Clinical trial results:
A placebo-controlled discontinuation trial of off-label used risperidone in people with intellectual disability

Summary

EudraCT number	2014-003718-10
Trial protocol	NL
Global end of trial date	04 April 2018

Results information

Result version number	v1 (current)
This version publication date	06 March 2019
First version publication date	06 March 2019
Summary attachment (see zip file)	Summary risperidone and ID (Abstract.docx)

Trial information

Trial identification

Sponsor protocol code	2014RISP-ID01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Netherlands Trial Register: NL5252

Notes:

Sponsors

Sponsor organisation name	University Medical Center Groningen
Sponsor organisation address	Hanzeplein 1, Groningen, Netherlands,
Public contact	Risperidone ID trial information, UMCG, 0031 592334100, l.ramerman@umcg.nl
Scientific contact	Risperidone ID trial information, UMCG, 0031 592334100, l.ramerman@umcg.nl

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is: To study the effect of controlled discontinuation of long-term used risperidone, for the treatment of challenging behaviour, on behaviour and health. Our hypothesis is that long-term use of risperidone for challenging behaviour is not more effective than a placebo.

Protection of trial subjects:

All trial subjects were allowed to deblind and stop participation in the study at any time. Furthermore, when withdrawal symptoms such as dyskinesia presented, additional medication was allowed (such as Lorazepam). In addition, the protocol provided information on medications to prescribe when behaviour worsened. When participants did not want to comply with blood withdrawal, the withdrawal would be stopped and participation continued without blood withdrawal.

Background therapy:

Psychotropic drugs, that were not antipsychotic drugs, were allowed during the study, such as sertraline, oxazepam, lorazepam and Ritalin. In both study arms, different psychotropic drugs were already used by approximately 50% of the participants before the start of the trial. In addition, during the trial, non-pharmacological treatments/behavioural interventions were allowed. This included restrictive measures, changes in daily schedule and the approach of supervisors to challenging behaviours. All these pharmacological and non-pharmacological measures were applied in an equal amount in the intervention and control arm.

Evidence for comparator:

In the trial, risperidone is compared to a placebo. There is no evidence for the effectiveness of long-term used risperidone when prescribed for reducing challenging behaviours. A previous trial of the short term effectiveness of risperidone in aggression did suggest that placebo is more effective than risperidone in reducing aggression. Furthermore, a previous discontinuation trial of long-term used antipsychotic drugs indicated that discontinuation is possible without a worsening in challenging behaviours.

Actual start date of recruitment	04 January 2016
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	Netherlands: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	0
Adolescents (12-17 years)	10
Adults (18-64 years)	13
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between the 4th of January 2016 and the 28th of February 2017 from 3 different organisations for intellectual disability care and 2 organisations for mental health care in the North of the Netherlands.

Pre-assignment

Screening details:

238 eligible participants were found, based on their level of intellectual disability (IQ<70), aged over 6 years, risperidone use > 1 year, no psychosis, schizophrenia or bipolar disorder. 157 were advised by their physician not to participate and 56 refused participation by them self.

Period 1

Period 1 title	baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To ensure blinding both the intervention group and the control group will receive two bottles: bottle A with risperidone 1mg/ml and bottle B with either placebo or risperidone 1mg/ml. All participants will decrease the quantity used of bottle A with 12.5% every two weeks and will increase the quantity used of bottle B with 12.5% every two weeks. The pharmacy provided a list with allocation of randomisation numbers per arm to the producer of the medication. Randomisation numbers were prescribed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Discontinuation

Arm description:

This arm discontinues risperidone to placebo with 12.5% every two weeks. After 14 weeks they use a placebo for 8 weeks, after which they were deblinded.

Arm type	Placebo
Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

All participants started the study at their original dosage, which was possible by switching to the liquid form of risperidone (1mg/ml). All received bottle A with risperidone 1mg/ml and bottle B with placebo. All participants decreased the quantity used of bottle A with 12.5% every two weeks and will increase the quantity used of bottle B with 12.5% every two weeks. Table 2 presents the discontinuation schedule of bottle A (active medication) to bottle B (active medication or placebo).
Caregivers will be trained in the use of the discontinuation schedule and the use of the calibrated dispenser. Furthermore, they will be instructed to mix the solutions of bottle A and B and delude the mix with a compatible beverage.

Arm title	Control

Arm description:

The control group were remained on their original dosage of risperidone. They received risperidone (1mg/ml) in both bottle A and B. After 24 weeks they were deblinded and were allowed to discontinue risperidone during a natural follow-up

Arm type	risperidone

Investigational medicinal product name	risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

To ensure blinding both the intervention group and the control group will receive two bottles: bottle A with risperidone 1mg/ml and bottle B with risperidone 1mg/ml. All participants will decrease the quantity used of bottle A with 12.5% every two weeks and will increase the quantity used of bottle B with 12.5% every two weeks.
Caregivers will be trained in the use of the discontinuation schedule and the use of the calibrated dispenser. Furthermore, they will be instructed to mix the solutions of bottle A and B and delude the mix with a compatible beverage.

Number of subjects in period 1	Discontinuation	Control
Started	11	14
Completed	11	14

Period 2

Period 2 title	Blind/discontinuation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To ensure blinding both the intervention group and the control group will receive two bottles: bottle A with risperidone 1mg/ml and bottle B with either placebo or risperidone 1mg/ml. All participants will decrease the quantity used of bottle A with 12.5% every two weeks and will increase the quantity used of bottle B with 12.5% every two weeks.

Arms

Are arms mutually exclusive?	Yes
Arm title	Discontinuation

Arm description:

This arm discontinues risperidone to placebo with 12.5% every two weeks. After 14 weeks they use a placebo for 8 weeks, after which they were deblinded.

Arm type	Placebo
Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid, Oral drops
Routes of administration	Oral use

Dosage and administration details:

All participants started the study at their original dosage, which was possible by switching to the liquid

form of risperidone (1mg/ml). All received bottle A with risperidone 1mg/ml and bottle B with placebo. All participants decreased the quantity used of bottle A with 12.5% every two weeks and will increase the quantity used of bottle B with 12.5% every two weeks. Table 2 presents the discontinuation schedule of bottle A (active medication) to bottle B (active medication or placebo).
Caregivers will be trained in the use of the discontinuation schedule and the use of the calibrated dispenser. Furthermore, they will be instructed to mix the solutions of bottle A and B and delude the mix with a compatible beverage.

Arm title	Control

Arm description:

The control group were remained on their original dosage of risperidone. They received risperidone (1mg/ml) in both bottle A and B. After 24 weeks they were deblinded and were allowed to discontinue risperidone during a natural follow-up

Arm type	risperidone
Investigational medicinal product name	risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

To ensure blinding both the intervention group and the control group will receive two bottles: bottle A with risperidone 1mg/ml and bottle B with risperidone 1mg/ml. All participants will decrease the quantity used of bottle A with 12.5% every two weeks and will increase the quantity used of bottle B with 12.5% every two weeks.
Caregivers will be trained in the use of the discontinuation schedule and the use of the calibrated dispenser. Furthermore, they will be instructed to mix the solutions of bottle A and B and delude the mix with a compatible beverage.

Number of subjects in period 2	Discontinuation	Control
Started	11	14
Completed	11	14

Baseline characteristics

Reporting groups	
Reporting group title	Discontinuation
Reporting group description:	
This arm discontinues risperidone to placebo with 12.5% every two weeks. After 14 weeks they use a placebo for 8 weeks, after which they were deblinded.	
Reporting group title	Control
Reporting group description:	
The control group were remained on their original dosage of risperidone. They received risperidone (1mg/ml) in both bottle A and B. After 24 weeks they were deblinded and were allowed to discontinue risperidone during a natural follow-up	

Reporting group values	Discontinuation	Control	Total
Number of subjects	11	14	25
Age categorical			
age was recorded at baseline in years.			
Units: Subjects			
Adolescents (12-17 years)	5	5	10
Adults (18-64 years)	5	8	13
From 65-84 years	1	1	2
Age continuous			
Age was recorded at baseline in years.			
Units: years			
arithmetic mean	33	28	
standard deviation	± 20.16	± 16.10	-
Gender categorical			
Units: Subjects			
Female	2	4	6
Male	9	10	19
Severity of intellectual disability			
severity of intellectual disability: mild, moderate, severe, profound			
Units: Subjects			
mild	6	7	13
moderate	1	5	6
severe	4	2	6
profound	0	0	0
use of other psychotropic drugs			
use of other psychotropic drugs			
Units: Subjects			
yes	6	6	12
no	5	8	13
start dosage of risperidone			
mean starting dosage of risperidone.			
Units: milligram(s)			
arithmetic mean	1.82	1.97	
standard deviation	± 1.28	± 1.14	-

End points

End points reporting groups

Reporting group title	Discontinuation
Reporting group description:	
This arm discontinues risperidone to placebo with 12.5% every two weeks. After 14 weeks they use a placebo for 8 weeks, after which they were deblinded.	
Reporting group title	Control
Reporting group description:	
The control group were remained on their original dosage of risperidone. They received risperidone (1mg/ml) in both bottle A and B. After 24 weeks they were deblinded and were allowed to discontinue risperidone during a natural follow-up	
Reporting group title	Discontinuation
Reporting group description:	
This arm discontinues risperidone to placebo with 12.5% every two weeks. After 14 weeks they use a placebo for 8 weeks, after which they were deblinded.	
Reporting group title	Control
Reporting group description:	
The control group were remained on their original dosage of risperidone. They received risperidone (1mg/ml) in both bottle A and B. After 24 weeks they were deblinded and were allowed to discontinue risperidone during a natural follow-up	

Primary: irritability

End point title	irritability
End point description:	
Irritability is a sub scale of the Aberrant Behavior Checklist.	
End point type	Primary
End point timeframe:	
measured at baseline, deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	15.36 (9.68 to 21.4)	13.57 (8.54 to 18.61)	14.18 (8.23 to 20.13)	10.36 (5.08 to 15.63)

Statistical analyses

Statistical analysis title	irritability, mixed methods repeated measures
Statistical analysis description:	
The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.	
Comparison groups	Discontinuation v Control v Discontinuation v Control

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.37 [1]
Method	Mixed models analysis

Notes:

[1] - there was no significant difference between the study arms over time on irritability.

Secondary: lethargy

End point title	lethargy

End point description:

lethargy is a sub scale of the Aberrant Behavior Checklist

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	11.73 (5.02 to 18.44)	11.07 (5.12 to 17.02)	10.91 (4.44 to 17.38)	6.86 (1.12 to 12.60)

Statistical analyses

Statistical analysis title	lethargy/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.345 [2]
Method	Mixed models analysis

Notes:

[2] - no time*group effect

Secondary: stereotypy

End point title	stereotypy

End point description:

stereotypy is a sub scale of the Aberrant Behavior Checklist

End point type	Secondary

End point timeframe:
baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	4.82 (1.32 to 8.32)	5.29 (2.18 to 8.39)	8.91 (5.44 to 12.38)	2.57 (0.50 to 5.65)

Statistical analyses

Statistical analysis title	stereotypy MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.003 [3]
Method	Mixed models analysis

Notes:

[3] - stereotypy increased in the discontinuation group over time, compared to the control group.

Secondary: hyperactivity

End point title	hyperactivity

End point description:

hyperactivity is a sub scale of the Aberrant Behavior Checklist

End point type	Secondary

End point timeframe:
baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	17.27 (10.44 to 24.10)	19.14 (3.09 to 25.20)	15.27 (8.87 to 21.68)	12.86 (7.18 to 18.53)

Statistical analyses

Statistical analysis title	hyperactivity/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.16 [4]
Method	Mixed models analysis

Notes:

[4] - no group*time effect

Secondary: inadequate speech

End point title	inadequate speech

End point description:

inadequate speech is a sub scale of the aberrant behaviour checklist

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	3.64 (1.62 to 5.65)	4.57 (2.78 to 6.36)	3.18 (1.11 to 5.26)	2.43 (0.59 to 4.27)

Statistical analyses

Statistical analysis title	Inad/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.072 [5]
Method	Mixed models analysis

Notes:

[5] - no group*time effect

Secondary: Dyskinesia/AIMS

End point title	Dyskinesia/AIMS

End point description:

Score on the Abnormal Involuntary Movement Scale

End point type	Secondary

End point timeframe:

baseline and delblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: point				
arithmetic mean (confidence interval 95%)	3.18 (1.09 to 5.27)	0.93 (-0.96 to 2.78)	4.46 (1.25 to 7.66)	1.71 (-1.13 to 4.55)

Statistical analyses

Statistical analysis title	AIMS/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.65 [6]
Method	Mixed models analysis

Notes:

[6] - no group*time effect

Secondary: Akathisia/BARS

End point title	Akathisia/BARS

End point description:

Barnes Akathisia Rating Scale

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	1.36 (0.41 to 2.32)	0.79 (-0.06 to 1.63)	01.7393 (0.43 to 3.03)	0.93 (-0.22 to 2.08)

Statistical analyses

Statistical analysis title	BARS/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.73 [7]
Method	Mixed models analysis

Notes:

[7] - no group*time effect

Secondary: Parkinsonism/UPDRS

End point title	Parkinsonism/UPDRS

End point description:

Unified Parkinson's Disease Rating Scale-motor items.

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	1.55 (0.41 to 2.68)	1.64 (0.63 to 2.65)	1.27 (0.24 to 2.31)	1.57 (0.65 to 2.49)

Statistical analyses

Statistical analysis title	UPDRS/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.75 [8]
Method	Mixed models analysis

Notes:

[8] - no group*time effect

Secondary: autonomic symptoms/SCOPA-AUT

End point title	autonomic symptoms/SCOPA-AUT

End point description:

SCale for Outcomes of PArkonsons disease- Autonomic symptoms

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	28.6 (24.6 to 32.7)	29.7 (25.7 to 33.7)	32.7 (28.1 to 37.3)	33.0 (28.5 to 37.5)

Statistical analyses

Statistical analysis title	SCOPA/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.52 [9]
Method	Mixed models analysis

Notes:

[9] - no group*time effect

Secondary: waist circumference

End point title	waist circumference

End point description:

waist circumference in cm

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: cm				
arithmetic mean (confidence interval 95%)	87.7 (76.2 to 99.2)	83.3 (73.0 to 93.6)	82.26 (71.24 to 93.29)	82.4 (72.7 to 92.2)

Statistical analyses

Statistical analysis title	Waist/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.012 [10]
Method	Mixed models analysis

Notes:

[10] - There is a significantly higher decrease in waist circumference in the discontinuation group over time, compared to the control group.

Secondary: BMI

End point title	BMI

End point description:

Body Mass Index

End point type	Secondary
End point timeframe: baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: kg/m^2				
arithmetic mean (confidence interval 95%)	22.3 (18.5 to 26.2)	23.1 (19.7 to 26.5)	20.11 (16.61 to 23.61)	22.8 (19.7 to 25.9)

Statistical analyses

Statistical analysis title	BMI/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03 [11]
Method	Mixed models analysis

Notes:

[11] - there was a significantly higher decrease in BMI in the discontinuation group, compared to the controls.

Secondary: systolic blood pressure

End point title	systolic blood pressure
End point description: systolic blood pressure	
End point type	Secondary
End point timeframe: baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: mm/HG				
arithmetic mean (confidence interval 95%)	117 (108 to 126)	115 (107 to 124)	102 (93 to 111)	114 (106 to 122)

Statistical analyses

Statistical analysis title	systolic/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005 [12]
Method	Mixed models analysis

Notes:

[12] - There was a significantly higher decrease in systolic blood pressure in the discontinuation group compared to the controls.

Secondary: diastolic blood pressure

End point title	diastolic blood pressure

End point description:

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: mm/HG				
arithmetic mean (confidence interval 95%)	68 (62 to 75)	71 (65 to 76)	65 (58 to 71)	70 (65 to 76)

Statistical analyses

Statistical analysis title	dias BP/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.48 [13]
Method	Mixed models analysis

Notes:

[13] - no group*time effect

Secondary: Sleepiness

End point title	Sleepiness

End point description:

Sleepiness measured with the Epworth Sleepiness Scale (ESS)

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: points				
arithmetic mean (confidence interval 95%)	4.09 (1.65 to 6.53)	3.43 (1.27 to 5.59)	5.36 (1.69 to 9.04)	4.07 (0.81 to 7.33)

Statistical analyses

Statistical analysis title	ESS/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.79 [14]
Method	Mixed models analysis

Notes:

[14] - no group*time effect

Secondary: weight

End point title	weight

End point description:

End point type	Secondary
End point timeframe: baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	14	11	14
Units: kilogram(s)				
arithmetic mean (confidence interval 95%)	67.6 (54.2 to 81.0)	69.9 (58 to 81.7)	61.7 (48.95 to 74.45)	69.1 (57.8 to 81.7)

Statistical analyses

Statistical analysis title	weight/MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.046 [15]
Method	Mixed models analysis

Notes:

[15] - there was a significantly higher decrease in weight in the discontinuation group, compared to the controls.

Secondary: Glucose

End point title	Glucose
End point description: Fasting glucose levels in mmol/l	
End point type	Secondary
End point timeframe: baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	8	11
Units: mmol/l				
number (confidence interval 95%)	6.16 (5.65 to 6.68)	5.38 (4.81 to 5.95)	5.67 (5.13 to 6.22)	5.35 (4.72 to 5.98)

Statistical analyses

Statistical analysis title	Glucose MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.31 [16]
Method	Mixed models analysis

Notes:

[16] - There was no significant time*group effect

Secondary: Total cholesterol

End point title	Total cholesterol
End point description:	
fasting total cholesterol in mmol/l	
End point type	Secondary
End point timeframe:	
baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	8	8
Units: mmol/l				
arithmetic mean (confidence interval 95%)	4.30 (3.79 to 4.81)	3.96 (3.39 to 4.52)	3.86 (3.39 to 4.32)	3.93 (3.42 to 4.45)

Statistical analyses

Statistical analysis title	cholesterol MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.11 [17]
Method	Mixed models analysis

Notes:

[17] - No significant group*time interaction

Secondary: LDL Cholesterol

End point title	LDL Cholesterol
End point description: fasting LDL cholesterol	
End point type	Secondary
End point timeframe: baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	8	11
Units: mmol/l				
arithmetic mean (confidence interval 95%)	2.56 (2.11 to 3.00)	2.39 (1.90 to 2.88)	2.18 (1.79 to 2.57)	2.22 (1.78 to 2.66)

Statistical analyses

Statistical analysis title	LDL MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.38 [18]
Method	Mixed models analysis

Notes:

[18] - no significant time*group effect on LDL cholesterol levels

Secondary: HDL Cholesterol

End point title	HDL Cholesterol

End point description:

End point type	Secondary
End point timeframe: baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	8	11
Units: mmol/l				
arithmetic mean (confidence interval 95%)	1.40 (1.21 to 1.59)	1.27 (1.06 to 1.48)	1.28 (1.08 to 1.48)	1.20 (0.98 to 1.43)

Statistical analyses

Statistical analysis title	HDL MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.61 [19]
Method	Mixed models analysis

Notes:

[19] - No significant time*group effect on HDL levels

Secondary: Tryglycerides

End point title	Tryglycerides

End point description:

End point type	Secondary
End point timeframe: baseline and deblinding	

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	8	11
Units: mmol/l				
arithmetic mean (confidence interval 95%)	1.05 (0.82 to 1.29)	0.96 (0.70 to 1.22)	1.05 (0.80 to 1.30)	1.01 (0.73 to 1.29)

Statistical analyses

Statistical analysis title	Tryglycerides MMRM
Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.66 [20]
Method	Mixed models analysis

Notes:

[20] - No significant time*group effects on Triglyceride levels

Secondary: Prolactin

End point title	Prolactin

End point description:

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	8	11
Units: mU/l				
arithmetic mean (confidence interval 95%)	738 (532 to 944)	629 (390 to 867)	327 (144 to 509)	626 (417 to 835)

Statistical analyses

Statistical analysis title	Prolactin MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.007 [21]
Method	Mixed models analysis

Notes:

[21] - There was a significant time*group effect for prolactin levels, showing a favourable effect in the discontinuation group, compared to the control group.

Secondary: Testosterone

End point title	Testosterone

End point description:

End point type	Secondary

End point timeframe:

baseline and deblinding

End point values	Discontinuation	Control	Discontinuation	Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	8	11
Units: nmol/l				
arithmetic mean (confidence interval 95%)	7.45 (4.77 to 11.8)	9.65 (4.76 to 14.5)	10.6 (4.77 to 16.43)	9.48 (2.92 to 16.00)

Statistical analyses

Statistical analysis title	Testosterone MMRM

Statistical analysis description:

The differences at baseline and week-24 between the discontinuation group and the continuation group were assessed with a mixed model for repeated measures with fixed effects for group, time and time*group. An unstructured covariance matrix was used. Analyses were done following the intention-to-treat principle.

Comparison groups	Discontinuation v Control v Discontinuation v Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.048 [22]
Method	Mixed models analysis

Notes:

[22] - There was a significant group* time effect on testosterone levels, showing a favourable effect in the discontinuation group, compared to the control group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

4th of January 2016 until 2nd of September 2017 (last patient deblinded)

Adverse event reporting additional description:

When adverse effent occured, participant contacted their own physician and the primary researcher of that organization. The primary researcher would inform the coordinating investigator as soon as possible of the AE.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Discontinuation

Reporting group description:

This arm discontinues risperidone to placebo with 12.5% every two weeks. After 14 weeks they use a placebo for 8 weeks, after which they were deblinded.

Serious adverse events	Discontinuation		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Discontinuation		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Nervous system disorders			
Dyskinesia	Additional description: Due to the withdrawal of risperidone, withdrawal dyskinesia can occur.		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		

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

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

The number of subjects included in the trial was substantially lower than anticipated. Furthermore, due to objections against participation by eligible participants physician, a selection bias can occur.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30609152