An open label study in two parallel groups, each receiving in a randomized, two period, cross-over design two single doses of Risperdal® Consta®, to explore the comparative bioavailability of two different batches of Risperdal® Consta® and the intra subject variability of one Risperdal® Consta® batch after intramuscular administration in healthy volunteers

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Primary objectives:* To explore the comparative bioavailability between 12.5 mg of Risperdal® Consta® prepared from a 25 mg dose strength of Risperdal® Consta® EU-sourced, and 12.5 mg of Risperdal® Consta® prepared from a 12.5 mg dose strength...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON44101

Source
ToetsingOnline

Brief title
RISPE1H15US

Condition

- Schizophrenia and other psychotic disorders

Synonym
Schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: TEVA Pharma
Source(s) of monetary or material Support: Teva Pharmachemie (legal entity: Pharmachemie BV)

Intervention

Keyword: Bioavailability, Risperidone, Schizophrenia, Tolerability

Outcome measures

Primary outcome

PK measurements includes:AUC0-t, AUC0-infinite, Cmax, Tmax, Cmax and Tmax

initial burst phase (timeframe 0-24h), Tlag, and terminal t1/2,.

Secondary outcome

Safety / tolerability parameters iclude: (S)AEs, hematology, clinical

chemistry, urinalysis, vital signs (supine and standing systolic and diastolic

blood pressure and heart rate), electrocardiogram (ECG), local tolerability at

the injection site, C-SSRS, ESRS, and prolactin levels.

Study description

Background summary

Teva Pharmachemie is developing a generic version of Risperdal® Consta®. Before starting pilot and pivotal bioavailability studies with the potential new

formulation, a PK study in healthy volunteers is designed to obtain the information on the intra-subject variability of the reference formulations (i.e. Risperdal® Consta®). In addition, this study will compare the bioavailability of 12.5 mg taken from a EU-sourced Risperdal® Consta® 25 mg marketed formulation versus 12.5 mg taken from a US-sourced Risperdal® Consta® 12.5 mg marketed formulation, to investigate the feasibility and effect on PK parameters of preparing a 12.5 mg dose from a EU-sourced Risperdal® Consta® 25 mg marketed formulation.

For registration of the formuliation in Europe, a single dose bioequivalence study is required in healthy volunteers. This is only possible with a low dose (12.5 mg). Because this strength is not available on the European market, the study will have to be conducted by preparing half of the dose strength of the 25 mg formulation, in a dose volume of 2 mL. The current study investigates whether this dose preparation results in the same bioavailability as a 12.5 mg dose from a 12.5 mg strength formulation currently available on the US market.

This data will support the design of a pivotal single dose bioequivalence study in healthy volunteers. Based on regional differences in regulatory requirements for registration of a generic formulation of Risperdal® Consta®, both EU and US-sourced reference products will be investigated in this study.

The data of this study will be used to optimize the design of the clinical studies comparing the test product with the reference product (Risperdal® Consta®) in order to demonstrate bioequivalence.

Study objective

Primary objectives:
* To explore the comparative bioavailability between 12.5 mg of Risperdal® Consta® prepared from a 25 mg dose strength of Risperdal® Consta® EU-sourced, and 12.5 mg of Risperdal® Consta® prepared from a 12.5 mg dose strength Risperdal® Consta® US-sourced, after a single-dose administered intramuscularly in healthy subjects.
* To estimate the intra-subject variability of Risperdal® Consta® US-sourced pharmacokinetics after twice a single 12.5 mg dose, administered intramuscularly in healthy subjects.
* To estimate the intra-subject variability of the Risperdal® Consta® US-sourced pharmacokinetics after a single 12.5 mg dose and the Risperdal® Consta® EU-sourced pharmacokinetics after a single 12.5 mg dose, administered intramuscularly in healthy subjects.

Secondary objective:
* To assess the safety and tolerability of different long-acting risperidone injection products.

Study design

This study is an open label, randomized, two-way cross over study with a washout of at least 10 weeks between subsequent intramuscular (IM) administrations. These administrations will be preceded by multiple dose administration of 1 mg risperidone for 3 days to determine individual tolerability to risperidone (Phase I, extended screening phase), at least two weeks prior to the first intramuscular administration (Phase II).

This study consists of two phases: during Phase I, which is an extended screening phase, subjects* tolerability to risperidone is determined; sufficient subjects (55) will be administered risperidone orally. During Phase II, two cohorts of 24 subjects each will start their two way cross-over part of the study and will be administered risperidone intramuscularly.

Phase I, extended screening phase to determine subjects* tolerability to 3 mg risperidone as an oral administration
Phase I is considered an extended screening phase. Subjects who do not tolerate this dose are not considered drop outs, rather screen failures.
Subjects will start this phase of the study to assess how well they tolerate multiple oral doses of 1 mg risperidone (immediate release formulation) once daily for 3 days. The CYP2D6 genotype will be determined to estimate the metabolic rate. They will come to the study center on the day before the first dosing (Day -1) for baseline assessments and to (re*) confirm eligibility. In the mornings of Day 1, 2 and 3, all subjects will receive an oral dose of 1 mg risperidone. Adverse events and vital signs will be recorded throughout this phase of the study. No pharmacokinetic samples will be collected. They will be discharged from the study center after at least 48 h after the last dosing and when medically justified.
Only those subjects, who tolerated this dose regimen well according to the principal investigator, will proceed to the next phase of the study.

Phase II, intramuscular administration of risperidone long-acting (Risperdal® Consta®)
After a wash-out period of at least two weeks after Phase I, two cohorts of 24 subjects each, will start their two way cross-over part of the study. All subjects of both cohorts will have the same schedule of assessments. Subjects will return to the clinic on the day before the first intramuscular dosing of Risperdal® Consta® (Day -1). After eligibility is (re)confirmed, the appropriate dose of Risperdal® Consta® (Treatment A or B) is given in the morning of Day 1 of Period 1. Confinement is scheduled till the morning of Day 3. Another confinement period is scheduled from the afternoon/evening of Day 22 till the morning of Day 35. Ambulatory visits for collecting PK samples and assessing safety and tolerability are scheduled for the mornings (at the same time as dosing) of Days 8, 12, 15, 18, 21, 36, 37, 39, 41, 44, 48, 52, 56, 63 and 70. Should safety or tolerability be a concern, subjects can be confined in

the study center any time during this period. Confinement itself will not be considered a Serious Adverse Event. At least 10 weeks after the first IM dosing, subjects will receive their second IM dosing with the other Treatment in Period 2 (= Day 1 of Period 2) for which they follow the same schedule of assessments as for Period 1. After the last blood sample taken on Day 70 of Period 2 or at early discontinuation, subjects will be subjected to an End*of* study examination.

Intervention

The study will start with phase 1, an extended screening phase to determine subjects' tolerance to multiple oral doses of 1 mg risperidone (immediate release formulation) once daily for 3 days. During the screening phase standard medical assessments including safety laboratory tests (blood draw, urine collection), an alcohol breath test, urine drug screen, a physical examination, ECG, vital signs, orthostatic challenge test, a questionnaire assessing suicidal ideation and suicidal behaviour, an assessment of drug-induced movement disorders by using the Extrapyramidal Symptom Rating Scale (ESRS) and a psychiatric measurement will be performed. Also a cognitive function questionnaire will be done (MMSE).
After the subject passes all above mentioned tests and the subject tolerates the multiple oral doses of 1 mg risperidone once daily for 3 days, the subject will be enrolled in phase 2 (intramuscular administration of risperidone long-acting formulation). During study, the subjects will enter the clinic and will receive Risperdal® Consta® during 2 periods. They will be asked on a regular basis for possible side effects, blood will be drawn for safety, prolactin measurements and PK measurements. ECG and vital signs will be checked regularly during the confinement periods and C-SSRS and ESRS will be filled out at regular intervals.
Finally an end of study visit will be performed. During this visit standard medical assessments including safety laboratory tests (blood draw, urine collection), blood draw for prolactin measurements, an alcohol breath test, urine drug screen, a physical examination, ECG, vital signs, and C-SSRS and ESRS will be performed.

Study burden and risks

Compounds that contain risperidone (oral and intramuscular formulations) have been previously tested in humans and were generally well tolerated. A number of side-effects, possibly linked to use of the study drug, were reported. The most common side-effects of Risperdal® tablets included insomnia, a disturbance in the movement patter similar to Parkinson*s disease, sleepiness, headache, pneumonia, infection of the chest (bronchitis), common cold, infection of the nasal cavity and sinuses, urine tract infection, ear infection, flu-like symptoms, swelling of the breasts, erection problems, decreased sexual desire or other sexual dysfunction, breast discomfort, leaking of milk from the

breasts, missed period or other problems with the menstrual cycle or fertility problems, weight increase, increased appetite, decreased appetite, irritability, depression, anxiety, restlessness, involuntary muscle movements (dystonia and dyskinesia), dizziness, shaking, blurred vision, eye infection, conjunctivitis, rapid pulse, increased blood pressure, dyspnea, sore throat, coughing, nose bleeding, nasal congestion, stomach pain, stomach discomfort, vomiting, nausea, obstipation, diarrhea, digestion problems, dry mouth, tooth ache, rash, red skin, muscle cramps, musculoskeletal pain, back pain, joint pain, urine incontinentia, swollen body, puffy arms or legs, fever, chest pain, weakness, fatigue, pain, and falling down.

The most common side-effects of Risperdal® Consta® injections included common cold, insomnia, depression, anxiety, a disturbance in the movement patter similar to Parkinson*s disease, headache, pneumonia, infection of the chest (bronchitis), infection of the nasal cavity and sinuses, urine tract infection, flu-like symptoms, anemia, erection problems, decreased sexual desire or other sexual dysfunction, breast discomfort, leaking of milk from the breasts, missed period or other problems with the menstrual cycle or fertility problems, high sugar levels in the blood, weight increase, weight decrease, increased appetite, decreased appetite, sleepiness, involuntary muscle movements (dystonia and dyskinesia), dizziness, shaking, blurred vision, rapid pulse, decreased blood pressure, chestpain, stomach pain, stomach discomfort, vomiting, nausea, stomach or intestinal infection, dry mouth, tooth pain, rash, muscle cramps, musculoskeletal pain, back pain, joint pain, urine incontinentia, swollen body, puffy arms or legs, fever, weakness, fatigue, injection site reaction, and falling down.

Side-effects of Risperdal® Consta® can occur later on, because this drug acts after a *pause* of 3 weeks.

The dose levels are selected on the basis of research results in animals and humans. The risk to health at these dose levels is limited but the subjects mmay experience one of the above mentioned side-effects or other symptoms not previously reported. Their health will be closely monitored during the trial to minimize these risks. Volunteers will be kept in-house for medical monitoring during oral tolerance determination (phase 1), several days after the intramuscular injections and a fairly long period of time around the expected Tmax.

The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally, fainting, bleeding or an infection at the blood sampling site can occur.

The injection side can be sensitive the first couple of days and may be red or swollen and feel somewhat hard.

Contacts

Public
TEVA Pharma

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NL
Scientific
TEVA Pharma

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Haarlem 2031 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Healthy male or non-pregnant, non-breastfeeding female subject, aged between 18 and 64 years of age (inclusive) with a minimum weight of 50 kg and BMI *18 kg/m2 and * 30 kg/m2.
* Not a poor metabolizer for CYP2D6.
* No signs of orthostatic hypotension.
* Demonstrated tolerability to oral risperidone in the extended screening phase.

Exclusion criteria

1. Subject shows clinically significant abnormalities in physical examination, vital signs, 12-lead ECG, or clinical laboratory parameters according to the Investigator*s judgment.
2. Subject who is a poor metabolizer for CYP2D6.

3. Subject has a medical history of allergies including hypersensitivity or idiosyncratic reaction against drug or any of its ingredients or any drug substances with similar activity or clinically significant allergies, incl. asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.
4. Subject has a medical history or presence of clinically significant abnormalities of hepatic, renal, respiratory system, endocrine system, nervous system, immune system, hematologic, psychiatric, cardiovascular system, cancer or has a history of cancer.
5. Subject has a QTc (Bazett and Fridericia) prolongation greater than or equal to 440 ms, or has significant electrocardiogram (ECG) abnormalities.
6. Subject has a known history or presence of stroke or cardiovascular disease, including heart failure, hypertension, hypotension, cardiac arrhythmias, myocardial infarction, percutaneous coronary intervention, coronary-artery bypass grafting, unstable angina, or thrombotic thrombocytopenic purpura.
7. Subject has known history or presence of involuntary movements of the tongue, mouth, face, or limbs.
8. Subject has a known history or presence of schizophrenia, manic or bipolar disorder, dementia, parkinsonism, any disorder involving falls or postural instability, Neuroleptic Malignant Syndrome (NMS), developmental disorder, autism, mental retardation, tic or movement disorder, or suicidal thoughts.
9. Subject has a history of seizures or other conditions that potentially lower the seizure threshold.
10. Subject has diabetes mellitus or impaired glucose tolerance.
11. Subject has presence of excessive hair, bruises, scars, or tattoo around the injection area (gluteal muscle).
12. Subject smokes more than 5 cigarettes or equivalents per day as per history taken.
13. Subject is unwilling or unable to refrain from smoking while in the clinical research unit.
14. Subject shows positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibodies (anti-HCV), or human immunodeficiency virus (HIV) I/II antibodies and antigen tests.
15. Subject has a supine SBP < 90mmHg or supine SBP > 140mmHg, or supine DBP < 55mmHg or supine DBP > 90mmHg, or Pulse rate > 100 per/min.
16. Subject has signs of orthostatic hypotension.
17. Subject scored *yes* on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or *yes* on any item of the Suicidal Behavior section, except for the *Non-Suicidal Self-Injurious Behavior* (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years).
18. Subject has used any prescription drug or herbal medicine within 14 days, OTC or vitamin supplements within 7 days prior to Day 1 of Phase I until the last PK sample in Phase II, period 2.
19. Subject participated in a previous clinical trial with administered IMP within 30 days prior to Day 1 of the oral dosing period.
20. Subject is a heavy alcohol consumer (alcohol > 23 units/week for males and > 13 units/week for females) or cannot stop drinking while in the clinical research unit.
21. Subject lost a volume of blood, including through blood donation, of more than 400 mL during the last 30 days prior to start of this study.
22. Subject is unwilling or unable to adhere to any specific protocol restriction as mentioned in Section 8.3.3 of this protocol.
23. Subject does not tolerate venipuncture or has a history of difficulty with donating blood.

24. For females: Subject is currently pregnant, breast feeding, or disagrees to avoid getting pregnant during the clinical study or in the 90 days following the treatment discontinuation.
25. Male subject who plans to father a child during the course of the study or in the 90 days following the treatment discontinuation.
26. Subject is legally incapable or has limited legal capacity at screening.
27. Subject used any anti-psychotic or psychiatric medication in the past with the exception of incidental use of sedatives for sleep.
28. Creatinine clearance (CrCl) < 80 mL / min. Obtained from the clinical laboratory tests performed at screening. CrCl can be estimated using the following equation: CrCl = [[140 - age(yr)]*weight(kg)]*[0.85 if female]/[serum Cr(mg/dL)*72].

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2016
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Risperdal®
Generic name:	risperidone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Risperdal® Consta® (EU sourced)
Generic name:	risperidone

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Risperdal® Consta® (US sourced)
Generic name:	risperidone

Ethics review

Approved WMO Date:	21-12-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-004428-78-NL
CCMO	NL55433.056.15