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Pharmacokinetics of terguride in healthy subjects with known CYP2D6 genotype

Submission date
24/02/2016

Recruitment status
No longer recruiting

Registration date
01/04/2016

Overall study status
Completed

Last Edited
09/06/2016

Condition category
Genetic Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Terguride is a type of drug which blocks the action of a chemical messenger in the brain (neurotransmitter) called serotonin. It has been approved for treating a number of conditions in Japan and was approved for use in the Czech Republic until 2008. This study is being carried out to find out how much terguride is in the urine and blood after a healthy person has taken it, and to look at the effects of food and another drug called itraconazole (an anti-fungal medication) on its concentration. In the body, terguride is broken down (metabolized) by a chemical (enzyme) in the liver called CYP2D6. There has been found to be a lot of variation in the efficiency of this enzyme and the amount produced in different people, which is determined by genes (genotypes). Some people are able to metabolize terguride very quickly (ultrarapid metabolizers, UMs), while others slowly (poor metabolizers, PMs). Between these two extremes are intermediate metabolizers (IMs) and extensive metabolizers (EMs). The aim of this study is to look at the way that terguride is processed by healthy adults with all of these genotypes, the effects of itraconazole on terguride metabolism in those with PM and EM genotypes, and the effects of food on people with EM genotypes.

Who can participate?
Healthy adults of either sex.

What does the study involve?
The study is made up of three different parts. In the first part of the study, all participants are given four single doses of terguride, increasing in strength on study days 1, 3, 5 and 7 (ending in maximum doses of 0.75 mg, 1.5 mg, 2.5 mg and 3.0 mg in PM, IM, EM, and UM patients respectively). In the second part of the study, participants with the genotype PM, and half of the participants with the genotype EM are given doses of terguride (at one dose lower than the best level for them as determined in part one) twice a day over two days. After this, participants also receive itraconazole twice a day for two days (alone) and then a single dose of itraconazole with a single dose of terguride.In the third part of the study, the other half of the participants with the genotype EM are randomly allocated to one of two groups. Participants in both groups receive a single dose of terguride (the best level for them as determined in part one). Those in the first group are given the dose after they have eaten a meal and those in the second group are given the dose when they have not eaten anything. After this, the dosing will be repeated

but with the group who had eaten having not eaten and those having not eaten having eaten. In all parts, after receiving each dose, blood and urine samples are taken so that the amount of terguride in the body can be tested. In part the first part of the study, participants all have an ECG (a test where the electrical activity of the heart is measure through sensors placed on the skin) to measure their heart rate.

What are the possible benefits and risks of participating?
There are no direct benefits to those taking part in this study, although participants will undergo a range of tests which could help them to learn more about their general health. Risks of participating involve the chance of developing side-effects to the study drug and the possibility of pain or bruising during blood tests.

Where is the study run from?
Celerion Research Phase I Unit, Belfast (UK)

When is the study starting and how long is it expected to run for?
September 2015 to October 2016

Who is funding the study?
medac GmbH (Germany)

Who is the main contact?
Dr Elena Osswald

Contact information

Type(s)
Scientific

Contact name
Dr Elena Osswald

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22880

Additional identifiers

Clinical Trials Information System (CTIS)
2015-003729-33

Protocol serial number
MC-TER.3/PK

Study information

Scientific Title

A phase 1, open-label trial to evaluate the effects of single and multiple doses, CYP3A4 inhibition, and food on the pharmacokinetics of terguride in healthy subjects with known CYP2D6 genotypes

Study objectives
The aim of this study will investigate the CYP2D6 dependency of terguride pharmacokinetics by inclusion of four groups of healthy subjects with known CYP2D6 genotype, i.e. PM, IM, EM, and UM.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Riverside Research Ethics Committee, 04/01/2016, ref: 15/LO/1987

Study design
Single-centre randomized three-part open-label phase 1 study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
CYP2D6 genotype

Interventions
The study takes place in three parts. Administered doses will depend on genotype and tolerability by the subject. Initial doses in Part 1 are 0.75 mg, 1.5 mg, 2.5 mg and 3.0 mg terguride in PM, IM, EM, and UM subjects, respectively. Doses administered in Part 2 and Part 3 will be based on well-tolerated individual dose, determined in Part 1 of the study.
Total duration of treatment for UM and IM subject is 7 days (drug to be administered every second day).
Total duration of treatment for PM subjects is 18 days (terguride to be administered on 7 days, itraconazole 200 mg BID to be administered on 3 days) with wash-out days in between.
Total duration of treatment for EM subjects is depending on randomisation:
1. 18 days (terguride to be administered on 7 days, itraconazole 200 mg BID to be administered on 3 days) with wash-out days in between or
2. 13 days (terguride to be administered on 6 days) with wash-out days in between.
Follow-up will be performed for all subjects 14 days after the last study drug administration.

Part 1 will be conducted as a 4-period dose titration. All subjects will participate in Part 1 of the study which will be composed of 4 groups defined by their CYP2D6 metabolic status (i.e., PM, IM, EM, and UM). On Study Days 1, 3, 5, and 7, single oral ascending doses of terguride will be administered followed by blood and urine sampling for PK and PD assessments. Cardiodynamic sampling will also be conducted following each dosing. Dose escalation will be performed depending on tolerability of the previous dose.

Part 2 will be conducted as a 2-group, 2-period, fixed sequence study. All PM subjects will continue to Part 2 of the study. EM subjects will continue in either Part 2 or Part 3 as per the

randomization schedule. In Period 1, multiple oral doses of terguride (at one dose level lower than the well-tolerated single dose level determined in Part 1) will be administered TID for 2 consecutive days (Study Days 10 and 11), with a single dose administered on the morning of Study Day 12. In Period 2, oral doses of itraconazole will be administered twice daily (BID) for 2 consecutive days (Study Days 15 and 16). In the morning of Study Day 17, a single dose of itraconazole will be coadministered with a single oral dose of terguride.

Part 3 will be conducted as a 1-group, 2-period, 2-way crossover study. 12 EM subjects will participate in Part 3. On Study Days 10 (Period 1) and 12 (Period 2) a single oral dose of terguride (at the well-tolerated single dose level determined in Part 1) will be administered under either fasting or fed conditions or vice versa as per the randomization schedule.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Terguride

Primary outcome(s)
Maximum concentration (Cmax) and area under the plasma concentration curve (AUC) of terguride is measured using blood analysis and uranlysis:
Part one: Study days 1, 3, 5, and 7
Part two: Study days 12 and 17
Part three: Study days 10 and 12

Key secondary outcome(s))
1. Cmax and AUC of N'-monodesethyl-terguride, measured using blood analysis and uranlysis:
Part one: Study days 1, 3, 5, and 7
Part two: Study days 12 and 17
Part three: Study days 10 and 12
2. Heart rate-corrected QT interval (QTcF) determined using EEG scanning in part one only, on study days 1, 3, 5, and 7

Completion date
06/05/2016

Eligibility

Key inclusion criteria
1. Medically healthy adults
2. Aged between 18-60 years inclusive at the time of screening
3. Non-smoker
4. Body mass index (BMI) ≥ 18.5 and ≤ 30.0 kg/m2 at screening
5. Known CYP2D6 genotype
6. No clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the PI
7. Appropriate contraception
8. Able to swallow multiple capsules and/or tablets

9. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
60 years

Sex
All

Key exclusion criteria
1. Mentally or legally incapacity
2. History or presence of clinically significant medical or psychiatric condition or disease
3. Alcoholism or drug abuse within the past 2 years
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug, itraconazole, metoclopramide (MCP) or related compounds
6. Female subjects who are pregnant or lactating
7. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antihepatitis C virus (antiHCV) antibodies screen
8. QTcF interval is >450 msec (males) or >470 msec (females) or clinically significant ECG findings at screening
9. Creatinine clearance < 80 mL/min
10. Drugs / herbals known to be significant inducers of CYP enzymes and/or P-gp
11. Diet incompatible with the on-study diet, lactose intolerance
12. Major surgery within 60 days prior to the first dose of study drug and throughout the study
13. Donation of blood or plasma within 90 days prior to the first dose of study drug
14. Donation of bone marrow within the last 6 months prior to the first dose of study drug
15. Participation in another clinical trial within 90 days prior to the first dose of study drug

Date of first enrolment
02/02/2016

Date of final enrolment
30/04/2016

Locations

Countries of recruitment
United Kingdom

Northern Ireland

Study participating centre
Celerion Research Phase I Unit
22-24 Lisburn Road
Belfast
United Kingdom
BT9 6AD

Sponsor information

Organisation
medac GmbH

ROR
https://ror.org/05e0gzh77

Funder(s)

Funder type
Industry

Funder Name
medac GmbH

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No