Clinical trial results:
Risperidone in the Treatment of Children and Adolescents With Autistic Disorder: A Double-Blind, Placebo-Controlled Study of Efficacy and Safety, Followed by an Open-Label Extension Study of Safety

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

Summary

EudraCT number	2015-001220-31
Trial protocol	Outside EU/EEA
Global end of trial date	09 March 2010

Results information

Result version number	v2 (current)
This version publication date	15 July 2016
First version publication date	06 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	RISAUT4002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00576732
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry Group-JB BV, Clinical Registry Group-JB BV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group-JB BV, Clinical Registry Group-JB BV, 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	09 March 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effectiveness (change in level of irritability and related behaviors) and safety and tolerability of the administration of 2 different fixed dose levels of risperidone (an atypical antipsychotic drug) compared with placebo in children or adolescents who have autism, and to evaluate the safety and tolerability of the drug for additional 26 weeks after the initial 6-week study period.

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. Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 November 2007
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: 96
Worldwide total number of subjects	96
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)	74
Adolescents (12-17 years)	22
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 96 subjects were enrolled in the study.

Period 1

Period 1 title	Overall study
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	Placebo

Arm description:

Subjects weighing 20 kg to <45 kg were started with 0.5 ml of placebo solution on Day 1 and were titrated up to 1.25 ml on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 ml of placebo solution on Day 1 and were titrated up to 1.75 ml on Day 4.

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

Dosage and administration details:

Subjects weighing 20 kg to <45 kg were started with 0.5 ml of placebo solution on Day 1 and were titrated up to 1.25 ml on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 ml of placebo solution on Day 1 and were titrated up to 1.75 ml on Day 4.

Arm title	Risperidone Low Dose

Arm description:

Subjects weighing 20 kg to <45 kg were started with 0.05 mg on Day 1 and were titrated up to 0.125 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.075 mg on Day 1 and were titrated up to 0.175 mg on Day 4.

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

Dosage and administration details:

Subjects weighing 20 kg to <45 kg were started with 0.05 mg on Day 1 and were titrated up to 0.125 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.075 mg on Day 1 and were titrated up to 0.175 mg on Day 4.

Arm title	Risperidone High Dose

Arm description:

Subjects weighing 20 kg to <45 kg were started with 0.5 mg on Day 1 and were titrated up to 1.25 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 mg on Day 1 and were titrated up to 1.75 mg on Day 4.

Arm type	Experimental

Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

ubjects weighing 20 kg to <45 kg were started with 0.5 mg on Day 1 and were titrated up to 1.25 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 mg on Day 1 and were titrated up to 1.75 mg on Day 4.

Number of subjects in period 1	Placebo	Risperidone Low Dose	Risperidone High Dose
Started	35	30	31
Completed	27	25	25
Not completed	8	5	6
Consent withdrawn by subject	1	1	3
Adverse event, non-fatal	-	-	1
Other	-	2	1
Lost to follow-up	-	1	1
Protocol deviation	1	-	-
Lack of efficacy	6	1	-

Period 2

Period 2 title	Open Label
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	OL Risperidone

Arm description:

Subjects who completed the double-blind phase, or discontinued after at least 3 weeks for reasons other than tolerability and, in the investigator's judgment needed risperidone treatment were eligible to enter the open-label phase. Risperidone was given as oral solution (1 mg/mL) for the first 3 days and as tablets from Day 4 on. On Day 1, subjects with a baseline weight of 20 kg to <45 kg were started on risperidone 0.125 mg/day, and subjects with a baseline weight of 45 kg or more were started on risperidone 0.175 mg/day. On Day 4, the dose was increased to 0.25 mg for all subjects. After Day 14, dose increments of 0.25 mg or 0.5 mg (upon the judgment of the investigator) were allowed every 2 weeks. The maximum allowed dose was 1.25 mg for subjects with baseline weight of 20 kg to <45 kg and 1.75 mg for subjects with a baseline weight of 45 kg or more.

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

Dosage and administration details:

Subjects who completed the double-blind phase, or discontinued after at least 3 weeks for reasons other than tolerability and, in the investigator's judgment needed risperidone treatment were eligible to enter the open-label phase. Risperidone was given as oral solution (1 mg/mL) for the first 3 days and as tablets from Day 4 on. On Day 1, subjects with a baseline weight of 20 kg to <45 kg were started on risperidone 0.125 mg/day, and subjects with a baseline weight of 45 kg or more were started on risperidone 0.175 mg/day. On Day 4, the dose was increased to 0.25 mg for all subjects. After Day 14, dose increments of 0.25 mg or 0.5 mg (upon the judgment of the investigator) were allowed every 2 weeks. The maximum allowed dose was 1.25 mg for subjects with baseline weight of 20 kg to <45 kg and 1.75 mg for subjects with a baseline weight of 45 kg or more.

Number of subjects in period 2	OL Risperidone
Started	79
Completed	56
Not completed	23
Consent withdrawn by subject	2
Adverse event, non-fatal	5
Other	2
Lost to follow-up	4
Protocol deviation	3
Lack of efficacy	7

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects weighing 20 kg to <45 kg were started with 0.5 ml of placebo solution on Day 1 and were titrated up to 1.25 ml on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 ml of placebo solution on Day 1 and were titrated up to 1.75 ml on Day 4.	
Reporting group title	Risperidone Low Dose
Reporting group description:	
Subjects weighing 20 kg to <45 kg were started with 0.05 mg on Day 1 and were titrated up to 0.125 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.075 mg on Day 1 and were titrated up to 0.175 mg on Day 4.	
Reporting group title	Risperidone High Dose
Reporting group description:	
Subjects weighing 20 kg to <45 kg were started with 0.5 mg on Day 1 and were titrated up to 1.25 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 mg on Day 1 and were titrated up to 1.75 mg on Day 4.	

Reporting group values	Placebo	Risperidone Low Dose	Risperidone High Dose
Number of subjects	35	30	31
Title for AgeCategorical Units: subjects			
Children (2-11 years)	30	20	24
Adolescents (12-17 years)	5	10	7
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	8.6	10.2	9.3
standard deviation	± 2.57	± 3.42	± 3.11
Title for Gender Units: subjects			
Female	4	5	3
Male	31	25	28

Reporting group values	Total		
Number of subjects	96		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	74		
Adolescents (12-17 years)	22		
Adults (18-64 years)	0		
From 65 to 84 years	0		
85 years and over	0		
Title for AgeContinuous Units: years			
arithmetic mean			
standard deviation	-		

Title for Gender Units: subjects			
Female	12		
Male	84		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects weighing 20 kg to <45 kg were started with 0.5 ml of placebo solution on Day 1 and were titrated up to 1.25 ml on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 ml of placebo solution on Day 1 and were titrated up to 1.75 ml on Day 4.

Reporting group title	Risperidone Low Dose

Reporting group description:

Subjects weighing 20 kg to <45 kg were started with 0.05 mg on Day 1 and were titrated up to 0.125 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.075 mg on Day 1 and were titrated up to 0.175 mg on Day 4.

Reporting group title	Risperidone High Dose

Reporting group description:

Subjects weighing 20 kg to <45 kg were started with 0.5 mg on Day 1 and were titrated up to 1.25 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 mg on Day 1 and were titrated up to 1.75 mg on Day 4.

Reporting group title	OL Risperidone

Reporting group description:

Subjects who completed the double-blind phase, or discontinued after at least 3 weeks for reasons other than tolerability and, in the investigator's judgment needed risperidone treatment were eligible to enter the open-label phase. Risperidone was given as oral solution (1 mg/mL) for the first 3 days and as tablets from Day 4 on. On Day 1, subjects with a baseline weight of 20 kg to <45 kg were started on risperidone 0.125 mg/day, and subjects with a baseline weight of 45 kg or more were started on risperidone 0.175 mg/day. On Day 4, the dose was increased to 0.25 mg for all subjects. After Day 14, dose increments of 0.25 mg or 0.5 mg (upon the judgment of the investigator) were allowed every 2 weeks. The maximum allowed dose was 1.25 mg for subjects with baseline weight of 20 kg to <45 kg and 1.75 mg for subjects with a baseline weight of 45 kg or more.

Subject analysis set title	Placebo/RIS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Open-label Period. Subjects in the double-blind placebo group who continued into open-label risperidone period. Risperidone oral solution 0.125 mg (if <45 kg) or 0.175 mg (if >=45 kg) for 3 days, 0.25 mg tablet on Day 4, flexible dose in 0.25 mg or 0.5 mg increments every 2 weeks, as clinically indicated, to a maximum dose of 1.25 mg (if <45 kg) or 1.75 mg (if >=45 kg).

Subject analysis set title	Ris Low Dose/RIS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Open-label Period. Subjects in the double-blind risperidone low dose group who continued into open-label risperidone period. Risperidone oral solution 0.125 mg (if <45 kg) or 0.175 mg (if >=45 kg) for 3 days, 0.25 mg tablet on Day 4, flexible dose in 0.25 mg or 0.5 mg increments every 2 weeks, as clinically indicated, to a maximum dose of 1.25 mg (if <45 kg) or 1.75 mg (if >=45 kg).

Subject analysis set title	Ris High Dose/RIS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Open-label Period. Subjects in the double-blind risperidone high dose group who continued into open-label risperidone period. Risperidone oral solution 0.125 mg (if <45 kg) or 0.175 mg (if >=45 kg) for 3 days, 0.25 mg tablet on Day 4, flexible dose in 0.25 mg or 0.5 mg increments every 2 weeks, as clinically indicated, to a maximum dose of 1.25 mg (if <45 kg) or 1.75 mg (if >=45 kg).

Primary: Change in Aberrant Behavior Checklist Irritability (ABC-I) Subscale

End point title	Change in Aberrant Behavior Checklist Irritability (ABC-I) Subscale

End point description:

Measure of irritability symptoms of autism. Score range 0 to 45 (lower score = lesser severity). All randomized subjects with at least one dose of study medication and both baseline and at least one postbaseline value. For subjects who discontinued, Week 6 data is imputed using the subject's last

nonmissing, postbaseline value in the double-blind period (Last Observation Carried Forward [LOCF]).

End point type	Primary
End point timeframe: Baseline and 6 weeks	

End point values	Placebo	Risperidone Low Dose	Risperidone High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	29	29	
Units: participants				
arithmetic mean (standard deviation)	-3.5 (± 10.67)	-7.4 (± 8.12)	-12.4 (± 6.52)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Risperidone High Dose
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.19
upper limit	-3.52
Variability estimate	Standard error of the mean
Dispersion value	2.18

Notes:

[1] - A step-down testing procedure was employed with the risperidone high dose versus placebo comparison tested first. If this comparison was significant the risperidone low dose versus placebo comparison would be performed. A clinically relevant difference in the change from baseline on the ABC Irritability subscale was assumed to be 6 with a standard deviation of 8. To achieve 80% power with Type I error rate of 5%, 93 subjects were required.

[2] - Type I error is preserved by the step down procedure, no multiple comparison adjustment is needed. A priori threshold for statistical significance was 0.05.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Risperidone Low Dose
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.164 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.36
upper limit	1.27
Variability estimate	Standard error of the mean
Dispersion value	2.17

Notes:

[3] - Type I error is preserved by the step down procedure, no multiple comparison adjustment is needed. A priori threshold for statistical significance was 0.05.

Secondary: Number of Participants Who Had at Least 25% Improvement in ABC-I

End point title	Number of Participants Who Had at Least 25% Improvement in ABC-I

End point description:

ABC-I is a measure of irritability symptoms of autism with score range 0 to 45 (lower score = lesser severity). All randomized subjects with at least one dose of study medication and both baseline and at least one postbaseline value. For subjects who discontinued, Week 6 data is imputed using the subject's last nonmissing, postbaseline value in the double-blind period (Last Observation Carried Forward [LOCF]).

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Risperidone Low Dose	Risperidone High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	29	29	
Units: participants	14	15	24	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Risperidone High Dose
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Cochran-Mantel-Haenszel test controlling for center (after pooling small centers) and baseline weight stratification.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Risperidone Low Dose

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.817 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - Cochran-Mantel-Haenszel test controlling for center (after pooling small centers) and baseline weight stratification.

Secondary: Change in Clinical Global Impression Severity (CGI-S)

End point title	Change in Clinical Global Impression Severity (CGI-S)

End point description:

Investigator evaluation of severity of illness and functional impairment on a 7-point scale (1="not ill", 2="very mild", 3="mild", 4="moderate", 5="marked", 6="severe", 7="extremely severe"). All randomized subjects with at least one dose of study medication and both baseline and at least one postbaseline value. For subjects who discontinued, Week 6 data is imputed using the subject's last nonmissing, postbaseline value in the double-blind period (Last Observation Carried Forward [LOCF]).

End point type	Secondary

End point timeframe:

Baseline and 6 weeks

End point values	Placebo	Risperidone Low Dose	Risperidone High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	29	29	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.3 (± 0.79)	-0.4 (± 0.73)	-1 (± 0.78)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Risperidone High Dose
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	-0.33
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[6] - Mean difference is change in Risperidone high dose arm minus change in placebo arm. P-value is not adjusted for multiple comparisons.
[7] - ANCOVA model included factors for treatment group, center (after pooling of small centers), baseline weight stratification, and baseline CGI-S value.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Risperidone Low Dose
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[8] - ANCOVA model included factors for treatment group, center (after pooling of small centers), baseline weight stratification, and baseline CGI-S value.

Secondary: Number of Participants Who Had Clinical Global Impression Change Ratings of Much or Very Much Improved

End point title	Number of Participants Who Had Clinical Global Impression Change Ratings of Much or Very Much Improved

End point description:

Investigator impression of change over time from double-blind baseline on a 7-point scale (1="very much improved", 2="much improved", 3="minimally improved", 4="no change", 5="minimally worse", 6="much worse", 7="very much worse"). All randomized subjects with at least one dose of study medication and at least one postbaseline value. For subjects who discontinued, Week 6 data is imputed using the subject's last nonmissing, postbaseline value in the double-blind period (Last Observation Carried Forward [LOCF]).

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Risperidone Low Dose	Risperidone High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	30	30	
Units: participants	5	5	19	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Risperidone Low Dose
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.985 [9]
Method	Cochran-Mantel-Haenszel

Notes:

[9] - Cochran-Mantel-Haenszel test controlling for center (after pooling small centers) and baseline weight stratification.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Risperidone High Dose v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - Cochran-Mantel-Haenszel test controlling for center (after pooling small centers) and baseline weight stratification.

Secondary: Change in Fasting Glucose (mg/dL) at 6 Weeks

End point title	Change in Fasting Glucose (mg/dL) at 6 Weeks

End point description:

All randomized subjects with at least one dose of study medication and both baseline and at least one postbaseline fasting laboratory samples. For subjects who discontinued, Week 6 data is imputed using the subject's last nonmissing, postbaseline value in the double-blind period (Last Observation Carried Forward [LOCF]).

End point type	Secondary

End point timeframe:

Baseline and 6 weeks

End point values	Placebo	Risperidone Low Dose	Risperidone High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	23	23	
Units: mg/dL				
arithmetic mean (standard deviation)	-0.4 (± 8.2)	-0.1 (± 8.81)	-0.3 (± 9.74)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Insulin Resistance (IR) at 6 Weeks

End point title	Change in Insulin Resistance (IR) at 6 Weeks

End point description:

Insulin resistance calculated using the homeostatic model assessment 1 (HOMA1)formula: fasting

glucose (mmol/L) times fasting insulin (uU/L) divided by 22.5. HOMA-IR is a widely used clinical tool for estimating insulin resistance based upon the balance between glucose output and insulin secretion. Normal values should be close to 1, while an increase indicates a decrease in insulin sensitivity (or increase in insulin resistance), a potential predictor for the development of Type 2 Diabetes Mellitus. All randomized subjects with >=1 dose of study medication and fasting glucose and insulin at baseline and at >=1 postbaseline time point. For subjects who discontinued, Week 6 data is imputed using the subject's last nonmissing, postbaseline value in the double-blind period. Means are adjusted for baseline weight (<45 kg, >=45 kg) and baseline IR.

End point type	Secondary

End point timeframe:

Baseline and 6 weeks

End point values	Placebo	Risperidone Low Dose	Risperidone High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[11]	21[12]	22[13]	
Units: units on a scale				
least squares mean (confidence interval 95%)	0.36 (-0.34 to 1.07)	-0.1 (-0.76 to 0.55)	0.45 (-0.18 to 1.08)	

Notes:

[11] - Here 'N' signifies subjects analyzed for this endpoint.

[12] - Here 'N' signifies subjects analyzed for this endpoint.

[13] - Here 'N' signifies subjects analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fasting Glucose (mg/dL) at 6 Months

End point title	Change in Fasting Glucose (mg/dL) at 6 Months

End point description:

All subjects with at least one dose of study medication in the open label phase and both double-blind baseline and at least one open-label period fasting laboratory samples. For subjects who discontinued, Month 6 data is imputed using the subject's last nonmissing, postbaseline value in the open-label period.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo/RIS	Ris Low Dose/RIS	Ris High Dose/RIS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	16	16	
Units: milligram per deciliters (mg/dL)				
arithmetic mean (standard deviation)	4 (± 12.27)	3.5 (± 12.27)	2.3 (± 8.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Insulin Resistance (IR) at 6 Months

End point title	Change in Insulin Resistance (IR) at 6 Months

End point description:

Insulin resistance calculated using the homeostatic model assessment 1 (HOMA1) formula: fasting glucose (mmol/L) times fasting insulin (uU/L) divided by 22.5. HOMA-IR is a widely used clinical tool for estimating insulin resistance based upon the balance between glucose output and insulin secretion. Normal values should be close to 1, while an increase indicates a decrease in insulin sensitivity (or increase in insulin resistance), a potential predictor for the development of Type 2 Diabetes Mellitus. All subjects with at least one dose of study medication in the open label phase and both double-blind baseline and at least one open-label period fasting laboratory samples. For subjects who discontinued, Month 6 data is imputed using the subject's last nonmissing, postbaseline value in the open-label period.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo/RIS	Ris Low Dose/RIS	Ris High Dose/RIS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	16	16	
Units: units on a scale				
arithmetic mean (standard deviation)	0.09 (± 2.67)	0.36 (± 0.89)	0.75 (± 0.91)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind period: 6 weeks. Open-label period: 6 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects weighing 20 kg to <45 kg were started with 0.5 ml of placebo solution on Day 1 and were titrated up to 1.25 ml on Day 4. Subjects weighing >=45 kg at baseline were started with 0.75 ml of placebo solution on Day 1 and were titrated up to 1.75 ml on Day 4.

Reporting group title	Risperidone Low Dose

Reporting group description:

Subjects weighing 20 kg to <45 kg were started with 0.05 mg on Day 1 and were titrated up to 0.125 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.075 mg on Day 1 and were titrated up to 0.175 mg on Day 4.

Reporting group title	Risperidone High Dose

Reporting group description:

Subjects weighing 20 kg to <45 kg were started with 0.05 mg on Day 1 and were titrated up to 0.125 mg on Day 4. Subjects weighing >=45 kg at baseline were started with 0.075 mg on Day 1 and were titrated up to 0.175 mg on Day 4.

Reporting group title	Open-label Risperidone

Reporting group description:

Subjects who completed the double-blind phase, or discontinued after at least 3 weeks for reasons other than tolerability and, in the investigator's judgment needed risperidone treatment were eligible to enter the open-label phase. Risperidone was given as oral solution (1 mg/mL) for the first 3 days and as tablets from Day 4 on. On Day 1, subjects with a baseline weight of 20 kg to <45 kg were started on risperidone 0.125 mg/day, and subjects with a baseline weight of 45 kg or more were started on risperidone 0.175 mg/day. On Day 4, the dose was increased to 0.25 mg for all subjects. After Day 14, dose increments of 0.25 mg or 0.5 mg (upon the judgment of the investigator) were allowed every 2 weeks. The maximum allowed dose was 1.25 mg for subjects with baseline weight of 20 kg to <45 kg and 1.75 mg for subjects with a baseline weight of 45 kg or more.

Serious adverse events	Placebo	Risperidone Low Dose	Risperidone High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)	0 / 30 (0.00%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 35 (2.86%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label Risperidone		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 79 (1.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Risperidone Low Dose	Risperidone High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 35 (57.14%)	12 / 30 (40.00%)	27 / 31 (87.10%)
Investigations			
Weight increased			
subjects affected / exposed	2 / 35 (5.71%)	3 / 30 (10.00%)	4 / 31 (12.90%)
occurrences (all)	7	4	5
Nervous system disorders			
Sedation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 30 (3.33%)	8 / 31 (25.81%)
occurrences (all)	0	1	10
Somnolence			

subjects affected / exposed	1 / 35 (2.86%)	0 / 30 (0.00%)	7 / 31 (22.58%)
occurrences (all)	1	0	7
Akathisia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	4 / 35 (11.43%)	2 / 30 (6.67%)	2 / 31 (6.45%)
occurrences (all)	4	2	2
Hypersomnia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2
Psychomotor hyperactivity			
subjects affected / exposed	2 / 35 (5.71%)	1 / 30 (3.33%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	4
Thirst			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 35 (8.57%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences (all)	5	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 35 (0.00%)	1 / 30 (3.33%)	2 / 31 (6.45%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	4
Nausea			

subjects affected / exposed	1 / 35 (2.86%)	1 / 30 (3.33%)	2 / 31 (6.45%)
occurrences (all)	1	1	2
Vomiting			
subjects affected / exposed	2 / 35 (5.71%)	2 / 30 (6.67%)	2 / 31 (6.45%)
occurrences (all)	4	5	4
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)	1 / 30 (3.33%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Cough			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 35 (0.00%)	2 / 30 (6.67%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	2 / 35 (5.71%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
Agitation			
subjects affected / exposed	2 / 35 (5.71%)	0 / 30 (0.00%)	1 / 31 (3.23%)
occurrences (all)	4	0	3
Depression			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 35 (0.00%)	2 / 30 (6.67%)	2 / 31 (6.45%)
occurrences (all)	0	3	10

Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	2 / 30 (6.67%)	4 / 31 (12.90%)
occurrences (all)	4	3	6
Upper respiratory tract infection			
subjects affected / exposed	1 / 35 (2.86%)	1 / 30 (3.33%)	3 / 31 (9.68%)
occurrences (all)	3	3	8
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	2 / 35 (5.71%)	5 / 30 (16.67%)	11 / 31 (35.48%)
occurrences (all)	2	5	11

Non-serious adverse events	Open-label Risperidone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 79 (49.37%)		
Investigations			
Weight increased			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Nervous system disorders			
Sedation			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	6		
Somnolence			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Akathisia			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Hypersomnia			

subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	7		
Thirst			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	3		
Psychiatric disorders			
Aggression			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences (all)	2		
Agitation			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	3		
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	11		
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	9		

Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	 9 / 79 (11.39%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported