A first-in-human, randomized, double-blind, placebo-controlled, study to evaluate the safety, tolerability, and pharmacokinetics of single ascending oral doses of GLPG4059 in adult, healthy, male subjects.

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Ethical review	Approved WMO
Status	Completed
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON55090

Source
ToetsingOnline

Brief title
GLPG4059 single ascending dose study to investigate safety and PK

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes Type 2

Research involving

Human

Sponsors and support

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

Intervention

Keyword: GLPG4059, Type 2 Diabetes

Outcome measures

Primary outcome

To evaluate the safety and tolerability of single ascending oral doses of

GLPG4059, in adult, healthy, male subjects compared with placebo.

Secondary outcome

To evaluate the pharmacokinetics (PK) of single ascending oral doses of

GLPG4059, in adult, healthy, male subjects.

Study description

Background summary

GLPG4059 is a new compound that may potentially be used for the treatment of type 2 diabetes. People with type 2 diabetes have too much sugar (glucose) in their blood and need medication to control their blood sugar level. GLPG4059 is able to lower blood sugar levels by inhibiting a protein, the so-called Per-Arnt-Sim Kinase (PASK), which is involved in the regulation of sugar levels in the body.

Study objective

This study will be performed in a maximum of 57 healthy male volunteers. The study will be performed in 2 parts, Part 1 and Part 2. Part 1 will consist of a maximum of 6 groups of 8 volunteers each. The volunteers can participate in one of these groups. Part 2 will consist of 1 group of 9 volunteers.

The purpose of this study is to investigate how safe the new compound GLPG4059

is and how well it is tolerated when it is administered to healthy male volunteers. Also, the concentrations of GLPG4059 in blood and urine will be measured (pharmacokinetics). In addition, the effect of food on the pharmacokinetics of GLPG4059 in the body will be investigated (Part 2 only). Also, the pharmacokinetics of 2 formulations (liquid and tablet) of GLPG4059 will be compared with each other. Furthermore, the effect of GLPG4059 on the sugar levels in the blood will be investigated (pharmacodynamics).

GLPG4059 has not been administered to humans before. It has been previously tested in the laboratory and on animals.

GLPG4059 will be given as orally as liquid and tested at various dose levels. In Part 1, the effects of GLPG4059 will be compared to the effects of a placebo. Whether the volunteers will receive GLPG4059 or placebo will be determined by chance.

Study design

For Part 1 the actual study will consist of 1 period during each of the volunteers will stay in the research center for 6 days (5 nights). Day 1 is the day of administration of the study compound. The volunteers are expected at the research center at 11:00 hrs in the morning of Day -1. They will leave the research center on Day 4.

For Part 2 the actual study will consist of 3 periods during each of the volunteers will stay in the research center for 6 days (5 nights). In each period, Day 1 is the day of administration of the study compound. In each period, the volunteers are expected at the research center at 11:00 hrs in the morning of Day -1. In each treatment period, they will leave the research center on Day 4 of each period. There will be at least 7 days between administration of the study compound in each period.

Just before administration of the study compound it will be decided based on the latest test results whether the volunteer is suitable for participation or not. One of the tests that will be done to make a final decision on the eligibility for participation will be a test to detect the presence of the coronavirus. This test will be done upon entry to the research center and is mandatory. Until the test results are available, volunteer will be separated from other volunteers and only have very limited contact with study staff. This is to avoid virus spread from potentially infected volunteers to other volunteers or to the study staff. Until the results are available, it is not certain whether the volunteer is infected or not and can thus potentially infect others. The test results will be available within one hour. If volunteer test positive for coronavirus, he cannot participate in the study.

When volunteer enter the research center 2 samples will be collected at the same time to test if volunteer is a carrier of SARS-CoV-2. This test will be

repeated on the day after dosing (Day 2) and at follow-up. It may be decided that more tests are needed (eg, if volunteer has COVID-19 symptoms).

Intervention

Part 1:
Volunteer will receive a single dose of the study compound in the morning of Day 1 orally as a liquid (between 0.15 and 15 milliliters. The study compound will be administered via a syringe into the mouth. After administration of the study compound, volunteer is required to drink 240 mL of water. The study compound will be administered after volunteer has fasted overnight for at least 10 hours (no eating and drinking except water). Following administration of the study compound, volunteer will fast for a period of 4 hours until the scheduled lunch. During fasting volunteer is allowed to drink water, except during 1 hour before and 1 hour after administration of the study compound (except for the 240 mL water taken with the dose). In each group, 6 volunteers will receive GLPG4059 and 2 volunteers will receive placebo.

For safety reasons, in each group, initially 2 volunteers will receive the study compound. One volunteer will receive GLPG4059, and 1 will receive placebo. After administration, the safety and tolerability of the study compound in these 2 volunteers will be closely monitored. If there are no concerns about the safety and tolerability 48 hours after administration, then the remaining 6 volunteers will receive the study compound (5 will receive GLPG4059 and 1 will receive placebo).

The lowest planned GLPG4059 dose is 15 mg. The GLPG4059 dose levels after Group A can be adjusted based on the results of the previous dose level(s). The maximum dose is expected to be 1000 mg GLPG4059. However, this can be increased depending on the level of GLPG4059 found in the blood after previous dose level(s). There are defined limits of the level of GLPG4059 in the blood that cannot be exceeded. These limits have been defined to ensure volunteer is not exposed to levels of the study compound that had adverse effects in animals. The next dose will only be increased if the lower dose level of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. Furthermore, the expected GLPG4059 blood concentrations of the next dose level should not exceed the predefined limits. The study will be discontinued if, in the opinion of the investigator and/or the Sponsor, unacceptable adverse effects appear.

Part 2:
The study consists of 3 treatment periods. In each treatment period, they will receive a single dose of the study compound in the morning of Day 1 orally as a liquid (1 treatment period) and as a tablet (2 treatment periods). The liquid formulation will be administered via a syringe (without a needle) into the mouth. After administration of the liquid formulation, they are required to drink 240 mL of water. The tablet formulation will be administered with 240 mL

of water.

In 2 of the 3 treatment periods, the study compound (liquid formulation in 1 treatment period and tablet formulation in 1 treatment period) will be administered after they have fasted overnight for at least 10 hours (no eating and drinking except water). Following administration of the study compound, you will fast for a period of 4 hours, until the scheduled lunch. During fasting you are allowed to drink water, except during 1 hour before and 1 hour after administration of the study compound (except for the 240 mL water taken with the dose).

In the other treatment period, the study compound will be administered 30 minutes after the start of a high-fat breakfast with a standard composition. This breakfast must be started exactly on time and must be finished within 20 minutes. Volunteer will have to consume the entire breakfast. The high-fat breakfast will be started after volunteer has fasted overnight for at least 10 hours. Following administration of the study compound, volunteer will fast for a period of 4 hours, until the scheduled lunch. During fasting volunteer is allowed to drink water, except during 1 hour before and 1 hour after administration of the study compound (except for the 240 mL water taken with the dose).

The GLPG4059 dose level to be administered will be the same in the fasted state and after a breakfast. The dose level of GLPG4059 will be selected based on the information obtained in Part 1. The dose will be selected such that the concentrations in the blood will not exceed those observed in Part 1 following doses that were safe and well tolerated. Before administration of the study compound volunteer will be informed about what dose level volunteer will receive. The study will be discontinued if, in the opinion of the investigators, unacceptable adverse effects appear.

Study burden and risks

As GLPG4059 will be administered to humans for the first time in this study, side effects of GLPG4059 in humans have not been reported to date. However, GLPG4059 has been studied extensively in the laboratory and in animals.

In rats, after multiple administrations of GLPG4059 in doses much higher than the one given in this study, adverse heart findings (dying of muscle cells of the heart, bleeding, inflammatory cells in the heart) were observed in 2 out of 15 female rats. No adverse effects were observed in male rats, which received the same dose.

Other findings consisted of microscopic changes in the kidneys, large intestines, thymus, spleen, and bone marrow, correlating with an increased red blood cell turnover. Additional findings consisted of disturbance of certain hormones (estrous cycle), increase in liver enzymes and bilirubin, changes in

blood proteins and a reduced calcium concentration. All these findings were fully reversible after a 2-week treatment-free period.
In dogs, after single dose of GLPG4059, a slight heart rate increase was observed.

In dogs, after multiple administrations of GLPG4059, adverse heart findings (dying of muscle cells of the heart, bleeding, inflammatory cells in the heart) were reported in both male and female dogs. In an additional study in dogs, effects were seen on the heart rate, blood pressure, and ECGs after multiple high doses. After the highest dose was administered (300 mg/kg body weight), the blood pressure first dropped and then increased (this is called compensatory mechanism) also leading to an increased heart rate. At the same time there were changes in the ECGs.

Based on experiments, GLPG4059 did not cause any damage to DNA.

With the treatment of GLPG4059 there is a risk on hypoglycemia (low blood sugar levels); however, this risk in healthy volunteers is considered very low. This low risk on hypoglycemia is because GLPG4059 seems to work by increasing the sensitivity of insulin; thus one dose of GLPG4059 is not expected to change this. Furthermore, healthy volunteers are able to counteract any effect of the drug on lowering glucose by certain hormones that oppose the action of another hormone.

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

Drawing blood and/or insertion of the indwelling cannula (tube in an arm vein) may be painful or cause some bruising.

To make a heart tracing, electrodes (small, plastic patches) will be placed at specific locations on the arms, chest and legs. To continuously monitor the heart rate, electrodes (small, plastic patches) will be pasted at specific locations on the chest and abdomen and will stay there for about 25 hours in each period (also during the night).
Prolonged use of these electrodes may cause skin irritation (rash and itching). The skin irritation usually disappears when the patches are removed.

Blood pressure and heart rate: an inflatable cuff will be placed on the arm and a machine will measure the blood pressure and heart rate. The volunteer may experience mild discomfort in your arm while the cuff is inflated.

Monitoring of your blood glucose for safety purpose will be performed in case of symptoms by use of finger prick.

The high-fat breakfast is a big breakfast consisting of 2 fried eggs, fried potatoes and bacon. The volunteer must consume this breakfast entirely. Particularly for light eaters, it can be difficult to consume the entire breakfast.

Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause the volunteer to gag. When the sample is taken from the back of the nose, they may experience a stinging sensation and the eyes may become watery.

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. Male between 18-54 years of age
2. A BMI) between 18.0-30.0 kg/m2, inclusive.
3. Judged to be in good health by the investigator based upon the results of a medical history, physical examination, vital signs, 12-lead ECG, and fasting clinical laboratory safety tests, available at screening and prior to randomization. ECG and vital signs parameters must be within the normal ranges as described in Appendix 1. Bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) must be no greater than 1.5x ULN. Fasting plasma glucose must be <6.99 mmol/L, fasting defined as no caloric intake for at least 8 hours and hemoglobin A1c (HbA1c) <6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is national glycohemoglobin standardization program (NGSP) certified and standardized to the diabetes control and complications trial (DCCT) assay. 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.
4. Subject must be able and willing to comply with restrictions on prior medication as described in Section 6.3.2.
5. Negative screen for drugs (amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates, methadone, tricyclic antidepressants) and alcohol.
6. Able and willing to comply with the protocol requirements and signing the informed consent form (ICF) as approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to any screening evaluations.

Exclusion criteria

1. Known hypersensitivity to IMP ingredients or history of a significant allergic reaction to IMP 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 IMP.

For the complete overview see the protocol.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-09-2020
Enrollment:	57
Type:	Actual

Ethics review

Approved WMO Date:	21-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2021
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	EUCTR2020-000036-22-NL
CCMO	NL73486.056.20

Study results

Date completed:	08-04-2021
Results posted:	11-03-2022

First publication
25-02-2022