A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of 14C-PTC299 Following Multiple Oral Dose Administrations in Healthy Volunteers

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In this study we will investigate how quickly and to what extent PTC299 is absorbed, transported, broken down (metabolized), and eliminated from the body. In this study, PTC299 is radioactively labelled with carbon-14 (14C). In this way PTC299 can...

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

Summary

ID

NL-OMON50826

Source
ToetsingOnline

Brief title
A phase 1 ADME Study in healthy volunteers

Condition

- Other condition

Synonym
Acute Leukemia

Health condition

COVID infectie

Research involving

Human

Sponsors and support

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

Intervention

Keyword: 14C-PTC299, ADME, Healthy volunteers, Pharmacokinetics

Outcome measures

Primary outcome

• To assess the rates and routes of excretion and calculate the mass balance of total radioactivity in urine and feces after a single oral dose of 16 mg/3.7 MBq of 14CPTC299 (day 7) which is preceded by 6 days of oral dosing of 16 mg/11.1 kBq 14C-PTC299 once daily.

• To assess the pharmacokinetics PK of total radioactivity in plasma pools after 6 days of oral dosing of 16 mg/11.1 kBq 14C-PTC299 once daily (Day 6).

• To assess the metabolite profiles and distribution of 14C-PTC299 and its metabolites in plasma, urine, and feces pools after 6 days of oral dosing of 16 mg/11.1 kBq 14C-PTC299 once daily (Day 6).

Secondary outcome

• To assess the PK of total radioactivity in whole blood and plasma after a single oral dose of 16 mg/3.7 MBq of 14C-PTC299 (day 7) which is preceded by 6 days of oral dosing of 16 mg/11.1 kBq 14C PTC299 once daily.

• To assess the PK of 14C-PTC299 and its metabolites in plasma after a single oral dose of 16 mg/3.7 MBq of 14C-PTC299 which is preceded by 6 days of oral dosing of 16 mg/11.1 kBq 14CPTC299 once daily.

• To assess the safety and tolerability of multiple oral doses of 16 mg

14C-PTC299 administered once daily for 7 days.

Study description

Background summary

PTC299 is a new compound that may potentially be used for the treatment of acute leukemia and coronavirus disease 2019 (COVID-19). Acute leukemia is a type of blood cancer that can develop in a short time and is life threatening when not treated. PTC299 blocks cell growth in rapidly dividing cells (including cancer cells) by blocking an enzyme called dihydroorotate dehydrogenase (DHODH). DHODH is also involved in virus replication and the growth of immune cells. Severe cases of COVID-19 have been associated with an excessive immune response. Blocking both virus replication and the excessive immune response may help in the treatment of patients with COVID-19.

The research medication is radio-labelled with carbon-14 (14c) so it is possible to follow the research medication in blood, urine and stool.

Study objective

In this study we will investigate how quickly and to what extent PTC299 is absorbed, transported, broken down (metabolized), and eliminated from the body. In this study, PTC299 is radioactively labelled with carbon-14 (14C). In this way PTC299 can be traced in blood, urine, and feces.

We also investigate how safe PTC299 is and how well it is tolerated when it is administered to healthy people.

PTC299 is in development and not available on the market, but it has been used by humans before. In addition, it has been extensively tested in the laboratory and on animals.

Study design

For the study it is necessary that subject stays in the research center for 1 period of up to 18 days (17 nights).

Day 1 is the first day when subject receives the study compound. Subject will leave the research center on Day 17 of the study.

If the amount of radioactivity in urine and feces complies with the predefined

levels on Day 17, subject does not need to return for additional visits. If the amount of radioactivity does not comply with the pre-defined levels on Day 17, subject will need to return to the research center for 24-hour collection of urine and feces. During the 24 hours prior to each additional stay at the research center, subject will also have to collect feces at home. Subjects will be contacted by telephone if they have to return for an additional 24 hour stay in the research center.

Below is an overview of the days subject stays at the research center, or when subject visits the research center.

Screening Day -28 up to 2
Arrival Day -1
In-house Stay Day -1 up to 17
Follow-up and Departure Day 17
Home Collection (if needed) Day 22 and 23
24-Hour Stay (if needed) Day 23 and 24
Home Collection (if needed) Day 29 and 30
24-Hour Stay (if needed) Day 30 and 31
Home Collection (if needed) Day 44 and Day 45
24-Hour Stay (if needed) Day 45 and Day 46
Home Collection (if needed) Day 58 and Day 59
24-Hour Stay (if needed) Day 59 and Day 60
Home Collection (if needed) Day 72 and Day 73
24-Hour Stay (if needed) Day 73 and Day 74
Home Collection (if needed) Day 86 and Day 87
24-Hour Stay (if needed) Day 87 and Day 88

Subject will be given 14C-PTC299 as an oral solution of 4 milliliters (mL) using a syringe without a needle. Thereafter subject is also required to drink an additional amount of 240 mL of water.

The table below shows the planned dose levels in the study.

Day(s)
Treatment
How often
1 to 6 16 mg PTC299, mixed with 11.1 kBq 14C-labeled PTC299 once daily
7 16 mg PTC299, mixed with 3.7 MBq 14C-labeled PTC299 once

Intervention

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Study burden and risks

PTC299 has already been studied in 145 healthy persons and 149 patients with solid tumors or acute leukemia. Most clinical studies were conducted with a capsule at doses ranging from 0.03 to 3 mg/kg bodyweight, or between 100 mg twice daily to 200 mg three times daily. A limited number of participants received 2 tablets as a single dose up to 1600 mg or as multiple doses of 600 mg per dose twice daily. Most of these doses were (much) higher than the dose in the current study.

In the healthy volunteers, who received PTC299 for no more than 7 consecutive days, no serious adverse events were reported.

The following side effects are observed very often in patients with solid tumors (in 1 in 10 people or more):
• Fatigue
• Nausea
• Diarrhea
• Hair loss (alopecia)
• Coughing
• Constipation
• Loss of appetite
• Headache
• Joint pain
• Dizziness
• Shortness of breath
• Pain on extremities (peripheral Neuropathy)
• Vomiting
• Back pain
• Muscle pain
• Increase of laboratory values for liver functions

The intensity ranged from mild to moderate, and these were generally side effects that are common for studies in patients with cancer. In 2 patients with cancer who received a high dose of the study compound over a longer period, severe liver damage was seen.

Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling

canula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment (bruising) of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, seating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about 500 milliliters (mL) of blood. 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 will be more than the amount indicated above.

Heart tracing
To make a heart tracing, electrodes will be placed at specific locations on arms, chest and legs. Prolonged use of these electrodes can cause skin irritation.

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

In this study we use radioactive compounds. The additional amount of radiation subject will be exposed to in this study is 0.49 mSv.

Contacts

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PTC Therapeutics, Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Sex: male.
2. Age: 18 to 55 years, inclusive, at screening.
3. Body mass index: 18.0 to 30.0 kg/m2, inclusive.
4. Status: healthy subjects.
5. Subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from admission to the clinical research center until 90 days after discharge on Day 17. Adequate contraception for the male subject (and his female partner) is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, a cervical cap, or a condom. Total abstinence, in accordance with the lifestyle of the subject, is also acceptable.

Exclusion criteria

1. Employee of PRA Health Sciences (PRA) or the Sponsor.
2. History of relevant drug and/or food allergies.
3. Smoking more than 5 cigarettes, 1 cigar, or 1 pipe per day on average.
4. History of alcohol abuse or drug addiction (including soft drugs like cannabis products).
5. Positive drug and alcohol screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at screening or admission to the clinical research center.

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):	10-02-2021
Enrollment:	7
Type:	Actual

Ethics review

Approved WMO Date:	31-12-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-01-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2021
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	EUCTR2020-005545-16-NL
CCMO	NL76179.056.20