Clinical trial results:
26-Week Open-Label Extension Study Evaluating The Safety And Tolerability Of Flexible Doses Of Oral Ziprasidone In Children And Adolescents With Bipolar I Disorder (Manic Or Mixed)

Summary

EudraCT number	2015-000607-15
Trial protocol	Outside EU/EEA
Global end of trial date	24 January 2008

Results information

Result version number	v2 (current)
This version publication date	26 March 2016
First version publication date	20 June 2015
Version creation reason	• Correction of full data set identified a missing information regarding “mutually exclusive arms” in the subject disposition section

Trial information

Trial identification

Sponsor protocol code	A1281133

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00265330
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., 001 800-718-1021, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.govCallCenter@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	10 July 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2008
Was the trial ended prematurely?	No

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 children and adolescents with Bipolar I Disorder - Single Manic Episode; Bipolar I Disorder – Most Recent Episode Manic, or Bipolar I Disorder – Most Recent Episode Mixed.

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	17 March 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	United States: 162
Worldwide total number of subjects	162
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)	41
Adolescents (12-17 years)	120
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The number of subjects entering this trial was determined by the number of subjects electing to continue treatment after completing or withdrawing from the preceding double-blind study (A1281132: NCT00257166; 2015-000606-20).

Pre-assignment

Screening details:

A total of 169 subjects from the parent study were assigned to the extension study and 162 continued on and received study treatment in the extension study.

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:

Dosing was flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability.

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

Dosage and administration details:

For subjects having a body weight of 45 kilograms (kg) or greater, the target dosage range was 40-80 milligrams (mg) twice per day (BID) (80-160 mg/day). For subjects having a body weight under 45 kg, the maximum permitted dose was 80 mg/day (40 mg BID).

Number of subjects in period 1	Ziprasidone
Started	162
Completed	67
Not completed	95
Consent withdrawn by subject	34
Withdrew Consent	1
Site Closed by Sponsor	1
Adverse Event	41
Subject Wanted to Start Psychotherapy	1
Discharged from Unit for Long Term Care	1
Began Taking Formulary Geodon	1

Protocol Violation	1
Lost to follow-up	8
Principal Investigators Request	1
Lack of efficacy	4
Family Scheduling Conflicts	1

Baseline characteristics

Reporting groups	
Reporting group title	Ziprasidone
Reporting group description:	
Dosing was flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability.	

Reporting group values	Ziprasidone	Total	
Number of subjects	162	162	
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	13.3		
standard deviation	± 2.1	-	
Gender, Male/Female Units: subjects			
Female	72	72	
Male	90	90	

End points

End points reporting groups

Reporting group title	Ziprasidone

Reporting group description:

Dosing was flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability.

Primary: Young Mania Rating Scale (YMRS) Total Score Change from Baseline

End point title	Young Mania Rating Scale (YMRS) Total Score Change from Baseline[1]

End point description:

YMRS: 11-item instrument with scales 0 (normal) to 4 (highest abnormal)for 7 items and 0 (normal) to 8 (highest abnormal) for 4 items. Total possible 0 - 60. Baseline is from parent study A1281132. The Safety Analysis Set includes all subjects who took at least one dose of study medication in this open-label extension study. (Row: n=number subjects with observation).

End point type	Primary

End point timeframe:

Baseline and 26 Weeks; 26 Weeks Last Observation Carried Forward (LOCF)

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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: score on scale				
arithmetic mean (standard deviation)				
Week 2 (n=153)	-3.8 (± 9)			
Week 6 (n=122)	-4 (± 9.1)			
Week 18 (n=76)	-6.3 (± 12.7)			
Week 26 (n=69)	-6.1 (± 11.6)			
Early Termination (n=59)	1.5 (± 11.3)			

observation).

End point type	Primary

End point timeframe:

Baseline and 26 Weeks; 26 Weeks LOCF

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: score on scale				
arithmetic mean (standard deviation)				
Week 1 (n=159)	-0.2 (± 0.9)			
Week 2 (n=150)	-0.5 (± 1.2)			
Week 6 (n=122)	-0.4 (± 1.1)			
Week 10 (n=99)	-0.7 (± 1.3)			
Week 14 (n=85)	-0.7 (± 1.2)			
Week 18 (n=76)	-0.7 (± 1.5)			
Week 22 (n=70)	-0.8 (± 1.3)			
Week 26 (n=69)	-1.1 (± 1.4)			
Early Termination (n=48)	0.4 (± 1.1)			
Week 26-LOCF (n=160)	-0.4 (± 1.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Lab Abnormalities

End point title	Incidence of Lab Abnormalities[3]

End point description:

Number of subjects with an abnormal lab value for those parameters with 5 percent (%) or greater incidence of abnormality. Total number of subjects with given laboratory test at given visit. Range: N=136-134, with the exception of Insulin (N=115).

End point type	Primary

End point timeframe:

Week 26

Notes:

[3] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	136			
Units: subjects				
number (not applicable)				
Bicarbonate (N=136)	44			
Urine blood/Hemoglobin (N=136)	34			

Urine ketones (N=136)	32			
Testosterone (N=134)	22			
Urine specific gravity (N=136)	13			
Urine red blood cells (N=136)	13			
Monocytes (N=134)	9			
Triglycerides (N=136)	10			
Urine white blood cells (N=136)	10			
Insulin (N=115)	8			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Low-Density Lipoprotein (LDL) Cholesterol and Fasting Cholesterol

End point title	Change in Low-Density Lipoprotein (LDL) Cholesterol and Fasting Cholesterol[4]

End point description:

Mean Change: lab value at observation minus lab value at baseline. The Safety Analysis Set includes all subjects who took at least one dose of study medication in this open-label extension study. (Row: n= total number of subjects with at least 1 observation of the given laboratory test).

End point type	Primary

End point timeframe:

Week 6, Week 26

Notes:

[4] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: milligram /deciliter (mg/dL)				
arithmetic mean (standard deviation)				
LDL cholesterol Week 6 (n=113)	-7.5 (± 19.7)			
LDL cholesterol Week 26 (n=59)	-8.9 (± 19.5)			
LDL cholesterol Early Termination (n=44)	-7.6 (± 20.1)			
Fasting cholesterol Week 6 (n=113)	-7.7 (± 21.8)			
Fasting cholesterol Week 26 (n=59)	-10.3 (± 22.7)			
Fasting cholesterol Early Termination (n=44)	-8.6 (± 24.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Hormones

End point title	Change in Hormones[5]

End point description:

Mean Change: lab value at observation minus lab value at baseline. The Safety Analysis Set includes all subjects who took at least one dose of study medication in this open-label extension study. (Row: n= total number of subjects with at least 1 observation of the given laboratory test).

End point type	Primary

End point timeframe:

Week 6, Week 26

Notes:

[5] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	131			
Units: nanogram/deciliter (ng/dL)				
arithmetic mean (standard deviation)				
Testosterone Week 6 (n=80)	0.9 (± 84.3)			
Testosterone Week 26 (n=38)	-23.4 (± 112.9)			
Testosterone Early Termination (n=32)	-0.4 (± 61.8)			
Prolactin Week 6 (n=110)	2.7 (± 13.2)			
Prolactin Week 26 (n=59)	1.9 (± 8.5)			
Prolactin Early Termination (n=40)	1 (± 11.6)			
Insulin-like growth factor Week 6 (n=95)	-19.9 (± 63.4)			
Insulin-like growth factor Week 26 (n=47)	-9.2 (± 68.1)			
Insulin-like growth factor Early Term (n=34)	-8.4 (± 66.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline in Supine Systolic Blood Pressure

End point title	Mean Change from Baseline in Supine Systolic Blood Pressure[6]

End point description:

Mean Change: vital sign value at observation minus vital sign value at baseline.

End point type	Primary

End point timeframe:

Week 1 through Week 26

Notes:

[6] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: millimeters of mercury (mm Hg)				
arithmetic mean (standard deviation)				
Week 1 (n=155)	0.4 (± 11.4)			
Week 2 (n=142)	1.1 (± 10.4)			
Week 6/pre-dose (n=115)	1.2 (± 9.5)			
Week 6/5-7 hours post dose (n=108)	1.2 (± 9.9)			
Week 10 (n=93)	1.4 (± 10.1)			
Week 14 (n=82)	-0.7 (± 10.1)			
Week 18 (n=74)	0.4 (± 11.7)			
Week 22 (n=69)	1.7 (± 10.5)			
Week 26 (n=68)	2.9 (± 11.4)			
Early Termination (n=75)	1.3 (± 11.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline in Supine Diastolic Blood Pressure

End point title	Mean Change from Baseline in Supine Diastolic Blood

End point description:

Mean Change: vital sign value at observation minus vital sign value at baseline.

End point type	Primary

End point timeframe:

Week 1 through Week 26

Notes:

[7] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: millimeters mercury (mm Hg)				
arithmetic mean (standard deviation)				
Week 1 (n=155)	-0.5 (± 8.8)			
Week 2 (n=142)	0.5 (± 8.7)			
Week 6/pre-dose (n=115)	0.6 (± 9.7)			
Week 6/5-7 hours post dose (n=108)	0.5 (± 8.8)			
Week 10 (n=93)	-0.4 (± 10.1)			
Week 14 (n=82)	-2.4 (± 8.3)			
Week 18 (n=74)	-0.6 (± 9.8)			
Week 22 (n=69)	-0.7 (± 9.4)			
Week 26 (n=68)	1.5 (± 10.4)			
Early Termination (n=75)	1.3 (± 8.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline in Supine Pulse Rates

End point title	Mean Change from Baseline in Supine Pulse Rates[8]

End point description:

Mean Change: vital sign value at observation minus vital sign value at baseline.

End point type	Primary

End point timeframe:

Week 1 through Week 26

Notes:

[8] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: beats per minute				
arithmetic mean (standard deviation)				
Week 1 (n=155)	1.4 (± 12.4)			
Week 2 (n=142)	2 (± 11.7)			
Week 6/pre-dose (n=115)	-1.8 (± 11.6)			
Week 6/5-7 hours post dose (n=108)	1 (± 12.3)			
Week 10 (n=93)	1.4 (± 11.8)			
Week 14 (n=82)	-3 (± 12.4)			
Week 18 (n=74)	-3.5 (± 12.2)			
Week 22 (n=69)	-2.1 (± 11.7)			
Week 26 (n=68)	-3 (± 11.2)			
Early Termination (n=75)	3.9 (± 13.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline in Standing Systolic Blood Pressure

End point title	Mean Change from Baseline in Standing Systolic Blood

End point description:

Mean Change: vital sign value at observation minus vital sign value at baseline.

End point type	Primary

End point timeframe:

Week 1 through Week 26

Notes:

[9] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: mm Hg				
arithmetic mean (standard deviation)				
Week 1 (n=154)	1.4 (± 10.5)			
Week 2 (n=141)	3.7 (± 11.7)			
Week 6/pre-dose (n=115)	1.6 (± 9.6)			
Week 6/5-7 hours post dose (n=108)	2 (± 9.5)			
Week 10 (n=93)	2.4 (± 11)			
Week 14 (n=82)	0.5 (± 11.3)			
Week 18 (n=74)	3.1 (± 10.5)			
Week 22 (n=70)	3.2 (± 10)			
Week 26 (n=68)	3.6 (± 10.9)			
Early Termination (n=75)	3 (± 11.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline in Standing Diastolic Blood Pressure

End point title	Mean Change from Baseline in Standing Diastolic Blood Pressure[10]

End point description:

Mean Change: vital sign value at observation minus vital sign value at baseline.

End point type	Primary

End point timeframe:

Week 1 through Week 26

Notes:

[10] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: mm Hg				
arithmetic mean (standard deviation)				
Week 1 (n=154)	0.7 (± 9.1)			
Week 2 (n=141)	2 (± 9.8)			
Week 6/pre-dose (n=115)	1.4 (± 9.8)			
Week 6/5-7 hours post dose (n=108)	1.2 (± 9.9)			
Week 10 (n=93)	1.6 (± 10.8)			

Week 14 (n=82)	-0.1 (± 9.8)			
Week 18 (n=74)	1.1 (± 8.8)			
Week 22 (n=70)	0.5 (± 8.5)			
Week 26 (n=68)	2.8 (± 8.3)			
Early Termination (n=75)	3.4 (± 10.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline in Standing Pulse Rates

End point title	Mean Change from Baseline in Standing Pulse Rates[11]

End point description:

Mean Change: vital sign value at observation minus vital sign value at baseline.

End point type	Primary

End point timeframe:

Week 1 through Week 26

Notes:

[11] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: beats per minute				
arithmetic mean (standard deviation)				
Week 1 (n=154)	3.5 (± 14)			
Week 2 (n=140)	2.9 (± 13.4)			
Week 6/pre-dose (n=115)	0.3 (± 13.1)			
Week 6/5-7 hours post dose (n=108)	3.8 (± 13.9)			
Week 10 (n=93)	2.6 (± 14.5)			
Week 14 (n=82)	0.5 (± 14.7)			
Week 18 (n=74)	-0.3 (± 12.5)			
Week 22 (n=70)	1.2 (± 14.7)			
Week 26 (n=68)	-0.9 (± 12.9)			
Early Termination (n=75)	4.8 (± 13.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline for Body Weight

End point title	Mean Change from Baseline for Body Weight[12]

End point description:

Mean change; body weight value at observation minus body weight value at baseline.

End point type	Primary

End point timeframe:

Week 6, Week 26

Notes:

[12] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: kilogram				
arithmetic mean (standard deviation)				
Week 6 (n=119)	1.3 (± 3)			
Week 26 (n=68)	3.9 (± 5.4)			
Early Termination (n=74)	1.4 (± 2.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline for Body Mass Index (BMI) Z-Score

End point title	Mean Change from Baseline for Body Mass Index (BMI) Z-Score[13]

End point description:

Mean change in body weight BMI -Z score calculated by subtracting median reference value of the population from observed value and dividing by standard deviation of reference population (kg/m squared). 0=no change.

End point type	Primary

End point timeframe:

Week 6, 26, early termination

Notes:

[13] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: score on scale				
arithmetic mean (standard deviation)				
Week 6 (n=119)	0 (± 0.3)			
Week 26 (n=68)	0.1 (± 0.5)			
Early Termination (n=74)	0 (± 0.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Body Mass Index (BMI) Z-score frequency

End point title	Body Mass Index (BMI) Z-score frequency[14]

End point description:

Change in body weight BMI -Z score calculated by subtracting median reference value of the population from observed value and dividing by standard deviation of reference population (kg/m squared). 0=no change.

End point type	Primary

End point timeframe:

Week 6

Notes:

[14] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: subjects				
Less than (<)-4	0			
Greater than or equal to (≥)-4 to <-3	0			
≥-3 to <-2	0			
≥-2 to <-1	0			
≥-1 to <0	53			
≥0 to <1	61			
≥1 to <2	1			
≥2 to <3	0			
≥3 to <4	0			
≥4	0			

Statistical analyses

No statistical analyses for this end point

Primary: Body Mass Index (BMI) Z-score frequency

End point title	Body Mass Index (BMI) Z-score frequency[15]

End point description:

Change in body weight BMI -Z score calculated by subtracting median reference value of the population from observed value and dividing by standard deviation of reference population (kg/m squared). 0=no change.

End point type	Primary

End point timeframe:

Week 26

Notes:

[15] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: subjects				
<-4	0			
≥-4 to <-3	0			
≥-3 to <-2	0			
≥-2 to <-1	1			
≥-1 to <0	27			
≥0 to <1	39			
≥1 to <2	0			
≥2 to <3	0			
≥3 to <4	0			
≥4	0			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change from Baseline for QTcF intervals

End point title	Mean Change from Baseline for QTcF intervals[16]

End point description:

QT intervals (observed in an electrocardiogram) corrected using Fridericia's formula (QTcF). Mean change: mean change of observation minus baseline. Baseline: last available observation in the parent double-blind study.

End point type	Primary

End point timeframe:

Baseline to Week 26 (end of study)

Notes:

[16] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: millisecond				
arithmetic mean (standard deviation)				
Week 1 (n=152)	4.8 (± 18.5)			
Week 2 (n=137)	3.5 (± 17.7)			
Week 6/pre-dose (n=111)	7.6 (± 17.7)			
Week 6/5-7 hours post dose (n=107)	7 (± 18.4)			
Week 10 (n=91)	4.3 (± 18.8)			
Week 14 (n=81)	6.2 (± 17.4)			
Week 18 (n=73)	7.4 (± 15.4)			
Week 22 (n=68)	8.1 (± 16.1)			
Week 26 (n=64)	7.1 (± 15.2)			
Early Termination (n=45)	2.7 (± 17)			

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of largest categorical increases in QTcF for males

End point title	Frequency of largest categorical increases in QTcF for males[17]

End point description:

QT intervals (observed in an electrocardiogram) corrected with Fridericia's Formula (QTcF). Number of subjects with corresponding categorical increase in QTcF.

End point type	Primary

End point timeframe:

Week 26 (end of study)

Notes:

[17] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	89			

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End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: subjects				
≥450 msec	3			
≥460 msec	0			
≥480 msec	0			
≥30 msec increase	10			
≥60 msec increase	2			

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of largest categorical increases in QTcF - all subjects

End point title	Frequency of largest categorical increases in QTcF - all

End point description:

QT intervals (observed in an electrocardiogram)corrected using Fridericia Formula (QTcF). Number of subjects with corresponding categorical increase in QTcF.

End point type	Primary

End point timeframe:

Week 26 (end of study)

Notes:

[19] - 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 endpoint.

End point values	Ziprasidone			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: subjects				
≥450 msec	3			
≥460 msec	0			
≥480 msec	0			
≥30 msec increase	38			
≥60 msec increase	2			

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:

Dosing was flexible, with dosing adjustments made at the discretion of the investigator to maintain optimal efficacy and tolerability. For subjects having a body weight of 45 kg or greater, the target dosage range was 40-80 mg BID (80-160 mg/day). For subjects having a body weight under 45 kg, the maximum permitted dose was 80 mg/day (40 mg BID).

Serious adverse events	Ziprasidone		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 162 (10.49%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Aggression			

subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bipolar disorder				
subjects affected / exposed	3 / 162 (1.85%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Conversion disorder				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucinations, mixed				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Delusion				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Negative thoughts				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Homicidal ideation				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Self-injurious behavior				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				

subjects affected / exposed	4 / 162 (2.47%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Oppositional defiant disorder			
subjects affected / exposed	2 / 162 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	1 / 162 (0.62%)		
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	123 / 162 (75.93%)		
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 162 (22.22%)		
occurrences (all)	53		
Dizziness			
subjects affected / exposed	12 / 162 (7.41%)		
occurrences (all)	14		
Sedation			
subjects affected / exposed	43 / 162 (26.54%)		
occurrences (all)	48		
Somnolence			
subjects affected / exposed	38 / 162 (23.46%)		
occurrences (all)	50		
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	11 / 162 (6.79%)		
occurrences (all)	11		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	15 / 162 (9.26%)		
occurrences (all)	16		
Vomiting			
subjects affected / exposed	12 / 162 (7.41%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	13 / 162 (8.02%)		
occurrences (all)	15		
Abdominal discomfort			
subjects affected / exposed	11 / 162 (6.79%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 162 (5.56%)		
occurrences (all)	10		
Nasal congestion			
subjects affected / exposed	12 / 162 (7.41%)		
occurrences (all)	13		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 162 (13.58%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2006	1- In assessments, fasting glucose and glycosylated hemoglobin (HbA1c) were added to clinical laboratory testing. 2- Daily dose of study medication for subjects with a body weight of ≥ 45 kg changed to 40-80 mg/day from 60-80 mg/day. 3- In trial design, minimum dose of the preceding double-blind study was decided for the dose reduction in subjects ≥45 kg, who cannot tolerate a dose of 80 mg/day. 4- In Trial Treatment, inhaled steroids were also added along with the topical steroids in the category of medicines for which use is allowed only if taken during preceding double-blind study with stable dose and clinical condition; and benzhexol and other anticholinergics were added in the category of medicines which are allowed without condition. 5- An additional category (≥460 msec) was used in QTcF reporting. 6- A change was made in the reporting priorities of AEs. A decision was made to report the treatment-emergent AEs as the main safety output, and "All AEs" were reported as additional tables. Combined data are the main analyses and consist of all subjects, regardless of the treatment assignment in the preceding double-blind study (A1281132).

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: