Clinical trial results:
Evaluation of Growth, Sexual Maturation, and Prolactin-Related Adverse Events in the Pediatric Population Exposed to Atypical Antipsychotic Drugs

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

Summary

EudraCT number	2009-012003-26
Trial protocol	NL BE GR
Global end of trial date	08 August 2011

Results information

Result version number	v2 (current)
This version publication date	21 July 2016
First version publication date	08 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	RIS-NAP-4022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01050582
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International, NV
Sponsor organisation address	Turnhoutseweg 30, 2340, Beerse, Belgium,
Public contact	Clinical Registry Group, Janssen-Cilag International, NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International, NV, ClinicalTrialsEU@its.jnj.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	08 August 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2011
Global end of trial reached?	Yes
Global end of trial date	08 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of risperidone as compared with other atypical antipsychotic medications on child growth and sexual maturation and to evaluate the risk of other prolactin-related adverse events associated with risperidone as compared with other atypical antipsychotic medications in a pediatric population

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2009
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	Belgium: 3
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	United States: 99
Worldwide total number of subjects	184
EEA total number of subjects	85

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)	75
Adolescents (12-17 years)	109
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 244 subjects were assessed for eligibility of whom 230 signed informed consent. Of the 230, 43 were found not to meet inclusion or exclusion criteria, 2 withdrew consent, and 1 was not kept in the study due to a site decision. A total of 184 subjects were included in the analysis.

Pre-assignment

Screening details:

A total of 350 paediatric subjects, (aged 8-16 years) with diagnosis of schizophrenia, bipolar mania, autistic disorder, or conduct and other DBDs, having medical records for atleast 1 year prior to start of qualifying antipsychotic medication from 2 exposure groups of 175 subjects each: risperidone group and other atypical antipsychotic group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Other Atypical Antipsychotics

Arm description:

Subjects with at least 6 months of exposure to an atypical antipsychotic other than risperidone within 24 months prior to enrollment. Subjects were to have no exposure to risperidone within the past 24 months, and total lifetime exposure to risperidone must have been less than or equal to 30 days total over their lifetime.

Arm type	Active comparator
Investigational medicinal product name	Other atypical antipsychotic drugs
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per local prescribing practices

Arm title	Risperidone

Arm description:

Subjects with at least 6 months of exposure to risperidone within 24 months prior to enrollment. Exposure to other atypical antipsychotics within 24 months was allowed.

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

Dosage and administration details:

As per local prescribing practices

Number of subjects in period 1	Other Atypical Antipsychotics	Risperidone
Started	51	133
Completed	51	133

Baseline characteristics

Reporting groups	
Reporting group title	Other Atypical Antipsychotics
Reporting group description:	
Subjects with at least 6 months of exposure to an atypical antipsychotic other than risperidone within 24 months prior to enrollment. Subjects were to have no exposure to risperidone within the past 24 months, and total lifetime exposure to risperidone must have been less than or equal to 30 days total over their lifetime.	
Reporting group title	Risperidone
Reporting group description:	
Subjects with at least 6 months of exposure to risperidone within 24 months prior to enrollment. Exposure to other atypical antipsychotics within 24 months was allowed.	

Reporting group values	Other Atypical Antipsychotics	Risperidone	Total
Number of subjects	51	133	184
Title for AgeCategorical Units: subjects			
Children (2-11 years)	20	55	75
Adolescents (12-17 years)	31	78	109
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	12.2	12.1	
standard deviation	± 2.48	± 2.53	-
Title for Gender Units: subjects			
Female	18	16	34
Male	33	117	150

End points

End points reporting groups

Reporting group title	Other Atypical Antipsychotics

Reporting group description:

Subjects with at least 6 months of exposure to an atypical antipsychotic other than risperidone within 24 months prior to enrollment. Subjects were to have no exposure to risperidone within the past 24 months, and total lifetime exposure to risperidone must have been less than or equal to 30 days total over their lifetime.

Reporting group title	Risperidone

Reporting group description:

Subjects with at least 6 months of exposure to risperidone within 24 months prior to enrollment. Exposure to other atypical antipsychotics within 24 months was allowed.

Primary: Height (cm) Z-score at Study Visit

End point title	Height (cm) Z-score at Study Visit

End point description:

Height (cm) measured at the study visit was converted to a Z-score based on the US Center for Disease Control 2000 growth charts for US subjects and European growth charts for ex-US subjects. A z-score indicates how many standard deviations a subject is away from the expected height for the subject's age and gender.

End point type	Primary

End point timeframe:

One single study visit, approximately one week after informed consent has been obtained

End point values	Other Atypical Antipsychotics	Risperidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[1]	132[2]		
Units: z-score				
arithmetic mean (standard deviation)	0.09 (± 1.079)	0.4 (± 1.189)		

Notes:

[1] - All subjects with a height assessment available at the study visit.

[2] - All subjects with a height assessment available at the study visit.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Risperidone v Other Atypical Antipsychotics
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	0.447

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.674
Variability estimate	Standard error of the mean
Dispersion value	0.116

Secondary: Age (Years) at Current Tanner Stage

End point title	Age (Years) at Current Tanner Stage

End point description:

Tanner stage is an evaluation of pubertal development with values ranging from 1 (pre-pubertal) to 5 (adult). A standardized, validated tool containing standardized pictures and written descriptions of the stages of pubic hair development, breast development for girls, and genital development for boys was used by physicians to make their assessment.

End point type	Secondary

End point timeframe:

One single study visit, approximately one week after informed consent has been obtained

End point values	Other Atypical Antipsychotics	Risperidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[3]	124[4]		
Units: Years				
arithmetic mean (standard deviation)				
Tanner Stage 1	10.34 (± 1.784)	10.22 (± 1.309)		
Tanner Stage 2	11.23 (± 1.729)	11.25 (± 1.68)		
Tanner Stage 3	12.15 (± 1.206)	13.07 (± 2.181)		
Tanner Stage 4	15 (± 1.458)	14.93 (± 1.265)		
Tanner Stage 5	14.98 (± 1.82)	15.1 (± 0.688)		

Notes:

[3] - subjects with a physician assessed Tanner stage value.

[4] - subjects with a physician assessed Tanner stage value.

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Risperidone v Other Atypical Antipsychotics
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.378
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	-0.221

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.711
upper limit	0.269
Variability estimate	Standard error of the mean
Dispersion value	0.25

Secondary: Number of Subjects With Retrospectively Reported Potentially Prolactin-Related Adverse Events

End point title	Number of Subjects With Retrospectively Reported Potentially Prolactin-Related Adverse Events

End point description:

Previous potentially prolactin-related adverse events, including hyperprolactinemia, were reviewed and abstracted from subjects' medical records. Potentially prolactin-related adverse events include breast symptoms, menstrual disorders, hyperprolactinemia, and prolactinoma.

End point type	Secondary

End point timeframe:

Retrospectively during the time of exposure for up to 2 years prior to the study visit

End point values	Other Atypical Antipsychotics	Risperidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	133		
Units: Subjects				
number (not applicable)	3	7		

Statistical analyses

Statistical analysis title	Statistical analysis 3
Comparison groups	Risperidone v Other Atypical Antipsychotics
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.999
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.865
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.189
upper limit	3.963

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time of signing informed consent to the study visit

Adverse event reporting additional description:

Adverse events include retrospectively reported prolactin-related events and prospectively reported events from the time of signing informed consent to the study visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Other Atypical Antipsychotics

Reporting group description:

Subjects with at least 6 months of exposure to an atypical antipsychotic other than risperidone within 24 months prior to enrollment. Subjects were to have no exposure to risperidone within the past 24 months, and total lifetime exposure to risperidone must have been less than or equal to 30 days total over their lifetime.

Reporting group title	Risperidone

Reporting group description:

Subjects with at least 6 months of exposure to risperidone within 24 months prior to enrollment. Exposure to other atypical antipsychotics within 24 months was allowed.

Serious adverse events	Other Atypical Antipsychotics	Risperidone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	0 / 133 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Other Atypical Antipsychotics	Risperidone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)	14 / 133 (10.53%)	
Investigations			
Weight Increased			
subjects affected / exposed	0 / 51 (0.00%)	2 / 133 (1.50%)	
occurrences (all)	0	1	
Blood Prolactin Increased			

subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Sedation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Drug Ineffective			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 51 (1.96%)	1 / 133 (0.75%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast Enlargement			
subjects affected / exposed	1 / 51 (1.96%)	0 / 133 (0.00%)	
occurrences (all)	0	0	
Amenorrhoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 133 (0.00%)	
occurrences (all)	0	0	
Galactorrhoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 133 (0.00%)	
occurrences (all)	0	0	
Breast Pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 133 (0.00%)	
occurrences (all)	1	0	

Gynaecomastia			
subjects affected / exposed	0 / 51 (0.00%)	4 / 133 (3.01%)	
occurrences (all)	0	1	
Scrotal Pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	0	
Psychiatric disorders			
Middle Insomnia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Endocrine disorders			
Early Menarche			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	0	
Infections and infestations			
Eye Infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 133 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 133 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 51 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2009	The overall reason for the amendment was to allow data collection from medical records as well as automated databases, and to exclude subjects with specific developmental disorders known to be associated with growth or sexual maturation delays. In addition,this amendment allowed for the previous brief use of risperidone and concomitant use of serotonin reuptake inhibitors (SSRIs), and changed the primary efficacy analysis endpoint to compare Z-scores for height, age at current Tanner stage (rather than age at entry into current Tanner stage) and prolactin-related AEs, between risperidone-exposed and OAA-exposed groups.
27 November 2009	The main reason for the amendment was to clarify AE reporting procedures to ensure that the investigator collected all AEs reported after signing of the Informed Consent Form (ICF), that the investigator collected Serious Adverse Drug Reactions (SADRs) related to any J&J compound, which occurred prior to signing of the ICF, and to clarify the sponsor's responsibilities to report SAEs appropriately to the regulatory authorities. In addition, this amendment provided clarification on the use of concomitant medications with potential growth and prolactin effects, and provided clarification regarding subject selection, including a new diagrammatic flow chart.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 August 2011	The study was terminated due to recruitment difficulties, which meant that the enrollment target could not be met.	-

Notes:

Limitations and caveats

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

Study was terminated early due to recruitment challenges in OAA(comparator) group such that the enrollment target was not achievable. In addition there were more subjects in risperidone treatment group (n=133) than in the OAA group (n=51).

Notes: