 (± 16.8)		
Behavior scale: ET	7.6 (± 15.2)	0.6 (± 17.1)		
Behavior scale: Week 6 [LOCF]	8.7 (± 16.7)	5.8 (± 17.4)		
Self-esteem: Week 6	6 (± 17.5)	9 (± 22.9)		
Self-esteem: ET	1 (± 20.6)	1.3 (± 14)		
Self-esteem: Week 6 [LOCF]	5 (± 18.2)	6.4 (± 20.2)		
General health perception: Week 6	1.1 (± 11.6)	3.3 (± 11.7)		
General health perception: ET	-2.2 (± 12.3)	-0.6 (± 10.8)		
General health perception: Week 6 [LOCF]	0.4 (± 11.8)	1.8 (± 11.5)		
Family activities: Week 6	9.2 (± 22.6)	14.6 (± 22.5)		
Family activities: ET	1.3 (± 16.8)	-4.6 (± 16.5)		
Family activities: Week 6 [LOCF]	7.5 (± 21.7)	7.8 (± 22)		
Change in health: Week 6	0.5 (± 1.1)	0.6 (± 1)		
Change in health: ET	-0.4 (± 1)	-0.1 (± 0.8)		
Change in health: Week 6 [LOCF]	0.3 (± 1.1)	0.3 (± 1)		
Physical health global subscale: Week 6	1.8 (± 9.7)	2.4 (± 9.8)		
Physical health global subscale: ET	-2.8 (± 11.8)	0.1 (± 4.4)		
Physical health global subscale: Week 6 [LOCF]	0.9 (± 10.3)	1.6 (± 8.2)		
Psychosocial health global subscale: Week 6	6.6 (± 9.5)	7.7 (± 11)		
Psychosocial health global subscale: ET	3.1 (± 10.4)	0 (± 5.7)		
Psychosocial health global subscale: Week 6 [LOCF]	5.9 (± 9.8)	4.8 (± 10)		

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. ITT; (n)= number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 1 through Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173[18]	74[19]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=165, 69)	-2.4 (± 7.1)	-1.3 (± 5.8)		
Week 2 (n=161, 71)	-2.5 (± 8)	-1 (± 6.2)		
Week 3 (n=146, 64)	-3 (± 6.7)	-0.7 (± 5.7)		
Week 4 (n=138, 51)	-2.7 (± 7.4)	-1 (± 6.5)		
Week 5 (n=126, 44)	-3.1 (± 7)	-0.8 (± 8.3)		
Week 6 (n=119, 42)	-3 (± 7.4)	-1.9 (± 6.7)		
Week 6 [LOCF] (n=167, 71)	-2.3 (± 8.2)	-0.3 (± 8.8)		

Notes:

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

[19] - 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. ITT; (n)=number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 1 through Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180[20]	84[21]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=179, 82)	-2.8 (± 6.6)	-1.4 (± 5.7)		
Week 2 (n=174, 80)	-4.2 (± 7.3)	-2.5 (± 5.6)		
Week 3 (n=157, 69)	-5.5 (± 7.4)	-3.2 (± 5.4)		
Week 4 (n=148, 59)	-6 (± 7.6)	-4.9 (± 6.6)		
Week 5 (n=135, 49)	-7 (± 8.5)	-5.6 (± 5.9)		
Week 6 (n=126, 47)	-7.9 (± 7.9)	-6.5 (± 5.5)		
Week 6 [LOCF] (n=178, 82)	-5.8 (± 8.7)	-4 (± 7.3)		

Notes:

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

[21] - 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): Suicide Ideation Item 13

End point title	Change From Baseline in Child Depression Rating Scale - Revised (CDRS-R): Suicide Ideation Item 13

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. Suicide Ideation (Item 13) detects changes in suicidality over time. Rated on a 7-point scale; range from 1 (no impairment) to 7 (indicates greater impairment). ITT; (n)=number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 1 through Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192[22]	90[23]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=188, 86)	-0.1 (± 0.4)	0 (± 0.5)		
Week 2 (n=182, 86)	0 (± 0.5)	-0.1 (± 0.5)		
Week 3 (n=165, 74)	-0.1 (± 0.5)	-0.1 (± 0.3)		
Week 4 (n=154, 63)	0 (± 0.5)	-0.1 (± 0.5)		

Week 5 (n=141, 54)	0 (± 0.4)	-0.1 (± 0.5)		
Week 6 (n=134, 52)	0 (± 0.3)	-0.1 (± 0.4)		
Week 6 [LOCF] (n=189, 87)	0 (± 0.6)	0 (± 0.5)		

Notes:

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

[23] - 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): Impaired Schoolwork Item 1

End point title	Change From Baseline in Child Depression Rating Scale - Revised (CDRS-R): Impaired Schoolwork Item 1

End point description:

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 resolved by using most impaired rating given by valid informant. Impaired Schoolwork (Item 1) assesses school function for the subgroup of subjects reported to be in school. Rated on a 7-point scale; range from 1 (no impairment) to 7 (indicates greater impairment). ITT; (n)=number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[24]	15[25]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=38, 15)	-0.3 (± 0.9)	-0.2 (± 0.7)		
Week 6 (n=30, 8)	-0.6 (± 1.1)	-0.1 (± 1.4)		
Week 6 [LOCF] (n=39, 15)	-0.6 (± 1)	-0.1 (± 1.1)		

Notes:

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

[25] - 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:

A computerized subject-administered test battery with subtests for verbal and visual memory, processing speed, nonverbal reasoning, executive functioning, working memory, and sustained attention. A computerized 7-point sedation item (0 [not sleepy] to 10 [very sleepy]) was completed prior to test battery. The Neurocognitive index score was derived from subtest scores per an algorithm.

The 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). ITT; (n)= number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. ET includes observations from visits not within windowing criteria. LOCF imputation used for Week 6 LOCF timepoint (last post-baseline non-missing visit).

End point type	Secondary
End point timeframe:	
Baseline, Week 6, ET	

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174[26]	83[27]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Sedation: Week 6 (n=124, 47)	0 (± 1.7)	-0.4 (± 1.8)		
Sedation: ET (n=23, 26)	0 (± 2.3)	0.2 (± 1.3)		
Sedation: Week 6 [LOCF] (n=147, 72)	0 (± 1.8)	-0.2 (± 1.7)		
Verbal Memory: Week 6 (n=124, 47)	1.3 (± 12.1)	0.5 (± 14)		
Verbal Memory: ET (n=24, 25)	-2.3 (± 13.9)	-2.6 (± 15.1)		
Verbal Memory: Week 6 [LOCF] (n=148, 71)	0.7 (± 12.4)	-0.5 (± 14.4)		
Visual Memory: Week 6 (n=124, 46)	0.5 (± 13.3)	2 (± 14.5)		
Visual Memory: ET (n=24, 26)	-3.8 (± 10.2)	0.4 (± 14.2)		
Visual Memory: Week 6 [LOCF] (n=148, 71)	-0.2 (± 12.9)	1.2 (± 14.3)		
Processing Speed: Week 6 (n=124, 46)	1.3 (± 13.5)	1 (± 12)		
Processing Speed: ET (n=24, 25)	-10.6 (± 34.5)	0.5 (± 5.4)		
Processing Speed: Week 6 [LOCF] (n=148, 70)	-0.6 (± 18.9)	0.6 (± 10.1)		
Reasoning: Week 6 (n=122, 46)	2.2 (± 12)	-0.7 (± 14.6)		
Reasoning: ET (n=23, 25)	1.3 (± 15.8)	3.3 (± 14)		
Reasoning: Week 6 [LOCF] (n=145, 70)	1.9 (± 12.7)	0.7 (± 14.1)		
Executive Functioning: Week 6 (n=123, 46)	2.9 (± 15.4)	2.7 (± 18.2)		
Executive Functioning: ET (n=23, 26)	-6.7 (± 9.1)	4.6 (± 13.2)		
Executive Functioning: Week 6 [LOCF] (n=146, 71)	1.4 (± 14.9)	3.2 (± 16.6)		
Working Memory: Week 6 (n=120, 45)	1.9 (± 12.9)	0.5 (± 12.9)		
Working Memory: ET (n=23, 24)	3.2 (± 13.5)	3.7 (± 11)		
Working Memory: Week 6 [LOCF] (n=143, 68)	2 (± 12.9)	1.3 (± 12.2)		
Sustained Attention: Week 6 (n=120, 45)	2 (± 12.3)	-1.6 (± 13.1)		
Sustained Attention: ET (n=23, 24)	0.5 (± 13.5)	1.5 (± 11.6)		
Sustained Attention: Week 6 [LOCF] (n=143, 68)	1.7 (± 12.4)	-0.9 (± 12.6)		

Notes:

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

[27] - 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:

A computerized subject-administered test battery with subtests for verbal and visual memory, processing speed, nonverbal reasoning, executive functioning, working memory, and sustained attention. A computerized 7-point sedation item (0 [not sleepy] to 10 [very sleepy]) was completed prior to test battery. The Neurocognitive index score was derived from subtest scores per an algorithm. The 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). ITT; (n)= number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. ET includes observations from visits not within windowing criteria. LOCF imputation used for Week 6 LOCF timepoint (last post-baseline non-missing visit).

End point type	Secondary

End point timeframe:

Baseline, Week 6, ET

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168[28]	79[29]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Neurocognitive Index: Week 6 (n=120, 45)	1.8 (± 7.1)	0.8 (± 7.5)		
Neurocognitive Index: ET (n=23, 23)	-2.7 (± 7.6)	2.2 (± 7.2)		
Neurocognitive Index: Week 6 [LOCF] (n=143, 67)	1 (± 7.4)	1.1 (± 7.4)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Change in Neurocognitive Index Score at Week 6

Statistical analysis description:

Difference from placebo. Observed cases at Week 6.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2613 [30]
Method	ANCOVA
Parameter estimate	Least squares mean
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	3.69

Variability estimate	Standard error of the mean
Dispersion value	1.19

Notes:

[30] - SAS PROC MIXED to fit a mixed model analysis of covariance with treatment and region as fixed effects and baseline score as covariate.

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

End point title	Change From Baseline in Movement Disorder Scales: 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. ITT; (n)= number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 1 through Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189[31]	87[32]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=189, 85)	0.5 (± 2.8)	0.1 (± 0.9)		
Week 2 (n=182, 85)	0.5 (± 2.4)	0 (± 0.5)		
Week 3 (n=165, 74)	0.7 (± 3.1)	0.3 (± 1.6)		
Week 4 (n=154, 62)	0.4 (± 2.6)	0 (± 0.6)		
Week 5 (n=141, 54)	0.2 (± 2.4)	0 (± 1)		
Week 6 (n=134, 52)	0.2 (± 2.5)	-0.2 (± 0.8)		
Week 6 [LOCF] (n=189, 86)	0.3 (± 2.5)	-0.1 (± 0.6)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Movement Disorder Scales: 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. ITT; (n)= number of

subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 1 through Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190[33]	88[34]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=190, 86)	0.1 (± 0.6)	0.1 (± 0.4)		
Week 2 (n=183, 86)	0.1 (± 0.7)	0 (± 0.3)		
Week 3 (n=166, 74)	0.1 (± 0.6)	0 (± 0.3)		
Week 4 (n=155, 63)	0.1 (± 0.6)	0 (± 0.2)		
Week 5 (n=142, 54)	0.1 (± 0.5)	0 (± 0.2)		
Week 6 (n=135, 52)	0 (± 0.5)	0 (± 0.2)		
Week 6 [LOCF] (n=190, 87)	0 (± 0.6)	0 (± 0.2)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Movement Disorder Scales: 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. ITT; (n)=number of subjects with analyzable data at post-baseline observation for ziprasidone and placebo, respectively. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 1 through Week 6

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190[35]	88[36]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=190, 86)	0.2 (± 1.6)	0 (± 0.4)		

Week 2 (n=183, 86)	0.1 (± 1.6)	0 (± 0.6)		
Week 3 (n=166, 74)	0.1 (± 1.3)	0.1 (± 1)		
Week 4 (n=155, 63)	0.1 (± 0.8)	0 (± 0.8)		
Week 5 (n=142, 54)	-0.1 (± 0.7)	0 (± 0.4)		
Week 6 (n=135, 52)	0 (± 0.6)	0 (± 0.5)		
Week 6 [LOCF] (n=190, 87)	0 (± 0.8)	0 (± 0.7)		

Notes:

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

[36] - 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. ITT; (n)=number of subjects with analyzable data at baseline and post-baseline observation for ziprasidone and placebo, respectively. ET includes observations from visits not within windowing criteria. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 6, ET

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189[37]	87[38]		
Units: subjects				
Baseline: Enrolled or attend (n=185, 85)	40	15		
Baseline: Not attend or mental illness (n=185, 85)	62	26		
Baseline: Not attend or other (n=185, 85)	2	0		
Baseline: Enrolled or vacation (n=185, 85)	20	19		
Baseline: Not enrolled/mental illness	36	12		
Baseline: Not enrolled or other (n=185, 85)	25	13		
Week 2: Enrolled or attend (n=179, 84)	38	20		
Week 2: Not attend or mental illness (n=179, 84)	59	24		
Week 2: Not attend or other (n=179, 84)	3	2		
Week 2: Enrolled or vacation (n=179, 84)	20	11		

Week 2: Not enrolled or mental illness (n=179, 84)	36	15		
Week 2: Not enrolled or other (n=179, 84)	23	12		
Week 6: Enrolled or attend (n=134, 51)	38	18		
Week 6: Not attend or mental illness (n=134, 51)	36	7		
Week 6: Not attend or other (n=134, 51)	3	0		
Week 6: Enrolled or vacation (n=134, 51)	14	5		
Week 6: Not enrolled or mental illness (n=134, 51)	23	11		
Week 6: Not enrolled or other (n=134, 51)	20	10		
ET: Enrolled or attend (n=32, 25)	5	3		
ET: Not attend or mental illness (n=32, 25)	8	14		
ET: Not attend or other (n=32, 25)	0	0		
ET: Enrolled or vacation (n=32, 25)	5	4		
ET: Not enrolled or mental illness (n=32, 25)	10	3		
ET: Not enrolled or other (n=32, 25)	4	1		
Week 6 [LOCF]: Enrolled or attend (n=183, 86)	47	23		
Week 6 [LOCF]: Not attend/mental illness	50	23		
Week 6 [LOCF]: Not attend or other (n=183, 86)	3	1		
Week 6 [LOCF]: Enrolled or vacation (n=183, 86)	21	10		
Week 6 [LOCF]: Not enrolled or mental illness	36	17		
Week 6 [LOCF]: Not enrolled or other (n=183, 86)	26	12		

Notes:

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

[38] - 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. ITT; (n)=number of subjects with analyzable data at baseline and post-baseline observation for ziprasidone and placebo, respectively. ET includes observations from visits not within windowing criteria. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 6, ET

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189[39]	87[40]		
Units: subjects				
Baseline: No absences (n=88, 42)	20	7		
Baseline: Only a few absences (n=88, 42)	16	15		
Baseline: Frequent absences (n=88, 42)	13	2		
Baseline: Did not attend (n=88, 42)	26	7		
Baseline: Not applicable or vacation (n=88, 42)	13	11		
Week 2: No absences (n=82, 36)	19	8		
Week 2: Only a few absences (n=82, 36)	14	9		
Week 2: Frequent absences (n=82, 36)	11	4		
Week 2: Did not attend (n=82, 36)	25	8		
Week 2: Not applicable or vacation (n=82, 36)	13	7		
Week 6: No absences (n=67, 24)	16	8		
Week 6: Only a few absences (n=67, 24)	22	12		
Week 6: Frequent absences (n=67, 24)	5	0		
Week 6: Did not attend (n=67, 24)	13	0		
Week 6: Not applicable or vacation (n=67, 24)	11	4		
ET: No absences (n=12, 12)	1	0		
ET: Only a few absences (n=12, 12)	4	0		
ET: Frequent absences (n=12, 12)	2	5		
ET: Did not attend (n=12, 12)	4	4		
ET: Not applicable or vacation (n=12, 12)	1	3		
Week 6 [LOCF]: No absences (n=89, 37)	18	8		
Week 6 [LOCF]: Only a few absences (n=89, 37)	26	13		
Week 6 [LOCF]: Frequent absences (n=89, 37)	11	4		
Week 6 [LOCF]: Did not attend (n=89, 37)	21	4		
Week 6[LOCF]: Not applicable or vacation(n=89,37)	13	8		

Notes:

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

[40] - 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. ITT; (n)=number of subjects with analyzable data at baseline and post-baseline observation for ziprasidone and placebo, respectively. ET includes observations from visits not within windowing criteria. LOCF imputation used for Week 6 LOCF timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 6, ET

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189[41]	87[42]		
Units: subjects				
Baseline: Excellent (n=64, 29)	4	2		
Baseline: Good (n=64, 29)	10	6		
Baseline: Fair (n=64, 29)	25	14		
Baseline: Poor (n=64, 29)	19	3		
Baseline: Very poor (n=64, 29)	6	4		
Week 2: Excellent (n=60, 26)	5	1		
Week 2: Good (n=60, 26)	12	8		
Week 2: Fair (n=60, 26)	20	10		
Week 2: Poor (n=60, 26)	17	5		
Week 2: Very poor (n=60, 26)	6	2		
Week 6: Excellent (n=52, 21)	4	1		
Week 6: Good (n=52, 21)	16	8		
Week 6: Fair (n=52, 21)	17	11		
Week 6: Poor (n=52, 21)	12	1		
Week 6: Very poor (n=52, 21)	3	0		
ET: Excellent (n=8, 7)	0	0		
ET: Good (n=8, 7)	0	1		
ET: Fair (n=8, 7)	5	3		
ET: Poor (n=8, 7)	2	1		
ET: Very poor (n=8, 7)	1	2		
Week 6 [LOCF]: Excellent (n=68, 28)	4	1		
Week 6 [LOCF]: Good (n=68, 28)	18	9		
Week 6 [LOCF]: Fair (n=68, 28)	24	14		
Week 6 [LOCF]: Poor (n=68, 28)	16	2		
Week 6 [LOCF]: Very poor (n=68, 28)	6	2		

Notes:

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

[42] - 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 a serious and non-serious episode of the same event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Ziprasidone

Reporting group description:

Ziprasidone capsules administered twice daily (BID) with meals.

Reporting group title	Placebo

Reporting group description:

Placebo matching ziprasidone administration.

Serious adverse events	Ziprasidone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 193 (4.66%)	1 / 90 (1.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 193 (0.52%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 193 (0.52%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			

subjects affected / exposed	0 / 193 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 193 (0.52%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 193 (0.52%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	1 / 193 (0.52%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hostility			
subjects affected / exposed	1 / 193 (0.52%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impulsive behaviour			
subjects affected / exposed	1 / 193 (0.52%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 193 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	2 / 193 (1.04%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	2 / 193 (1.04%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	Ziprasidone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 193 (56.99%)	27 / 90 (30.00%)	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	11 / 193 (5.70%)	4 / 90 (4.44%)	
occurrences (all)	11	4	
Nervous system disorders			
Akathisia			
subjects affected / exposed	13 / 193 (6.74%)	3 / 90 (3.33%)	
occurrences (all)	15	3	
Dizziness			
subjects affected / exposed	18 / 193 (9.33%)	1 / 90 (1.11%)	
occurrences (all)	18	1	
Extrapyramidal disorder			
subjects affected / exposed	22 / 193 (11.40%)	1 / 90 (1.11%)	
occurrences (all)	23	1	
Headache			
subjects affected / exposed	15 / 193 (7.77%)	2 / 90 (2.22%)	
occurrences (all)	23	2	
Somnolence			
subjects affected / exposed	38 / 193 (19.69%)	6 / 90 (6.67%)	
occurrences (all)	50	6	
Tremor			
subjects affected / exposed	15 / 193 (7.77%)	1 / 90 (1.11%)	
occurrences (all)	19	1	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	17 / 193 (8.81%)	4 / 90 (4.44%)	
occurrences (all)	19	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 193 (9.84%)	2 / 90 (2.22%)	
occurrences (all)	19	2	
Vomiting			
subjects affected / exposed	12 / 193 (6.22%)	3 / 90 (3.33%)	
occurrences (all)	13	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	18 / 193 (9.33%)	13 / 90 (14.44%)	
occurrences (all)	30	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2006	1. A physical exam including body temperature was completed at week 6 or end of treatment. 2. Extensive electrocardiogram (ECG) monitoring was performed throughout the study, including triplicate ECGs at baseline and excluding Week 4. 3. Subjects who could not tolerate a dose of 120 mg/day were allowed to have a dose reduction and to continue study treatment at 100 mg/day or as low as 80 mg/day. Subjects weighing <45 kilograms (kg) were to be allowed a minimum dose of 40 mg/day. Subjects who could not tolerate the dose range of 80 to 160 mg/day for children above 45 kg or 40-80 mg/day for children <45 kg, discontinue and might be eligible to enter the extension trial. 4. 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. 5. Exposure In Utero definition was amended to include paternal exposure. 6. It was recommended that subjects should complete the CNS Vital Signs battery before any intrusive assessments such as blood draws, if at all possible. 7. Possibly Suicide-Related Adverse Events (PSRAEs) were included in adverse event reporting.
09 November 2007	1. Subjects who could not tolerate a dose of 120 mg/day were allowed to have a reduction and to continue study treatment at 100 mg/day or as low as 80 mg/day. Subjects weighing <45 kg were to be allowed a minimum dose of 40 mg/day. Subjects who could not tolerate the dose range of 80 to 160 mg/day for children above 45 kg or 40-80 mg/day for children <45 kg, should discontinue and might be eligible to enter the extension trial. This statement was added in section summary, Trial Design, Trial Treatments. 2. Concominant medication section amended to include lorazepam(up to 2 mg/day) or (if lorazepam is not available in the country diazepam up to 5 mg/day) for anxiety or agitation. 3. Protocol amended to provide subject status information on supplemental analysis addressing “pre-pause” and "post-pause” study enrollment, general clarifications and consistencies, and redesign of the study drug blister card to decrease the chance for dosing errors (usually overdosing beyond protocol specified dose). Subjects enrolled prior to the pause used the original blister card packaging, while subjects entering after the pause, used the improved blister card packaging. A sensitivity analysis was performed to assess the effect, if any, of this change.
24 January 2008	1. The scheduling of post-dose sampling paired to ECG measurement was changed from within 10 minutes of ECG to immediately after ECG.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

09 November 2007	During the conduct of the trial, the study was "paused" to improve the blister card packaging. The original card provided for mulitiple dose levels. The replacement card provided a single dose level for each specific card, while still preserving the flexible dosing capability. The blister card design was changed after approximately 1/3 of the subjects had enrolled. The study was interrupted (paused) for approximately 4 months pending re-packaging of the drug.	26 February 2008

Notes:

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: