A PHASE 1, OPEN-LABEL, FIXED SEQUENCE, 2-PERIOD STUDY IN HEALTHY ADULT MALE PARTICIPANTS TO ASSESS THE MASS BALANCE, ABSOLUTE BIOAVAILABILITY, FRACTION ABSORBED, AND PHARMACOKINETICS OF [14C]PF-06882961

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

Summary

ID

NL-OMON49480

Source
ToetsingOnline

Brief title
PF-06882961 ADME trial

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer, Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: [14C]PF-06882961, Bioavailability, Mass balance, Pharmacokinetics

Outcome measures

Primary outcome

Total recovery of radioactivity in urine and feces, and both routes combined,

expressed as a percent of total oral radioactive dose administered.

Secondary outcome

Metabolic profiling/identification and determination of relative abundance of

[14C]PF-06882961 and the metabolites of [14C]PF-06882961 in plasma, urine, and

feces.

AUClast, AUCinf, maximum concentration (Cmax), time of maximum concentration

(Tmax), and plasma elimination half-life (t*) to describe single oral dose PK

of:

* Total radioactivity in plasma;

* PF-06882961 in plasma.

Parameters to describe intravenous plasma PK: AUClast, AUCinf, t*, MRT, CL &

Vss.

Absolute oral bioavailability (F) computed from plasma AUCinf of oral unlabeled PF-06882961 in Period 2 and intravenous microtracer of [14C]PF-06882961 in Period 2.

Fraction absorbed calculated from ratio of total urinary radioactivity following oral administration of [14C]PF-06882961 in Period 1 and intravenous administration of [14C]PF-06882961 in Period 2.

Safety endpoints including physical examinations, adverse events, clinical laboratory measurements, vital signs, and ECG.

Study description

Background summary

PF-06882961 is a new investigational compound that may potentially be used for the treatment of Type-2 Diabetes Mellitus (T2DM).

T2DM is characterized by insulin resistance, a disorder in which cells do not respond effectively to insulin, resulting in higher blood glucose levels. While existing treatment of diabetes may provide satisfactory blood glucose control for some patients, there remains a large number of patients who do not achieve target blood glucose levels, suggesting a need for additional therapeutic options.

Glucagon like peptide 1 (GLP-1) is a hormone that is predominantly released from the small intestine in response to food intake. Activation of the GLP-1 receptor (GLP-1R) via GLP-1 stimulates insulin release, inhibits glucagon secretion, and delays gastric emptying. In addition, GLP-1 has been shown to increase satiety and suppress food intake.

PF 06882961 is a molecule that binds to GLP-1R that is currently being investigated as an addition to diet and exercise to improve blood glucose levels in adult participants with T2DM.

Study objective

The purpose of this study is to investigate how quickly and to what extent PF-06882961 is absorbed and eliminated from the body.

The study will also investigate how safe the new compound PF-06882961 is and how well it is tolerated when it is administered to healthy volunteers. In addition, the taste of the oral solution of PF-06882961 will be assessed.

Study design

Subjects will be admitted to the research center 1 day before the administration of study compound (Day -1). The actual study will consist of 2 periods. During Period 1, they will stay in the research center for a minimum of 5 days (4 nights) and maximum of 15 days (14 nights). The second period will start 16 days after administration of the study compound in the first period, and subjects will stay in the research center for a maximum of 8 days (7 nights).

The volunteers will be tested for the presence of coronavirus upon admission to the research center. Until the test results are available, they will be separated from other participants and only have very limited contact with study staff. This is to avoid virus spread from potentially infected participants to other participants or to the study staff because, until the results are available, it is not certain whether they are infected or not and can thus potentially infect others. The test results will be available within one hour. If they test positive for coronavirus, they cannot participate in the study.

Intervention

In Period 1 on Day 1 subjects will be given PF-06882961 with the radioactive label as a drink of 100 mL.

In Period 2 on Day 1 subjects will be given PF-06882961 without the radioactive label as a drink of 100 mL, similar as in Period 1. About 3 hours after the drink, they will receive PF-06882961 with radioactive label as an intravenous infusion of 10 mL. The infusion will last about 15 minutes.

Study burden and risks

The study compound may cause side effects. As of 27 September 2019, there have been three completed studies with PF-06882961, including men and women of non-childbearing potential. In 2 of these studies, PF 06882961 was taken by healthy adult participants, and in the third study, PF-06882961 was taken by participants with type 2 diabetes. To date, PF-06882961 has been generally safe and well tolerated, and there have been no serious side effects reported

related to dosing of PF 06882961.

In the first study, 25 healthy participants received single doses of PF-06882961 ranging from 3 mg to 300 mg by mouth, or a matching placebo. In these participants, who received either PF-06882961 or placebo, 100 side effects were reported. A majority of these side effects were deemed mild, except for 5 side effects that were reported as *moderate* in severity. The most common side effects were related to the gastrointestinal system and included nausea, decreased appetite, and vomiting.

In the second study, 12 healthy participants received single doses of PF-06882961 (of different formulations) ranging from 25 mg to 100 mg by mouth. In these participants, 30 side effects were reported, all of which were deemed mild. The most common side effects were headache, nausea and skin abrasion.

In the third study, participants with type 2 diabetes taking metformin were given PF-06882961 doses ranging from 10 mg twice daily to 120 mg twice daily (or matching placebo), or single daily doses up to 200 mg (or matching placebo), by mouth for 28 days. In this study, 73 participants received PF-06882961 and 25 received placebo. In
these 98 participants, 319 side effects were reported, of which a majority (92%) were mild in severity, 7% were moderate in severity and 1% (2 of the 319) were severe. The most frequently reported side effects were nausea, dyspepsia (stomach upset), vomiting, diarrhea, headache, constipation and decreased appetite. Some participants
experienced a mild increase in heart rate, ranging from 5-15 beats per minute, with most heart rate measurements in the normal range.

In addition, in this third study, there was one participant who received PF-06882961 120 mg twice daily who experienced 2 serious side effects during the follow up period of the study, after completion of dosing and after discharge from the clinical research unit. These serious side effects were determined not to be related to PF 06882961. This participant reported symptoms of chest pain at the follow up visit and received a cardiac evaluation, which led to the diagnosis of an acute myocardial infarction (heart attack). The participant admitted to symptoms of chest pain for 6 to 12 months before study participation but did not report this when enrolling in the study. This participant did not have symptoms of chest pain during the dosing phase of the study. After the diagnosis of acute myocardial infarction in the follow-up period, the participant was determined to have multi vessel coronary artery disease (blockages in several blood vessels in the heart) and underwent coronary artery bypass graft (CABG) surgery. After this surgery, the second non-treatment related serious side effect of wound dehiscence (wound breakdown) related to the surgical incision was reported.

Possible discomforts due to procedures
Drawing blood and/or insertion of the indwelling cannula may be painful or

cause some bruising.

In total, we will take about 310 milliliters of blood.

To make a heart tracing, electrodes will be pasted at specific locations on the arms, chest and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

A sample for the coronavirus test will be taken from the back of the nose and throat using a swab. Taking the sample 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 their eyes may become watery.

Contacts

Public
Pfizer, Inc.

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US
Scientific
Pfizer, Inc.

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New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Age and Sex:
1. Male participants must be 18 to 54 years of age, inclusive, at the time of signing the
informed consent document (ICD).
Type of Participant and Disease Characteristics:
2. Male participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and ECG.
3. Participants who are willing and are able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
Weight:
4. Body mass index (BMI) of 17.5 to 30 kg/m2; and a total body weight >=50 kg (110 lb).
Informed Consent:
5. Capable of giving signed informed consent as described in the protocol, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

Exclusion criteria

Medical Conditions:
1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).
2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).
3. History of irregular bowel movements (eg, irritable bowel syndrome or frequent episodes of diarrhea or constipation) or lactose intolerance.
4. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into
this study.

Prior/Concomitant Therapy:
5. Use of prescription or non-prescription drugs and dietary and herbal supplements within 14 days prior to the first dose of investigational product.

(Refer to Section 6.5 for additional details). As an exception, ibuprofen or acetaminophen may be used at doses of <=1 g/day. Limited use of non-prescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

Prior/Concurrent Clinical Study Experience:
6. Previous administration with an investigational drug within 60 days (or as determined by the local requirement) preceding the first dose of investigational product used in this study.
7. Known prior participation in a trial involving PF-06882961 or known intolerance to a GLP-1R agonist.

Further criteria apply

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):	22-07-2020
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO

Date:	27-05-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	13-07-2020
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	EUCTR2019-002584-10-NL
CCMO	NL71993.056.20