A Phase I, drug-drug interaction study between oral doses of GLPG1205 and an OCT2 probe substrate (metformin) or a BCRP probe substrate (rosuvastatin) in healthy male subjects

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PrimaryTo assess the effect of GLPG1205 on the single dose pharmacokinetics (PK) of an OCT2 probe substrate, metformin, in healthy male subjects.To assess the effect of GLPG1205 on the single dose pharmacokinetics (PK) of a BCRP probe substrate,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON44647

Source
ToetsingOnline

Brief title
GLPG1205-CL-104 (CS0286)

Condition

- Peripheral neuropathies

Synonym
inflammation induced pain, nociceptive pain, sensitization induced pain

Research involving
Human

Sponsors and support

Primary sponsor: Galapagos NV
Source(s) of monetary or material Support: Galapagos NV

Intervention

Keyword: Drug-drug interaction, Pharmacokinetics

Outcome measures

Primary outcome

GLPG1205, Metformin and Rosuvastatin PK

Secondary outcome

Safety and tolerability

Study description

Background summary

The potential of GLPG1205 to inhibit key transporters was investigated in vitro using different assays and probe substrates. Inhibition of human efflux transporters (P-glycoprotein, and breast cancer resistance protein (BCRP)) and uptake transporters (organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3, organic cation transporter (OCT) 1 and OCT2, organic anion transporter (OAT) 1 and OAT3) was assessed in presence of GLPG1205 at concentrations up to 75 µM (i.e. 28.4 µg/mL). No significant inhibition of OAT1 by GLPG1205 was observed at concentrations up to 75 µM. In vitro inhibition by GLPG1205 of P-glycoprotein, BCRP, OATP1B1/B3, OAT3, OCT1 and OCT2 was observed with IC50 values ranging from 0.25 (BCRP) to 43.4 µM (P-glycoprotein) which are below up to 4.2-fold the total Cmax value (3.91 µg/mL) in humans at a dose of 100 mg GLPG1205 q.d. Consequently, GLPG1205 dosed at 100 mg q.d. may potentially interact with drugs, in particular those known to be OCT2 and BCRP substrates. To confirm the relevance of these findings in a clinical setting, a Phase I study in healthy subjects administered with metformin (OCT2) or rosuvastatin (BCRP) and GLPG1205 is deemed appropriate. Both metformin and rosuvastatin are recognized substrates for OCT2 and BCRP respectively as documented in e.g. the FDA guideline on Drug Interaction Studies. The study is an open label parallel group study, run in 2 cohorts. In cohort 1, on Day 1 and Day 12, subjects will receive a single dose of 850 mg metformin as OCT2 probe substrate with and without GLPG1205. In cohort 2, on Day 1 and Day 12, subjects will receive a

single dose of 20 mg rosuvastatin as BCRP probe substrate with and without GLPG1205. All subjects will receive a loading dose of 500mg of GLPG1205 on Day 9 followed by a daily dose of 100mg GLPG1205 from Day 10 until Day 14. Covariates that may impact GLPG1205 disposition are currently not known. Thus, to minimize the variability that covariates could generate on GLPG1205, metformin/rosuvastatin PK, only healthy male, non-Asian subjects will be included in this drug-drug interaction study.

Study objective

Primary

To assess the effect of GLPG1205 on the single dose pharmacokinetics (PK) of an OCT2 probe substrate, metformin, in healthy male subjects.
To assess the effect of GLPG1205 on the single dose pharmacokinetics (PK) of a BCRP probe substrate, rosuvastatin, in healthy male subjects.

Secondary

To evaluate the safety and tolerability of GLPG1205 administered with and without transporter substrates in healthy male subjects.

Study design

This study is a Phase I, open-label, single-center, parallel-group, drug-drug interaction (DDI) study.
The study will be divided in 2 cohorts of 20 healthy male subjects each, eligible based on the inclusion and exclusion criteria.
The study will consist of a screening period of approximately 3 weeks, a dosing period of 15 days and a Follow-up visit approximately 21 days after last intake of study drug.
After assessing eligibility during the screening period, 40 healthy male subjects will participate in the study. Reconfirmation of eligibility will be assessed pre-dose on Day 1. For the dosing part, subjects will come to the clinic on the day before first administration of study drug (Day -1). Subjects will remain in the clinic until finalization of Day 2 study procedures and for 3 additional days from the evening of Day 11 until finalization of Day 13 study procedures. Subjects will be asked to come to the clinic for ambulatory visits in the morning of Day 3, 4, 9, 10, 11, 14 and 15, as specified in the study flow chart (see protocol Section 1).
Subjects will be divided into 2 cohorts of 20 subjects each. In cohort 1, subjects will receive 850 mg metformin as OCT2 probe substrate with and without GLPG1205. In cohort 2, subjects will receive 20 mg rosuvastatin as BCRP probe substrate with and without GLPG1205. The dosing period for each cohort will consist of 3 different administrations of either probe substrate

(metformin/rosuvastatin) or GLPG1205 or both (see protocol Section 1, Table 4-1 and Table 4-2).
Safety and tolerability will be assessed throughout the study by vital signs, 12-lead ECG, fasting laboratory safety tests and adverse events (AEs) questioning and management.

Intervention

GLPG1205, Metformin and Rosuvastatin administration

Study burden and risks

The dose levels of the study drugs are based on the previous clinical trials that were conducted by the sponsor. The risk to health at the chosen dosage is limited but subjects may experience one of the in the ICF mentioned side-effects or symptoms not previously reported. The subjects health will be closely monitored during the study to minimize these risks. If the subjects experience any side effects, the research physician will treat these where necessary. If new information becomes available about the safety of the study drug, the subjects will be informed as soon as possible.

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.

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

1. Subject has signed the informed consent form prior to any study related activity.
2. Subject is a healthy male volunteer between 18 and 50 years of age (inclusive) at the time of informed consent signature.
3. Subject has a BMI equal to or higher than 18.0 kg/m2 and equal to or lower than 30.0 kglm2 at the screening
4. Subject is appropriate for the study in the judgment of the investigator, based on physical examination, 12-lead electrocardiogram (ECG), laboratory tests, and subject's interview.
5. Subject has a high probability for compliance with and completion of the study.
6. Discontinuation of all medications (including over-the-counter medications, vitamin and herbal supplements) with the exception of occasional paracetamol (maximum dose of 2 g/day and maximum 10 g/2 weeks) at least 3 weeks, or 5 half-lives of the drug, whichever is longer, prior to the first study drug administration.
7. A non-smoker and not using any nicotine-containing products for at least 1 year prior to the study screening.
8. Negative tests for drug screen (amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, and opiates), alcohol screen, and cotinine screen.
9. Subject agrees that he will use a condom and that in addition to that he (and his female partner of child-bearing potential) will use a highly effective method of contraception and will not donate sperm from the first study drug administration to 12 weeks after the last study drug administration.

Exclusion criteria

1. Subject shows clinically significant abnormalities in Screening, Day -1 or Day 1 physical examination, ECG or vital signs, according to the investigator*s judgment.
2. Subject has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases.
3. History of malignancy in the last 5 years, except basal cell carcinoma of the skin that has been treated and with no evidence of recurrence.
4. Subject has been exposed to GLPG1205 before.

5. Known hypersensitivity to GLPG1205 or excipients of the formulation, metformin, biguanides or rosuvastatin. A history of significant allergic reaction to any drug, such as anaphylaxis requiring hospitalization.
6. Having a contraindication as indicated in the respective Summary of Product Characteristics (or Package Leaflets) for metformin or rosuvastatin.
7. Subject is of Asian origin.
8. Subject had major surgery, donated or lost 1 unit of blood or plasma (approximately 500 mL) within 6 weeks prior to the first intake of the study drug.
9. Subject has participated in another investigational trial within 90 days prior to the first intake of the study drug in this study.
10. Subject has used any type of medication (including herbal medicine and vitamin supplements) within 3 weeks prior to the first intake of the study drug.
11. Clinically significant illness in the 12 weeks prior to study dosing, including severe vomiting or diarrhoea.
12. Presence or having sequelae of GI, liver or kidney (creatinine clearance * 90 mL/min using the Cockcroft formula) or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
13. Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff or relative thereof who is directly involved in the conduct of the study.
14. Any history of vitamin B12 deficiency.
15. Clinically significant abnormalities detected on laboratory safety testing during Screening or Day -1, including (but not limited to):
a. Hemoglobin < 10 g/dL
b. WBC count < 3.0 x 10^9 cells/L
c. Neutrophil count < 1.5 x 10^9 cells/L
d. Platelet count < 100 x 10^9 cells/L
e. Serum ALT or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN)
f. Total bilirubin level > 1.5 x ULN, except in the case of documented Gilbert*s syndrome
16. Subject has a positive urinary drug screen during Screening or Day -1 (incl. amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, morphine, phencyclidine, and tricyclic antidepressants).
17. History of abuse of alcohol or drugs in the last 2 years (alcohol >23 units/week).
18. Subject has a positive test for HIV antibody, HBsAg, or HCV antibody.
19. Subject has a positive alcohol test during Screening or Day -1.
20. Subject consumes more than 5 cups of caffeine containing beverages per day.
21. Clinically significant abnormalities, during Screening or Day -1 on ECG of rhythm or conduction (e.g., QTcF > 450 ms, known long-QT syndrome), excluding first degree heart block.
22. Subject plans to father a child during the course of the 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):	25-09-2017
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CRESTOR
Generic name:	Rosuvastatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Glucophage
Generic name:	Metformin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	12-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	25-09-2017
Application type:	First submission
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	EUCTR2017-000777-36-NL
CCMO	NL63137.056.17