An open-label study to investigate the effects of emvododstat on the pharmacokinetics of CYP2D6 and BCRP substrates in healthy volunteers

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

Summary

ID

NL-OMON50753

Source
ToetsingOnline

Brief title
Emvododstat (PTC299) DDI study with CYP2D6 and BCRP substrates

Condition

- Leukaemias

Synonym
Acute Leukemias, Cancer

Research involving
Human

Sponsors and support

Primary sponsor: PTC Therapeutics, Inc.

Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Emvododstat, Healthy Volunteers, Pharmacokinetics

Outcome measures

Primary outcome

Endpoints for assessment of emvododstat as a perpetrator when administered with a CYP2D6 substrate (dextromethorphan) and BCRP substrate (rosuvastatin):

PK Parameters:

- Dextromethorphan and dextrophan: AUC0-t, AUC0-inf, Cmax

- Rosuvastatin: AUC0-t, AUC0-inf, Cmax

Secondary outcome

PK Parameters:

- Dextromethorphan and dextrophan: T1/2, Tmax, apparent clearance (CL/F), and terminal elimination rate constant (kel)

- Rosuvastatin: T1/2, Tmax, kel, CL/F

Endpoints for safety and tolerability assessment when emvododstat is administered in combination with a CYP2D6 (dextromethorphan) and BCRP (rosuvastatin) substrates:

- Adverse events

- Chemistry and hematology laboratory panels

- 12 lead ECGs

- Vital signs

- Physical examinations

Study description

Background summary

Emvododstat is a new compound that may potentially be used for the treatment of acute leukemia. Acute leukemia is a rapidly progressing cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood stream.

Emvododstat inhibits a certain enzyme (the enzyme called dihydroorotate dehydrogenase) that plays a role in the production of rapidly dividing cells, such as leukemia cells. Inhibition of this enzyme stops the cell cycle and in the end may results in cell death of rapidly dividing cells.

Emvododstat may also inhibit the replication of viral cells. As such, emvododstat may also potentially be used for the treatment of COVID 19, the disease that is caused by the coronavirus (officially SARS CoV 2). COVID-19 is an infectious disease that causes respiratory tract infections and is spread worldwide.

Dextromethorphan reduces the tendency to cough and is used for tickling cough./ Rosuvastatin lowers cholesterol and other fats in your blood. It also reduces clogging of our arteries.

Study objective

In this study, we will investigate what the effect of the new compound emvododstat is on how quickly and to what extent 2 approved medications (dextromethorphan in Part 1 and rosuvastatin in Part 2) are absorbed, transported, and eliminated from the body. To be able to investigate this possible interaction, the volunteer will be given both emvododstat and dextromethorphan (in Part 1) or emvododstat and rosuvastatin (in Part 2).

We also investigate how safe emvododstat is and how well it is tolerated when it is used in combination with dextromethorphan (in Part 1) and rosuvastatin (in Part 2) by healthy participants.

For this study, we are looking for 36 healthy male and female participants. Each part will consist of 18 subjects.

Emvododstat has been used by humans before. In addition, it has been extensively tested in the laboratory and on animals. Dextromethorphan/Rosuvastatin is no new compound; it is an approved drug and already being used in various doses by patients.

When we use the term study compound in this document, we mean emvododstat, dextromethorphan, rosuvastatin, or a combination of these compounds.

Study design

Part 1:
For the study, it is necessary that the volunteer stays in the research center for 1 period of 8 days (7 nights)/ . Furthermore, we will call the volunteer for a follow-up approximately 2 weeks after discharge (Day 21) and approximately 30 days after the last administration of the study compound. On Day 29 and approximately 180 days after the last administration of the study compound, women of childbearing potential will need to perform a pregnancy test at home.
The volunteer will be given emvododstat and dextromethorphan as oral tablets with 240 milliliters (mL) of water.

Part 2:
For the study, it is necessary that the volunteer stays in the research center for 1 period of 16 days (15 nights). Furthermore, we will call the volunteer for a follow-up approximately 2 weeks after discharge (Day 29) and approximately 30 days after the last administration of the study compound. On Day 29 and approximately 180 days after the last administration of the study compound, women of childbearing potential will need to perform a pregnancy test at home.
The volunteer will be given emvododstat and rosuvastatin as oral tablets with 240 milliliters (mL) of water.

Intervention

Part 1:
Day | Study compound | How much | How often
1 | Dextromethorphan | 30 mg | Once
2 to 4| - | - | -
5 | Emvododstat | 250 mg | Once
| Dextromethorphan | 30 mg | Once

Part 2:
Day | Study compound | How much | How often
1 | Rosuvastatin | 20 mg | Once
2 to 7 | - | - | -
8 to 11 | Emvododstat | 100 mg | Twice daily
12 | Emvododstat | 100 mg | Twice
| Rosuvastatin | 20 mg | Once
13 to 14| Emvododstat | 100 mg | Twice daily

Study burden and risks

Blood draw
Drawing blood may be painful or cause some bruising. On the days of administration of dextromethorphan/rosuvastatin, blood will be sampled very frequently using an indwelling cannula (a tube in a vein in the arm) to determine the course of the concentration of dextromethorphan/rosuvastatin in the blood over time. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and/or bruising around the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, sweating, low heart rate, and/or a drop in blood pressure with dizziness or fainting.

In total, we will take about 200 mL of blood from the volunteer. This amount does not cause any problems in adults . To compare: a blood donation involves 500 mL of blood being taken each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn may be more than the amount indicated above.

Heart tracing
To make a heart tracing, electrodes (small, plastic patches) will be placed on the volunteer's arms, chest, and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

Fasting
If the volunteer has to fast for a prolonged time during the study, this may lead to symptoms such as dizziness, headache, stomach upset, or fainting.

Coronavirus test
Samples for the coronavirus test will be taken from the back of the volunteer's 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 volunteer's throat may cause him to gag. When the sample is taken from the back of his nose, he may experience a stinging sensation and his eyes may become watery.

Contacts

Public
PTC Therapeutics, Inc.

Corporate Court 100
South Plainfield 07080

US
Scientific
PTC Therapeutics, Inc.

Corporate Court 100
South Plainfield 07080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy adult, non-smokers (no use of tobacco products within 6 months prior to Screening), >=18 and <=65 years of age.
2. Body mass index >18.0 and <30.0 kg/m2 and body weight >=50.0 kg and <=110.0 kg.
3. Ability to swallow tablets
4. Women of child-bearing potential (as defined in (CTFG 2014)) must have a negative pregnancy test at Screening and agree to abstinence or the use at least one of the following highly effective forms of contraception (with a failure rate of <1% per year when used consistently and correctly) in addition to barrier method for their sexual partner. Contraception or abstinence must be continued for the duration of the study following discharge from the hospital, and for up to 180 days after the last dose of study drug:
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
- Oral
- Intravaginal
- Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
- Oral
- Injectable
- Implantable

- Intrauterine device
- Intrauterine hormone-releasing system
- Vasectomized partner with confirmed azoospermia
All females will be considered of child-bearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group without other known or suspected cause) or have been sterilized surgically (eg, bilateral tubal ligation, hysterectomy, bilateral oophorectomy).
5. Sexually active and fertile males must use a condom during intercourse while taking study drug and for 90 days after stopping study drug and should not father a child in this period. A condom is required to be use by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Further criteria apply

Exclusion criteria

1. For Part 1 (CYP2D6 substrate), subjects who are poor metabolizers of CYP2D6 isoenzymes are excluded.
2. Pregnant or lactating subjects or those sexually active subjects who are unwilling to comply with proper birth control methods; females of child-bearing potential must have a negative pregnancy test at Screening and during the Baseline Visit.
3. Aspartate aminotransferase or alanine aminotransferase above the upper limit of normal (ULN) at the time of Screening or Baseline. Values above ULN may be allowed if considered not clinically significant at the discretion of the Investigator.
4. International normalized ratio >=1.5×ULN at time of Screening or Baseline or clinically significant bleeding, as determined by the Investigator.
5. Serum creatinine >=1.5×ULN at time of Screening or Baseline.

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):	05-10-2021
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Dextromethorphan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Emvododstat
Product type:	Medicine
Brand name:	N/A
Generic name:	Rosuvastatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-09-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-11-2021
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	EUCTR2021-004626-29-NL
CCMO	NL78966.056.21

Study results

Results posted: 08-07-2022

First publication
29-06-2022

URL result
Type
int
Naam
M2.1 Wetenschappelijke samenvatting M2.1. scientific summary 29Jun22
URL
Type
int
Naam
M2.1 Wetenschappelijke samenvatting M2.1. scientific summary 29Jun22
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