A Phase 1, non-randomized, fixed sequence, open-label, drug-drug interaction study to evaluate the effect of GLPG3970 on the pharmacokinetics of methotrexate and sulfasalazine in adult, healthy subjects

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Primary:To evaluate the effect of GLPG3970 on the pharmacokinetics (PK) of methotrexate (MTX) and its active metabolite 7-hydroxymethotrexate (7-OH MTX) in healthy subjectsTo evaluate the effect of GLPG3970 on the PK of sulfasalazine and its active...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49569

Source
ToetsingOnline

Brief title
GLPG3970 DDI study with methotrexate and sulfasalazine

Condition

- Other condition

Synonym
chronic inflammatory diseases, rheumatoid arthritis

Health condition

chronic inflammatory diseases

Research involving
Human

Sponsors and support

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

Intervention

Keyword: drug-drug interaction, GLPG3970, methotrexate, sulfasalazine

Outcome measures

Primary outcome

MTX and 7-OH MTX PK parameters: maximum observed concentration (Cmax) and area

under the plasma concentration-time curve from time zero to

infinity (AUC0-*)

Sulfasalazine and sulfapyridine PK parameters:

Cmax and AUC0-*

Sulfapyridine to sulfasalazine AUC ratio

Secondary outcome

Safety and tolerability, assessed by the incidence and severity of treatment

emergent adverse events (TEAEs)

Safety and tolerability, assessed by the incidence and severity of TEAEs

GLPG3970 PK parameters such as trough concentrations (Ctrough), Cmax, time of

occurrence of Cmax (tmax), and AUC0-t

Study description

Background summary

GLPG3970 is a new compound that may eventually be used for the treatment of chronic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease. GLPG3970 is an inhibitor (suppressor) of a certain substance called a kinase, which regulates cytokines. Cytokines are signaling substances that regulate the immune response and these kinases play an important role in the production and balance of pro-inflammatory and anti-inflammatory cytokines. GLPG3970 is expected to shift the balance of these cytokines so the immune system starts working better, and the inflammation decreases.

Methotrexate (MTX) and sulfasalazine are common background therapies in RA and IBD and consequently they will be used in future clinical studies with GLPG3970. This clinical study will therefore assess the potential for a drug-drug interaction (DDI) following coadministration of GLPG3970 with these intended concomitant medications.

Study objective

Primary:
To evaluate the effect of GLPG3970 on the pharmacokinetics (PK) of methotrexate (MTX) and its active metabolite 7-hydroxymethotrexate (7-OH MTX) in healthy subjects
To evaluate the effect of GLPG3970 on the PK of sulfasalazine and its active metabolite sulfapyridine in healthy subjects

Secondary:
To evaluate the safety and tolerability of the coadministration of GLPG3970 with MTX in healthy subjects
To evaluate the safety and tolerability of the coadministration of GLPG3970 with sulfasalazine in healthy subjects
To evaluate the PK of GLPG3970 in presence of MTX or sulfasalazine in healthy subjects

Study design

This is a non-randomized, fixed sequence, open-label, drug-drug interaction (DDI) study designed to assess

the impact of concomitant administration of GLPG3970, a potential in vivo breast cancer resistance protein
(BCRP) inhibitor, on the PK of MTX and sulfasalazine, both BCRP substrates.

The study will consist of 2 separate assessments performed in 2 parallel groups.

Group 1 will receive a single oral dose of MTX alone (Period 1), followed by a single oral dose of MTX in
combination with repeated dosing with GLPG3970 (Period 2).

Group 2 will receive a single dose of sulfasalazine alone (Period 1), a single dose of sulfasalazine in
combination with a single dose of GLPG3970 (Period 2), followed by a single dose of sulfasalazine given
2 hours prior to a single dose of GLPG3970 (Period 3).

The study will consist of a screening period of up to 6 weeks, an open-label study period of 11 days for
Group 1 and 14 days for Group 2, and a follow-up (FU) period of 2 weeks following the last investigational
medicinal product (IMP) administration.

Subjects in both groups will be confined to the site during the entire treatment and PK blood collection
periods.

Intervention

Group 1:
Day/ Treatment/ Timing
1) 7.5 mg methotrexate as 3 oral tablets of 2.5 mg
5) 350 mg GLPG3970 as oral solution 7.5 mg methotrexate as 3 oral tablets of 2.5 mg
A maximum of 1 minute between GLPG3970 and methotrexate administration
6-8) 350 mg GLPG3970 as oral solution

Group 2:
Day/ Treatment/ Timing
1) 1000 mg sulfasalazine as 2 oral tablets of 500 mg
5) 350 mg GLPG3970 as oral solution 1000 mg sulfasalazine as 2 oral tablets of 500 mg
A maximum of 1 minute between GLPG3970 and sulfasalazine administration
9) 1000 mg sulfasalazine as 2 oral tablets of 500 mg 350 mg GLPG3970 as oral solution
Sulfasalazine will be administered 2 hours before GLPG3970

Study burden and risks

GLPG3970
The study compound may cause side effects.

A clinical study in which GLPG3970 is administered for the first time in humans is currently ongoing. Overall, no mortalities or other SAEs have been reported to date and an ongoing-blinded review of adverse events (AEs), vital signs, laboratory safety tests, ECG morphology and ECG time intervals indicate that single doses of GLPG3970 up to 500 mg and 14 days repeated once daily doses of GLPG3970 up to 400 mg have been well-tolerated.

The study compound may also have side effects that are still unknown. In addition to unknown side effect, there is a (small) chance that an allergic reaction will occur. This can be caused by the study compound or the excipients.

If during the study more information becomes available regarding side effects that may be related to the study compound, the responsible doctor will inform the volunteer about this.

Methotrexate
Methotrexate is used to treat psoriasis and other inflammatory diseases.

The very common side effects are (>10%): inflammation and ulceration of the mucosa of the mouth and throat (especially during the first 24-48 hours after administration), dyspepsia (indigestion), loss of appetite, abdominal pain, nausea, vomiting, increase in liver enzymes.

The common side effects are (1-10%): diarrhea (especially during the first 24-48 hours after administration), rash, erythema (redness of the skin), pruritus (itch), headache, fatigue, drowsiness, pneumonia, interstitial alveolitis/pneumonitis (inflammation of the lung), leukopenia (decrease in white blood cell count), anemia (decrease in red blood cell count), thrombocytopenia (decrease in blood platelet count).

These side effects are seen in patients who took methotrexate for a longer period of time.

Sulfasalazine
Sulfasalazine can be used for the treatment of Crohn disease (chronic inflammation of the digestive tract, such as the intestines).

The very common side effects are (> 10%): stomach complaints, nausea.

The common side effects are (1-10%): leukopenia (decrease in white blood cell count), decreased appetite, dizziness, headache, taste disturbances, tinnitus, cough, abdominal pain, diarrhea, vomiting, pruritus (itch), purpura (blood spots or skin hemorrhages), arthralgia (joint pain), proteinuria (increase of protein in urine), fever.

These side effects are seen in patients who took sulfasalazine for a longer period of time.

Contacts

Public
Galapagos NV

Generaal De Wittelaan L11 A3
Mechelen 2800
BE
Scientific
Galapagos NV

Generaal De Wittelaan L11 A3
Mechelen 2800
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female Caucasian between 18-55 years of age (extremes included), on the date of signing the informed consent form (ICF).

2. Females should be of non-childbearing potential defined as permanently surgically sterile (bilateral oophorectomy, i.e. surgical removal of ovaries, bilateral salpingectomy or hysterectomy, i.e. surgical removal of uterus), or with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level >35 IU/L. These subjects must also have a negative pregnancy test. For surgical sterilization, documented confirmation will be requested.
3. A body mass index (BMI) between 18-30 kg/m2, inclusive.
4. A BCRP c421C/C genotype.
5. Judged to be in good health by the investigator based upon the results of a medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and fasting clinical laboratory safety tests, available at screening and prior to the first non investigational medicinal product (NIMP) administration. Bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) must be no greater than 1.5x upper limit of normal range (ULN). Other clinical laboratory safety test results must be within the reference ranges or test results that are outside the reference ranges need to be considered not clinically significant in the opinion of the investigator.

Exclusion criteria

1. Known hypersensitivity to the IMP (GLPG3970), or NIMPs (MTX and sulfasalazine), or sulfa drugs, or to their ingredients, or history of a significant allergic reaction to IMP or NIMPs ingredients as determined by the investigator.
2. Positive serology for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus (HCV) or history of hepatitis from any cause with the exception of hepatitis A that was resolved at least 3 months prior to first dosing of the NIMP.
3. History of or a current immunosuppressive condition (e.g. human immunodeficiency virus [HIV]
infection).
4. Having any illness, judged by the investigator as clinically significant, in the 3 months prior to first
dosing of the NIMP.
5. Presence or sequelae of gastrointestinal, liver, kidney (creatinine clearance <=80 mL/min using the
Cockcroft-Gault formula: if calculated result is <=80 mL/min, a 24-hours urine collection can be done) or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
6. Subjects with a N-acetyltransferase (NAT) 2 slow acetylator genotype (only applicable to Group 2
receiving sulfasalazine).

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	27-08-2020
Enrollment:	27
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	sulfasalazine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2020

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2020
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	EUCTR2020-000391-37-NL
CCMO	NL73255.056.20

Study results

Date completed:	08-12-2020
Results posted:	07-05-2021

First publication
22-04-2021