Clinical trial results:
A Randomized, Open-Label, Cross-over Study to Assess the Relative Bioavailability of LY03004 and EU Risperdal® Consta® at 50 mg Following Multiple Intramuscular Injections in Stable Patients with Schizophrenia

Summary

EudraCT number	2016-005010-22
Trial protocol	HR
Global end of trial date	24 August 2020

Results information

Result version number	v1 (current)
This version publication date	22 October 2021
First version publication date	22 October 2021

Trial information

Trial identification

Sponsor protocol code	LY03004/CT-EUR-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Project number (CRO): CLY16001

Notes:

Sponsors

Sponsor organisation name	Nanjing Luye Pharmaceutical Co., Ltd.
Sponsor organisation address	No.28, Gaoxin Road; Nanjing Hightech Industrial Development Zone, Nanjing, China, 210061
Public contact	Sponsor´s Vice President Project Management / Clinical Operations, Luye Pharma Group, Ltd., +1 609-212-0609, joe.tai@luye.com
Scientific contact	Sponsor´s Vice President Project Management / Clinical Operations, Luye Pharma Group, Ltd., +1 609-212-0609, joe.tai@luye.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2020
Global end of trial reached?	Yes
Global end of trial date	24 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the relative bioavailability of a test preparation containing 50 mg risperidone [Test IMP: LY03004, manufactured by Nanjing Luye Pharmaceutical Co., Ltd., China] as compared to a market standard [Reference IMP: EU RISPERDAL® CONSTA® 50 mg (risperidone), Janssen] following multiple doses of deep intramuscular gluteal injection of 50 mg risperidone at stead-ystate under fasting conditions in two different periods.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline and the local laws and regulations of the countries of clinical sites.

Background therapy:

Patients with schizophrenia stabilized on risperidone (given either orally or as a depot medication) at a dose equivalent (for intramuscular dosing) or proportional (for oral dosing) to 50 mg dose in the form of a depot medication for intramuscular administration for at least 4 weeks prior to screening. (FOR SERBIA)

Patients with schizophrenia on a stable dose of oral antipsychotic medication(s) or on Risperidone depot 50 mg for at least 4 weeks prior to screening. (FOR ALL OTHER COUNTRIES)

Evidence for comparator:

In the EU, Risperdal® Consta® has been approved for the maintenance treatment of schizophrenia in patients currently stabilized with oral antipsychotics at 25, 37.5 and 50 mg doses supplied with three dosage forms (25 mg, 37.5 mg and 50 mg vial kits).

50 mg was selected for both LY03004 and EU Risperdal® Consta® in this study, since it is the commonly used dose for Risperdal® Consta® in EU. Similar dose regimen (four biweekly injections) and PK sampling time points were applied in this study to allow relevant comparison of the two treatments within the same study and comparison of this study to published studies with EU Risperdal® Consta®. Further the BfArM had given the scientific advice to use 50 mg in this trial.

Actual start date of recruitment	31 May 2019
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	Moldova, Republic of: 34
Country: Number of subjects enrolled	Serbia: 40
Country: Number of subjects enrolled	Russian Federation: 96
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Croatia: 20
Country: Number of subjects enrolled	Bulgaria: 65

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 12
Worldwide total number of subjects	280
EEA total number of subjects	110

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)	0
Adults (18-64 years)	280
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population consisted of male or non-pregnant female patients, 18 to 65 years old, BMI 18.0 to 38.0 kg/m2, with schizophrenia who were on a stable dose of oral risperidone (FOR SERBIA) / antipsychotic medication(s) (FOR ALL OTHER COUNTRIES) or on Risperidone depot 50 mg for at least 4 weeks prior to screening.

Pre-assignment

Screening details:

The screening period lasted up to 28 days before treatment period 1.

A total number of 280 patients were screened. Two hundred fifty-five patients were randomized; thereof 246 patients were treated with study medication.

Pre-assignment period milestones

Number of subjects started	280
Number of subjects completed	255[1]

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 13
Reason: Number of subjects	Screening failure: 12

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: A total number of 255 subjects were randomized. Nine subjects were randomized, but dropped out before receiving any study medication. Therefore, 246 subjects were treated with study medication (patients starting period 1). But for 4 subjects all data were lost in a fire accidient. Due to this reason, the number of subjects starting period 1 was 242.

Period 1

Period 1 title	Treatment (Period 1 / 2) (overall trial) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Test

Arm description:

LY03004 (risperidone), 50 mg

Arm type	Experimental
Investigational medicinal product name	LY03004
Investigational medicinal product code	Test IMP (T)
Other name	
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

- 50 mg risperidone (extended-release microspheres and diluent for prolonged-release suspension for intramuscular injection)
- Multiple dose (4 doses in total)
- For deep intramuscular gluteal injections every 2 weeks (14 days)

Arm title	Reference

Arm description:	
EU Risperdal® Consta®, 50 mg	
Arm type	Active comparator
Investigational medicinal product name	EU Risperdal® Consta®
Investigational medicinal product code	Reference IMP (R)
Other name	
Pharmaceutical forms	Powder and solvent for prolonged-release suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

- 50 mg risperidone (powder and solvent for prolonged-release suspension for intramuscular injection)
- Multiple dose (4 doses in total)
- For deep intramuscular gluteal injections every 2 weeks (14 days)

Number of subjects in period 1	Test	Reference
Started	228	227
Completed	205	203
Not completed	23	24
Consent withdrawn by subject	17	17
Adverse event, non-fatal	6	4
Lost to follow-up	-	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups[1]	
Reporting group title	Treatment (Period 1 / 2) (overall trial)
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total number of 280 subjects signed informed consent, were screened, and therefore have to be regarded as enrolled into the trial (= worldwide number of subjects enrolled). 255 of the 280 screened subjects were randomized, 9 were randomized, but dropped out before receiving any IMP. Therefore, 246 subjects were treated with IMP (patients starting period 1). For 4 subjects all data were lost in a fire accidient. Due to this reason, the number of subjects in the baseline period is 242.

Reporting group values	Treatment (Period 1 / 2) (overall trial)	Total	
Number of subjects	242	242	
Age categorical Units: Subjects			
<18 years	0	0	
Adults (18-39 years)	102	102	
Adults (40-65 years)	140	140	
>65 years	0	0	
Age continuous Units: years			
arithmetic mean	42.0		
standard deviation	± 10.9	-	
Gender categorical Units: Subjects			
Female	86	86	
Male	156	156	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	241	241	
Unknown	1	1	
Height Units: cm			
arithmetic mean	173.7		
standard deviation	± 8.8	-	
Weight Units: kg			
arithmetic mean	82.1		
standard deviation	± 16.5	-	
Body Mass Index Units: kg/m^2			
arithmetic mean	27.1		
standard deviation	± 4.6	-	

Subject analysis sets	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Primary BE evaluation: 190 patients (per protocol set) were included in the statistical evaluation regarding the primary bioequivalence evaluation.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

255 patients were randomized; thereof 246 patients were treated with at least one dose of study medication. In a fire accidient at one Bulgarian study site the data of 4 patients got completely lost. Due to this reason the safety analysis set comprises data from only 242 patients.

Reporting group values	Per protocol set	Safety set	
Number of subjects	190	242	
Age categorical Units: Subjects			
<18 years	0	0	
Adults (18-39 years)	81	102	
Adults (40-65 years)	109	140	
>65 years	0	0	
Age continuous Units: years			
arithmetic mean	42.0	42.0	
standard deviation	± 11.3	± 10.9	
Gender categorical Units: Subjects			
Female	62	86	
Male	128	156	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	189	241	
Unknown	1	1	
Height Units: cm			
arithmetic mean	174.1	173.7	
standard deviation	± 9.0	± 8.8	
Weight Units: kg			
arithmetic mean	82.8	82.1	
standard deviation	± 17.1	± 16.5	
Body Mass Index Units: kg/m^2			
arithmetic mean	27.2	27.1	
standard deviation	± 4.7	± 4.6	

End points

End points reporting groups

Reporting group title	Test
Reporting group description: LY03004 (risperidone), 50 mg	
Reporting group title	Reference
Reporting group description: EU Risperdal® Consta®, 50 mg	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description: Primary BE evaluation: 190 patients (per protocol set) were included in the statistical evaluation regarding the primary bioequivalence evaluation.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: 255 patients were randomized; thereof 246 patients were treated with at least one dose of study medication. In a fire accidient at one Bulgarian study site the data of 4 patients got completely lost. Due to this reason the safety analysis set comprises data from only 242 patients.	

Primary: AUCss-tau [h*pg/mL] per protocol set

End point title	AUCss-tau [h*pg/mL] per protocol set
End point description:	
End point type	Primary
End point timeframe: Treatment (Period 1 / 2) (overall trial)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	190		
Units: h*pg/mL				
geometric mean (standard deviation)	2872487.90 (± 4287077.22)	3144335.92 (± 5027028.61)		

Statistical analyses

Statistical analysis title	T vs. R per protocol set
Comparison groups	Test v Reference

Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Geometric mean ratio
Point estimate	91.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	85.87
upper limit	97.18

Primary: Css-max [pg/mL] per protocol set	
End point title	Css-max [pg/mL] per protocol set
End point description:	
End point type	Primary
End point timeframe:	
Treatment (Period 1 / 2) (overall trial)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	190		
Units: pg/mL				
geometric mean (standard deviation)	13626.50 (± 17732.14)	15846.44 (± 26066.72)		

Statistical analyses

Statistical analysis title	T vs. R per protocol set
Comparison groups	Reference v Test
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	85.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	80.02
upper limit	92.41

Primary: Ctrough [pg/mL] per protocol set	
End point title	Ctrough [pg/mL] per protocol set
End point description:	

End point type	Primary
End point timeframe:	
Treatment (Period 1 / 2) (overall trial)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	190		
Units: pg/mL				
geometric mean (standard deviation)	5767.44 (± 10322.81)	7433.14 (± 11537.38)		

Statistical analyses

Statistical analysis title	T vs. R per protocol set
Comparison groups	Test v Reference
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Geometric mean ratio
Point estimate	77.59
Confidence interval	
level	90 %
sides	2-sided
lower limit	69.43
upper limit	86.72

Other pre-specified: Css-min [pg/mL] per protocol set	
End point title	Css-min [pg/mL] per protocol set
End point description:	

End point type	Other pre-specified
End point timeframe:	
Treatment (Period 1 / 2) (overall trial)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	190		
Units: pg/mL				
geometric mean (standard deviation)	4193.53 (± 9394.36)	4081.80 (± 7573.00)		

Statistical analyses

Statistical analysis title	T vs. R per protocol set
Comparison groups	Test v Reference
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Geometric mean ratio
Point estimate	102.74
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.06
upper limit	113.42

Other pre-specified: Css-avg [pg/mL] per protocol set	
End point title	Css-avg [pg/mL] per protocol set
End point description:	

End point type	Other pre-specified
End point timeframe:	
Treatment (Period 1 / 2) (overall trial)	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	190		
Units: pg/mL				
geometric mean (standard deviation)	8549.07 (± 12759.16)	9358.14 (± 14961.39)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fluctuation [%] per protocol set

End point title	Fluctuation [%] per protocol set

End point description:

End point type	Other pre-specified

End point timeframe:

Treatment (Period 1 / 2) (overall trial)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	190		
Units: per cent				
geometric mean (standard deviation)	95.84 (± 106.51)	115.65 (± 77.40)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tss-max [h] per protocol set

End point title	Tss-max [h] per protocol set

End point description:

End point type	Other pre-specified

End point timeframe:

Treatment (Period 1 / 2) (overall trial)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	190		
Units: hour				
arithmetic mean (standard deviation)	121.13 (± 76.294)	101.19 (± 95.968)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Collection of adverse events started after signing informed consent form during the pre-assignment period [non treatment emergent adverse events (AEs)] and during the treatment period of the trial [treatment emergent adverse events (TEAEs).

Adverse event reporting additional description:

Non treatment emergent AEs and TEAEs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Test

Reporting group description:

LY03004 (risperidone), 50 mg

Reporting group title	Reference

Reporting group description:

EU Risperdal® Consta®, 50 mg

Serious adverse events	Test	Reference	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 228 (1.32%)	1 / 227 (0.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	2 / 228 (0.88%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Breast abscess			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Test	Reference	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 228 (17.11%)	54 / 227 (23.79%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Polycythaemia vera			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 228 (0.00%)	2 / 227 (0.88%)	
occurrences (all)	0	2	
Hypotension			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	1	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Affect lability			

subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	3 / 228 (1.32%)	5 / 227 (2.20%)	
occurrences (all)	3	5	
Delusion			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	5 / 228 (2.19%)	9 / 227 (3.96%)	
occurrences (all)	5	9	
Libido decreased			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Psychotic disorder			
subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	1	
Schizophrenia			
subjects affected / exposed	0 / 228 (0.00%)	2 / 227 (0.88%)	
occurrences (all)	0	2	
Sleep disorder			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 228 (1.75%)	2 / 227 (0.88%)	
occurrences (all)	4	2	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Blood prolactin increased			
subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Sinus tachycradia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Dyskinesia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Extrapyramidal disorder			

subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 228 (0.88%)	3 / 227 (1.32%)	
occurrences (all)	2	4	
Parkinsonism			
subjects affected / exposed	0 / 228 (0.00%)	2 / 227 (0.88%)	
occurrences (all)	0	2	
Reduced facial expression			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	2 / 228 (0.88%)	1 / 227 (0.44%)	
occurrences (all)	2	1	
Tremor			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	1	
Leukopenia			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Accommodation disorder			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Blepharitis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	2 / 228 (0.88%)	0 / 227 (0.00%)	
occurrences (all)	2	0	
Dental caries			
subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Pancreatitis chronic			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Hepatic steatosis			
subjects affected / exposed	1 / 228 (0.44%)	1 / 227 (0.44%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Leukocyturia			

subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Renal pain			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	5 / 228 (2.19%)	6 / 227 (2.64%)	
occurrences (all)	5	6	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 228 (0.00%)	3 / 227 (1.32%)	
occurrences (all)	0	3	
Bronchitis bacterial			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 228 (0.44%)	3 / 227 (1.32%)	
occurrences (all)	1	3	
Fungal infection			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 228 (0.00%)	2 / 227 (0.88%)	
occurrences (all)	0	2	
Otitis media			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Periodontitis			

subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 228 (0.44%)	3 / 227 (1.32%)	
occurrences (all)	1	3	
Respiratory tract infection viral			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 228 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2018	This study was initially planned to be performed with 25 mg risperidone (Study protocol Version 1.6, dated 11-Aug-2017). Due to a deficiency letter from the German authority BfArM Amendment 1.0 and new study protocol (Version 2.0, dated 29-Jan-2018) was prepared, modifying some inclusion and exclusion criteria, adding Moldova to the participating countries and changing the project manager of the sponsor.
25 July 2018	The main reason for preparing Amendment 2.0 was the change of dose strength from 25 mg to 50 mg according to a scientific advice from the German authority BfArM. For implementing the changes updated version of study protocol (Version 3.6, dated 25-Jul-2018) and related documents were prepared.
21 December 2018	Local Amendment 3.0 became necessary due to deficiency letter from the Serbian Medicines and Medical Devices Agency. In Serbia only patients who were stabilized on risperidone (given either orally or as a depot medication) at a dose equivalent (for intramuscular dosing) or proportional (for oral dosing) to 50 mg dose in the form of a depot medication for intramuscular administration could be included into the present trial. Due to this reason, country-specific study protocol, version 4.0 (dated 21-Dec-2018) was prepared.
20 January 2020	Due to the shelf life of the batch of the reference product (June 2020) it was possible that for the last subjects randomized in the trial a new batch of the same reference product might be needed. Amendment 3.0 introduced no changes to the study protocol; only new labels had to be prepared.
08 April 2020	This Amendment described urgent measures in connection with the COVID-19 (Coronavirus) pandemic. It is based on the recommendations of the EMA Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic. Also new version of study protocol (Version 5.0, dated 16-Apr-2020) was prepared, as this is mandatory in some countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported