A single-center, open-label study to evaluate the absorption, distribution, metabolism and excretion (ADME) and pharmacokinetics of TNO155 following a single oral dose of [14C]TNO155 in healthy male participants

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

Summary

ID

NL-OMON51295

Source
ToetsingOnline

Brief title
ADME and PK of a single dose [14C] TNO155

Condition

- Other condition

Synonym
Cancer

Health condition

Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma AG
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: [14C] TNO155, ADME, PK

Outcome measures

Primary outcome

Group 1:

• Excretion/mass balance of [14C]-radioactivity recovered in urine, feces, vomitus (if applicable), and expired air as percentage (%) of both the administered dose and the recovered dose.

• Cmax, Tmax, AUClast, AUCinf, T1/2 and any other PK parameters as appropriate from the concentration-time data of 14C-radioactivity in whole blood and plasma.

• Cmax, Tmax, AUClast, AUCinf, T1/2, Vz/F (TNO155 only), CL/F, (TNO155 only), Ae, CLr and any other PK parameter as appropriate from concentration vs. time data of TNO155 and the metabolite NIH741 in plasma and urine.

Secondary outcome

Group 1 and 2:

•Frequency and severity of AEs including changes in laboratory values, vital signs and ECG intervals.

Study description

Background summary

TNO155 is a new compound that may potentially be used for the treatment of cancer, such as non-small cell lung cancer, malignant tumors in the head and neck area, , solid tumors and melanomas. TNO155 binds to a small protein in the body called SHP2 (Sarcoma homology-2 domain containing protein tyrosine phosphatase 2). This prevents the activation of this protein, and this it reduces the growth of cancer cells. TNO155 can also activate some cells of the immune system (T-cells) which can attack the cancer cells.

Study objective

In this study, we will investigate how quickly and to what extent TNO155 is absorbed, transported, and eliminated from the body. TNO155 will be radioactively labeled with carbon-14. In this way, TNO155 can be traced in blood, urine, feces, and expired air.

For Part B, TNO155 will also be measured in bile. The bile will be collected via a nasoduodenal tube.

We will also investigate how safe the new compound TNO155 is and how well it is tolerated when it is used by healthy participants.

We also investigate whether the genetic information has an effect on how the body metabolizes TNO155. This part of the study is not mandatory.

Study design

For the study it is necessary that the volunteer stays in the research center for 1 period of 22 days (21 nights).

Day 1 is the day when the volunteer receives the study compound. The volunteer is expected at the research center the day before the day of administration of the study compound (Day -1). The volunteer will leave the research center on Day 21 of the study.

From Day 1 until Day 21, all the urine and feces will be collected and blood and expired air samples will be taken frequently to measure the amount of radioactivity in the urine, feces, blood, and expired air. The volunteer should be aware that if the radioactivity levels are still above predefined levels on Day 21, he will need to return to the research center for up to 4 additional 24 hour visits.

For the additional 24-hour visits, the volunteer is expected at the research center at 11:00 h in the morning of Day 28, 35, 42, and 49. The volunteer will leave the research center on Days 29, 36, 43, and 50, respectively. Each time the volunteer leaves the research center, he will be contacted by phone as soon as possible and be told whether he has to come back for the next 24-hour visit or not.

During 24 hours prior to entry into the research center for the inhouse stay and for the 24-hour visits, the volunteer will have to collect feces at home and bring this to the research center.

The volunteer will be given 50 milligram (mg) of 14C labeled TNO155 as a capsule with 240 milliliters (mL) of (tap) water. This amount contains 0.7 MBq (18.9 µCi) radioactivity.

Intervention

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Study burden and risks

Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment 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 491 milliliters (mL) of blood from the volunteer.

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

Ultrasound of the heart
For the exam a special gel will be applied to the skin. This prevents friction when moving the ultrasound transducer on the skin. The transducer has a similar appearance to a microphone. The gel also helps transmit the sound waves. The procedure is painless and there are no health risks. Only in rare cases the jelly can cause an allergic reaction.

Eye exam
For the exam the volunteer will receive eye drops in the eyes. The eye drops may give the volunteer a blurred vision for some time.

Nasoduodenal tube (Part B only)
Gastroscopy, placement of a nasoduodenal tube and duodenal fluid sampling are safe procedures and serious complications are rare. Usually these procedures are done without any problem. Nose bleeds and nausea are common after placement of a nasoduodenal tube. If, after removal of the nasoduodenal tube, the volunteers feels very nauseated or he has to vomit, the responsible doctor may treat this with certain medication.

Pain experience is different for everyone and many people find the insertion of the gastroscope unpleasant because they have to gag. Sometimes people experience shortness of breath, which is because there is a tube in their throat.

Some people have a mildly sore throat for a day or so after gastroscopy.

To minimize pain and discomfort, a gastroscope used in young children, in combination with local anesthesia is chosen as method for placement of the nose tube.

Serious complications occur rarely. On average, per 1000 gastroscopies 1 or 2 times a complication occurs:
There is a slightly increased risk of developing a lung infection or pneumonia due to vomiting and aspiration. The risk of this happening increases if the volunteer did not fast for long enough before the procedure.
In rare cases the gastroscope or nasoduodenal tube may cause some damage to the wall of the gastrointestinal tract. This may cause bleeding, infection and very rarely a small puncture.

To numb the throat, xylocaine (lidocaine) will be used. The following side effects are described: hypersensitivity reactions (1 to 10 in 1000 users), severe allergic reactions (with hypotension, paleness, anxiety, weak and fast pulse, clammy skin, and decreased consciousness as a result of a sudden vasodilation [anaphylactic shock]), loss of voice, hoarseness, sore throat, local irritation on the place of application (incidence cannot be assessed based on the current data).

Coronavirus test
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 your throat may cause the volunteer to gag. When the sample is taken from the back of the nose, the volunteer may experience a stinging sensation and the eyes may become watery.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signed informed consent must be obtained prior to participation in the study.
2. Healthy males age 18 to 55 years, inclusive, at screening.
3. In good health as determined by no clinically significant findings from medical history, physical examination, vital signs, ECG, echocardiogram, and laboratory tests, at screening.
4. At screening and at baseline (Day -1), vital signs after 5 minutes in supine position must be within the following ranges (inclusive):
• Body temperature between 35.0 and 37.5°C°.
• Systolic blood pressure (BP) between 90 and 139 mmHg.
• Diastolic BP between 45 and 89 mmHg.
• Pulse rate between 45 and 90 bpm.
5. Weight at least 50 kg with a body mass index (BMI) within the range of 18.0 to 29.9 kg/m2, inclusive.

Further criteria apply.

Exclusion criteria

1. Use of other investigational drugs within 6 months prior to admission (in case of therapeutics with expected long half-lives such as immunoglobin G antibodies) or use of other investigational drugs within 30 days prior to dosing (for small-molecule drugs with daily dosing scheme), or longer if required by local regulations.
2. Contraindication or hypersensitivity to the investigational compound/compound class or excipients being used in this study.
3. History or presence of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
4. Recent history (<3 months) of nicotine product use or a urine cotinine level >500 ng/mL, at screening or baseline.
5. Use of any prescription drugs (including moderate and strong CYP3A and UGT1A3 inhibitors or inducers), over-the-counter (OTC) medications, herbal supplements, or prescribed medicinal use of cannabis/marijuana/cannabidiol-containing products, or administration of any vaccine within the last 4 weeks prior to dosing.

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):	04-02-2022
Enrollment:	9

Type:	Actual

Ethics review

Approved WMO Date:	01-02-2022
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	EUCTR2021-004988-27-NL
CCMO	NL80253.056.22