SINGLE-CENTER, OPEN-LABEL STUDY INVESTIGATING THE EXCRETION BALANCE, PHARMACOKINETICS AND METABOLISM OF A SINGLE ORAL DOSE OF [14C]-LABELED RO4917523 AND AN INTRAVENOUS TRACER DOSE OF [13C]-LABELED RO4917523 IN HEALTHY MALE VOLUNTEERS

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Following an oral dose of 1 mg [14C]-labeled RO4917523 of 2.22 MBq (60uCi) and an intravenous tracer dose of 0.1 mg [13C]-labeled RO4917523:Primary:To characterize the mass balance, metabolism routes and rates of elimination of [14C]-labeled...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON35686

Source
ToetsingOnline

Brief title
RO4917523 ADME study

Condition

- Mood disorders and disturbances NEC

Synonym
anxiety, depressive disorders

Research involving
Human

Sponsors and support

Primary sponsor: F Hoffmann-La Roche Ltd
Source(s) of monetary or material Support: Farmaceutische industrie.

Intervention

Keyword: ADME, ernstige depressie, Fragiele-X-Syndroom, RO4917523

Outcome measures

Primary outcome

safety

tolerability

absorption, distribution, metabolizing and elimination

Secondary outcome

N.a.

Study description

Background summary

The study medication to be given, RO4917523, is a new investigational compound that may eventually be used as a treatment to be added to the treatments usually prescribed for Major Depressive Disorder and Fragile X Syndrome. Major Depressive Disorder is a mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem and by loss of interest or pleasure in normally enjoyable activities. Fragile X Syndrome represents the most common inherited cause of mental retardation. It is characterized by mental handicap and behavior resembling autism and it is frequently associated with certain facial characteristics. The study medication is still under development. The study medication is thought to block a certain protein (receptor), a subclass of the metabotropic glutamate (mGlu) receptors in the brain. This receptor is

thought to play a role in anxiety and depressive disorders and in certain symptoms of the Fragile X Syndrome. This new compound is not registered as a drug but has been given to 237 healthy subjects and 62 patients before.

Study objective

Following an oral dose of 1 mg [14C]-labeled RO4917523 of 2.22 MBq (60uCi) and an intravenous tracer dose of 0.1 mg [13C]-labeled RO4917523:

Primary:
To characterize the mass balance, metabolism routes and rates of elimination of [14C]-labeled RO4917523
to determine plasma concentration of RO4917523, total drug related radioactivity and related pharmacokinetic parameters after oral administration of RO4917523, using conventional analytical methods and AMS if necessary

Secondary:
To identify and quantify circulating and excreted metabolites of RO4917523 in plasma, urine and fecal samples based on radioactive metabolic profiling, using conventional analytical methods and AMS if necessary.
to determine the absolute oral bioavailability and further characterize the PK of RO4917523 using a stable isotope technique

Study design

Design:
a non-randomized, open-label ADME study in six healthy male subjects receiving a single oral dose of [12C/14C]-RO4917523 as capsule, containing approximately 2.22 MBq radiocarbon, followed by a 30 min intravenous microdose of [13C]-RO4917523

Procedures and assessments:
Screening and follow-up:
Clinical laboratory (including TSH and T4), physical examination, weight, 12-lead ECG; at eligibility screening: medical history, C-SSRS, temperature, height, alcohol breath test, drug screen, urine cotinine test, psychiatric assessment on psychiatric condition,HBsAg, anti HCV, anti-HIV 1/2; brief physical examination, clinical laboratory, vital signs, 12-lead ECG, alcohol breath test, drug screen and cotinine test to be repeated upon admission

Observation period:
In clinic from -17 h up to 312 h (Day 14) after drug administration with a possible extension to Day 18 release criteria are not met, and 24 h visits on Days 25-26, 32-33, 39-40, 46-47, 53-54, 60-61, and 67-68 ; subjects will meet the release criteria once the cumulative total radioactivity in urine and faeces excreted is less than 1% of administered dose within 24 h

Blood sampling:
For pharmacokinetics of RO4917523 and its metabolites in plasma: pre-dose and 30, 35, 40, 45, 50, 55 min, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 168 (Day 8), 216 (Day 10), 264 (Day 12) and 312 h (Day 14) post-dose
for total radioactivity: pre-dose and 30, 35, 40, 45, 50, 55 min, 1, 1.5, 2, 4, 6, 6, 8, 10, 12, 24, 48, 72, 96, 120, 168, 216 and 312 h post-dose and then every 24 h until the release criteria are met
for metabolic profiling: predose and 2, 4, 8, and 24h post dose
for genotyping: once on day 1

Urine sampling:
For pharmacokinetics of RO4917523, total radioactivity and metabolic profiling: pre-dose and intervals 0-12, 12-24 h post-dose and thereafter 24 h intervals until the release criteria are met

Faeces sampling:
For total radioactivity and metabolic profiling: pre-dose and 24 h intervals until the release criteria are met

vomitus collection: if subject spontaneously vomits within 4 hours after the oral dose, vomitus will be collected and analyzed for total radioactivity

Safety assessments:
Adverse events: throughout the study; vital signs and 12-lead ECG: pre-dose and 1, 5, 10, 24 and 48 h post-dose and once on the day of discharge; clinical laboratory: once on Day 10; brief physical examination: once on the day of discharge; C-SSRS: 48 h post-dose
contnuous cardiac monitoring: 15 min before iv administration until 15 min after iv administration is completed
Bioanalysis:
Analysis of plasma and urine RO4917523 and its metabolites samples using a LC/MS-MS method by Sponsor
analysis of total radioactivity in plasma, urine and faeces using validated methods by PRA
Metabolic profiling by Sponsor

Intervention

Treatment
A single oral dose of 1 mg [12C/14C]-RO4917523 as capsule, containing approximately 2.22 MBq radiocarbon, followed by a 30 min intravenous microdose of 100 µg [13C]-RO4917523

Study medication
Active substance: RO4917523
Activity: potent metabotropic glutamate 5 (mGlu5) receptor antagonist
Indication: serious Depression (TRD) and Fragile X Syndrome

Strength: unknown
Dosage form: capsule and iv infusion

Study burden and risks

To date, 8 studies testing the study medication have been carried out in healthy volunteers and 2 studies in patients with Fragile X Syndrome and Treatment-Resistant Depression (a subclass of Major Depressive Disorder). From a total of 359 individuals who participated in these studies, 295 received the study medication: 163 received single oral doses of 0.25 to 2 2 milligrams and 132 subjects received multiple doses of 0.1 to 2 milligrams; 64 received placebo (drug without active ingredient).

In the previous studies conducted in healthy volunteers, the study medication was safe and generally well tolerated. The most common adverse events were linked to the central nervous system (dizziness, somnolence, reduced sense of touch), or were psychiatric disorders (hallucinations, paranoia, psychotic episode, acute state of anxiety) and gastrointestinal disorders (mostly nausea).
Two serious adverse events have been reported by 2 subjects on the study medication: 1 subject with acute psychotic state and 1 subject with mania with suicidal ideation

Ten subjects were withdrawn because of adverse events related to the study medication: 1 subject with acute psychotic state mentioned in the preceding paragraph, 1 subject with mania with suicidal ideation, 1 subject with acute state of anxiety, 1 subject with insomnia and nightmares, 1 subject with severe headache, 4 subjects with elevated liver enzymes and 1 subject with slowing down of cardiac conduction.

With the dose(s) used in this study no serious adverse effects are expected. However, the possibility that any of the above-mentioned or other adverse effects could occur cannot be excluded. The adverse events one may expect to occur are described above. However, you should take into account that some risks are still unknown at this moment. Should information become available from current studies elsewhere, you will be informed immediately. You can then decide to continue with your participation in the study.

Procedures: pain, light bleeding, haematoma, possibly an infection

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age: 18 - 65 years (inclusive)
BMI: 18.0 - 32.0 kg/m2 (inclusive)
Gender: healthy male subjects

Exclusion criteria

Suffering from: hepatitus B, cancer or HIV/AIDS. In case of participation in another study within 60 days before the start of this study or being a blood donor within 90 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior to the start of this study.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-01-2012
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	03-01-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	27-03-2012
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	EUCTR2011-004597-28-NL
CCMO	NL38794.056.11