Clinical trial results:
Four Week, Double-Blind, Placebo Controlled Phase III Trial Evaluating The Efficacy, Safety And Pharmacokinetics Of Flexible Doses Of Oral Ziprasidone In Children And Adolescents With Bipolar I Disorder (Manic Or Mixed)

Due to a system error, the data reported in version v1 is not correct and has been removed from public view.

Summary

EudraCT number	2015-000606-20
Trial protocol	Outside EU/EEA
Global end of trial date	26 July 2007

Results information

Result version number	v2 (current)
This version publication date	25 March 2016
First version publication date	19 June 2015
Version creation reason	• Correction of full data set deletion of extra milestone

Trial information

Trial identification

Sponsor protocol code	A1281132

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00257166
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.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, 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	23 June 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To establish efficacy of oral ziprasidone (60-80 milligram [mg] twice a day [BID]) compared with placebo in the treatment of 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; as measured by the change from baseline to Week 4 in Young Mania Rating Scale (YMRS) total score.
•To evaluate the safety and tolerability of oral ziprasidone (60-80 mg BID) over 4 weeks in the treatment of children and adolescents with Bipolar I Disorder (manic or 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	13 January 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 237
Worldwide total number of subjects	237
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)	50
Adolescents (12-17 years)	186
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 36 sites in the United States. Study started on 13 January 2006 and completed on 26 July 2007. Total 238 subjects were randomized to treatment, of which 237 received treatment. One subject was randomized, but not treated. Study disposition is provided for the treated subjects.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ziprasidone

Arm description:

Ziprasidone capsule administered orally in 2 divided doses with a starting dose of ziprasidone 20 milligram per day (mg/day) as an evening dose on Day 1. This was followed by dose escalation as per investigator’s discretion.

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:

Ziprasidone capsule administered in 2 divided doses daily in the morning and evening with a starting dose of 20 mg/day as an evening dose on Day 1. This was followed by dose escalation of 20 mg/day every other day up to a target dose of 120 to 160 mg/day for subjects with greater than or equal to (>=) 45 kilogram (kg) weight and 60 to 80 mg/day for subjects with less than (<) 45 kg weight over 2 weeks, as per investigator’s discretion. Flexible dosing of ziprasidone capsule 80 to 160 mg/day for subjects with >=45 kg weight and ziprasidone capsule 40 to 80 mg/day for subjects with <45 kg weight orally in 2 divided doses daily in the morning and evening up to Week 4, as per investigator's discretion.

Arm title	Placebo

Arm description:

Placebo matched to ziprasidone capsule orally twice daily up to Week 4.

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 matched to ziprasidone daily up to Week 4.

Number of subjects in period 1	Ziprasidone	Placebo
Started	149	88
Completed	97	51
Not completed	52	37
Consent withdrawn by subject	9	2
Adverse Event	18	13
Unspecified	16	21
Laboratory abnormality	1	-
Lost to follow-up	8	1

Baseline characteristics

Reporting groups	
Reporting group title	Ziprasidone
Reporting group description:	
Ziprasidone capsule administered orally in 2 divided doses with a starting dose of ziprasidone 20 milligram per day (mg/day) as an evening dose on Day 1. This was followed by dose escalation as per investigator's discretion.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to ziprasidone capsule orally twice daily up to Week 4.	

Reporting group values	Ziprasidone	Placebo	Total
Number of subjects	149	88	237
Age, Customized Units: subjects			
10 to 13 years	74	35	109
14 to 17 years	74	53	127
>=18 years	1	0	1
Gender, Male/Female Units: subjects			
Female	65	41	106
Male	84	47	131

End points

End points reporting groups

Reporting group title	Ziprasidone
Reporting group description:	
Ziprasidone capsule administered orally in 2 divided doses with a starting dose of ziprasidone 20 milligram per day (mg/day) as an evening dose on Day 1. This was followed by dose escalation as per investigator's discretion.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to ziprasidone capsule orally twice daily up to Week 4.	

Primary: Change from Baseline in Young Mania Rating Scale (YMRS) Score at Week 4

End point title	Change from Baseline in Young Mania Rating Scale (YMRS) Score at Week 4
End point description:	
YMRS: an 11-item scale that measured the severity of manic episodes. Four items were rated on a scale from 0 (symptom absent) to 8 (symptom extremely severe). The remaining items were rated on a scale from 0 (symptom absent) to 4 (symptom extremely severe). YMRS total score ranged from 0 to 60, higher score indicated higher severity of mania. Intent-to-treat (ITT): all randomized subjects who had baseline measurements, took at least (>=) 1 dose of study medication (ziprasidone or placebo) and had >=1 post-baseline visit. Here, 'n' signifies those subjects who were available for this measure at given time points for each group.	
End point type	Primary
End point timeframe:	
Baseline, Week 4	

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	86		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=143,86)	26.2 (± 6.6)	27 (± 6.6)		
Change at Week 4 (n=97,51)	-13.8 (± 7.8)	-9.9 (± 7.7)		

Statistical analyses

Statistical analysis title	Change at Week 4
Statistical analysis description:	
Mixed effects repeated measures Analysis of Covariance (ANCOVA) model with center and subject within center as random effects, treatment, visit and visit by treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.	
Comparison groups	Placebo v Ziprasidone

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-5.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.12
upper limit	-2.31
Variability estimate	Standard error of the mean
Dispersion value	1.48

Secondary: Change from Baseline in Young Mania Rating Scale (YMRS) Score at Week 1, 2 and 3

End point title	Change from Baseline in Young Mania Rating Scale (YMRS) Score at Week 1, 2 and 3

End point description:

YMRS: an 11-item scale that measured the severity of manic episodes. Four items were rated on a scale from 0 (symptom absent) to 8 (symptom extremely severe). The remaining items were rated on a scale from 0 (symptom absent) to 4 (symptom extremely severe). YMRS total score ranged from 0 to 60, higher score indicated higher severity of mania. ITT population. 'n' signifies those subjects who were available for this measure at given time points for each group respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131[1]	85[2]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Week 1 (n=131,85)	-9.3 (± 7.5)	-6.3 (± 7.1)		
Change at Week 2 (n=120,81)	-11.5 (± 8.7)	-8.1 (± 7.9)		
Change at Week 3 (n=108,65)	-13 (± 8.1)	-9 (± 7.3)		

Notes:

[1] - Subjects who were available for this measure.

[2] - Subjects who were available for this measure.

Statistical analyses

Statistical analysis title	Change at Week 1

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.2545
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1045
upper limit	-1.4046
Variability estimate	Standard error of the mean
Dispersion value	0.9422

Statistical analysis title	Change at Week 2

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0117
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.5857
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3705
upper limit	-0.8009
Variability estimate	Standard error of the mean
Dispersion value	1.4184

Statistical analysis title	Change at Week 3

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.

Comparison groups	Ziprasidone v Placebo

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.8665
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2345
upper limit	-1.4985
Variability estimate	Standard error of the mean
Dispersion value	1.7154

Secondary: Change from Baseline in Clinical Global Impression - Severity (CGI-S) Score at Week 1, 2, 3 and 4

End point title	Change from Baseline in Clinical Global Impression - Severity (CGI-S) Score at Week 1, 2, 3 and 4

End point description:

CGI-S: 7-point clinician rated scale to assess severity of subject's current illness state; range: 1 (normal - not ill at all) to 7 (among the most extremely ill). ITT population. Here, 'n' signifies those subjects who were available for this measure at given time points for each group respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	86		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=143,86)	4.5 (± 0.7)	4.5 (± 0.7)		
Change at Week 1 (n=131,85)	-0.9 (± 0.8)	-0.5 (± 0.9)		
Change at Week 2 (n=120,82)	-1.1 (± 1)	-0.6 (± 0.9)		
Change at Week 3 (n=108,65)	-1.3 (± 1)	-0.7 (± 1)		
Change at Week 4 (n=96,51)	-1.4 (± 1.1)	-0.9 (± 0.9)		

Statistical analyses

Statistical analysis title	Change at Week 1

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3754
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5696
upper limit	-0.1812
Variability estimate	Standard error of the mean
Dispersion value	0.0989

Statistical analysis title	Change at Week 2

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.5596
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8256
upper limit	-0.2936
Variability estimate	Standard error of the mean
Dispersion value	0.1355

Statistical analysis title	Change at Week 3

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.

Comparison groups	Ziprasidone v Placebo

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.6798
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0024
upper limit	-0.3572
Variability estimate	Standard error of the mean
Dispersion value	0.1643

Statistical analysis title	Change at Week 4

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate was used for the analysis.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.6884
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0342
upper limit	-0.3426
Variability estimate	Standard error of the mean
Dispersion value	0.1761

Secondary: Clinical Global Impression - Improvement (CGI-I) Score

End point title	Clinical Global Impression - Improvement (CGI-I) Score

End point description:

CGI-I: 7-point clinician rated scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved), 2 (much improved), or 3 (minimally improved) on the scale. ITT population. ‘n’ signifies those subjects who were available for this measure at given time points for each group respectively.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4

End point values	Ziprasidone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132[3]	85[4]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=132,85)	2.8 (± 0.9)	3.4 (± 0.9)		
Week 2 (n=120,82)	2.5 (± 1.1)	3.2 (± 1.1)		
Week 3 (n=108,65)	2.4 (± 1)	3.1 (± 1.3)		
Week 4 (n=96,51)	2.3 (± 1)	2.8 (± 1.1)		

Notes:

[3] - Subjects who were evaluable for this measure.

[4] - Subjects who were evaluable for this measure.

Statistical analyses

Statistical analysis title	Change at Week 4

Statistical analysis description:

Mixed effects repeated measures ANCOVA model with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects was used for the analysis.

Comparison groups	Ziprasidone v Placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.21

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 6 days after last dose of study drug

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as nonserious in another, or 1 subject may have experienced both serious, nonserious event during study. EU BR specific AE tables were generated separately as per EU format using latest coding.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Ziprasidone

Reporting group description:

Ziprasidone capsule administered orally in 2 divided doses daily in the morning and evening with a starting dose of ziprasidone 20 mg/day as an evening dose on Day 1. This was followed by dose escalation of 20 mg/day every other day up to a target dose of ziprasidone 120 to 160 mg/day for subjects with >=45 kg weight and ziprasidone 60 to 80 mg/day for subjects with <45 kg weight over 2 weeks, as per investigator's discretion. Flexible dosing of ziprasidone capsule 80 to 160 mg/day for subjects with >=45 kg weight and ziprasidone capsule 40 to 80 mg/day for subjects with <45 kg weight orally in 2 divided doses daily in the morning and evening up to Week 4, as per investigator's discretion.

Reporting group title	Placebo

Reporting group description:

Placebo matched to ziprasidone capsule orally twice daily up to Week 4.

Serious adverse events	Ziprasidone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 149 (4.03%)	5 / 88 (5.68%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 149 (0.67%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 149 (0.67%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Dystonia			
subjects affected / exposed	1 / 149 (0.67%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 149 (0.67%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 149 (0.67%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	1 / 149 (0.67%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 149 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersexuality			
subjects affected / exposed	1 / 149 (0.67%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self-injurious ideation			
subjects affected / exposed	1 / 149 (0.67%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bipolar I disorder			
subjects affected / exposed	0 / 149 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	128 / 149 (85.91%)	42 / 88 (47.73%)	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	6 / 149 (4.03%)	5 / 88 (5.68%)	
occurrences (all)	6	5	
Nervous system disorders			
Akathisia			
subjects affected / exposed	8 / 149 (5.37%)	1 / 88 (1.14%)	
occurrences (all)	9	1	
Dizziness			
subjects affected / exposed	19 / 149 (12.75%)	2 / 88 (2.27%)	
occurrences (all)	23	2	
Tremor			
subjects affected / exposed	9 / 149 (6.04%)	0 / 88 (0.00%)	
occurrences (all)	11	0	
Somnolence			
subjects affected / exposed	37 / 149 (24.83%)	7 / 88 (7.95%)	
occurrences (all)	43	7	
Headache			
subjects affected / exposed	33 / 149 (22.15%)	19 / 88 (21.59%)	
occurrences (all)	40	22	
Sedation			

subjects affected / exposed	49 / 149 (32.89%)	5 / 88 (5.68%)	
occurrences (all)	55	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	23 / 149 (15.44%)	6 / 88 (6.82%)	
occurrences (all)	23	6	
Eye disorders			
Vision blurred			
subjects affected / exposed	9 / 149 (6.04%)	1 / 88 (1.14%)	
occurrences (all)	9	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	21 / 149 (14.09%)	6 / 88 (6.82%)	
occurrences (all)	24	6	
Abdominal pain upper			
subjects affected / exposed	8 / 149 (5.37%)	3 / 88 (3.41%)	
occurrences (all)	8	3	
Vomiting			
subjects affected / exposed	12 / 149 (8.05%)	1 / 88 (1.14%)	
occurrences (all)	15	1	
Psychiatric disorders			
Restlessness			
subjects affected / exposed	8 / 149 (5.37%)	1 / 88 (1.14%)	
occurrences (all)	8	1	
Insomnia			
subjects affected / exposed	14 / 149 (9.40%)	3 / 88 (3.41%)	
occurrences (all)	18	3	
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	8 / 149 (5.37%)	0 / 88 (0.00%)	
occurrences (all)	8	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	8 / 149 (5.37%)	0 / 88 (0.00%)	
occurrences (all)	8	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2006	1- Change in Trial Treatment to indicate that dosing adjustments could be made between 40-80 mg/day for subjects weighing under 45 kg.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported