A PHASE 1 TRIAL TO ASSESS THE MASS BALANCE, ABSOLUTE BIOAVAILABILITY, AND PHARMACOKINETICS OF 14C-E7727 IN HEALTHY VOLUNTEERS >=65 YEARS OF AGE

Published: 05-02-2019
Last updated: 09-04-2024

To identify and quantify the main excretion pathways of E7727.

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

Summary

ID

NL-OMON48473

Source
ToetsingOnline

Brief title
[14C]-E7727 Mass Balance study

Condition

- Other condition

Synonym
MDS, Myelodysplastic syndromes

Health condition

Myelodysplastisch syndroom

Research involving

Human

Sponsors and support

Primary sponsor: Astex Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: 14C-E7727, Bioavailability, Mass balance, Pharmacokinetics

Outcome measures

Primary outcome

To identify and quantify the main excretion pathways of E7727.

Secondary outcome

To determine the F of E7727 after single dose administration in the fasted

condition.

To determine the Fa of E7727.

To determine the PK of E7727 following oral and IV administration.

To determine the safety and tolerability of E7727 following oral and IV

administration.

To identify the metabolites of E7727 in plasma, urine, and feces, if possible.

Study description

Background summary

E7727 is a new compound that may eventually be used in combination with another product for the treatment of myelodysplastic syndromes (MDS), which are a group of cancers in which blood cells in the bone marrow do not mature and therefore do not become healthy blood cells. Hypomethylating agents (HMAs), have proven to be an effective treatment against MDS. However, effective oral administration of not worked because HMAs are broken down in the gut and liver, specifically by the enzyme cytidine deaminase (CDA). E7727 is a new compound

that suppresses CDA in the gut and liver, which could help HMAs be better absorbed in the body.

Study objective

To identify and quantify the main excretion pathways of E7727.

Study design

The study consists of 3 phases: pre-treatment, treatment and follow-up. The pre-treatment lasts a maximum of 21 days and will consist of a screening phase and a baseline phase, in which the suitability of each volunteer will be determined.

The treatment period consists of 2 periods. During period 1 the volunteers receive unlabeled E7727 orally in combination with intravenous radioactive E7727. During period 2 the volunteers receive radioactive E7727 orally. Period 2 will start after a complete wash-out of E7727.

The subject remains in the clinic for 5 days (4 nights) (Period 1) and up to 11 days (10 nights) (Period 2) in the research center with at least 4 days between each period.

Each period has a Day 1, this is the day on which the research product is administered.

Finally, the volunteers will come back for a follow-up visit.

Intervention

E7727 will be given as oral capsules with 240 milliliters (mL) of (tap) water and an intravenous infusion (solution of the compound that will be administered directly in a blood vessel).

Day 1, Period 1 E7727, 100 mg Oral capsule - Once
Day 1, Period 1 E7727, 100 microgram (µg) containing 14C radiolabeled E7727 Intravenous solution - Once
Day 1, Period 2 E7727, 100 mg containing 14C-radiolabeled E7727 Oral capsule - Once

Study burden and risks

Study compound
The study compound may cause side effects.

E7727 has not yet been administered to healthy volunteers. E7727 has only been

administered to MDS patients in combination with decitabine. It was found that the adverse events that were reported in the combination with 100 mg E7727 and 35 mg decitabine were similar to 35 mg decitabine alone. Decitabine will not be administered in this study.

E7727 has been studied extensively in the laboratory and in animals. The E7727 dose to be used in this study (100 mg) is 1/40th of the dose in human equivalent terms that was evaluated in animals in studies; i.e. an approximately 40-fold higher dose of E7727 when dosed daily to monkeys or mice for 7 consecutive days did not cause any significant toxicities. You will receive only 2 doses of E7727, approximately 9 days apart.

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

In total, we will take about 272 mL of blood from the subject. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken.

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

Exposure to radiation
This study involves using radioactive markers. The additional radiation burden in this study due to the administration of radiolabeled E7727 is calculated to be approximately 1 mSv and is considered acceptable. The average environmental background radiation burden in The Netherlands is approximately 2.5 mSv per year.

Contacts

Public
Astex Pharmaceuticals, Inc.

4420 Rosewood Drive Suite 200
Pleasanton CA94588
US
Scientific
Astex Pharmaceuticals, Inc.

4420 Rosewood Drive Suite 200
Pleasanton CA94588

US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Gender: male or female; females must be postmenopausal
2. Age: >=65 years, at screening.
3. Body mass index (BMI): 18.0 to 32.0 kg/m2, inclusive.
4. Status: healthy subjects
5. Male subjects, if not surgically sterilized, with a female partner of childbearing potential must agree to use adequate contraception and not donate sperm from first admission to the clinical research center until 90 days after the follow-up visit. 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.
6. All prescribed medication must have been stopped at least 30 days prior to each admission to the clinical research center.
7. All over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (eg, St. John*s Wort) must have been stopped at least 14 days prior to each admission to the clinical research center. An exception is made for paracetamol, which is allowed up to each admission to the clinical research center.
8. Ability and willingness to abstain from alcohol, methylxanthine-containing beverages or food (coffee, tea, soft drinks, chocolate, energy drinks), and grapefruit (juice) and tobacco products from 48 hours prior to each admission to the clinical research center.
9. Satisfactory physical and mental health on the basis of medical history, physical examination, clinical laboratory, 12-lead electrocardiogram (ECG), and vital signs, as judged by the PI.
10. Willing and able to sign the ICF.
11. Subject is able to understand and comply with the study procedures and understands the risks involved in the study

Exclusion criteria

1. Employee of PRA or the Sponsor.
2. History of relevant drug and/or food allergies.
3. Using tobacco products and/or alcohol in the 48 hours (2 days) prior to first admission to the clinical research center is not allowed.
4. Known significant mental illness or other condition, such as active alcohol or other substance abuse or addiction, that in the opinion of the investigator predisposes the subject to high risk of noncompliance with the protocol.
5. Positive drug and alcohol screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at screening and each admission to the clinical research center.
6. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits).
7. Positive screen for hepatitis B surface antigen (HBsAg), antihepatitis C virus (HCV) antibodies, or antihuman immunodeficiency virus (HIV) 1 and 2 antibodies.
8. Participation in an investigational drug study within 60 days prior to the first drug administration in the current study. Participation in more than 4 other drug studies in the year prior to the first drug administration in the current study.
9. Donation or loss of more than 100 mL of blood within 60 days prior to the first drug administration. Donation or loss of more than 1.5 liters of blood (for male subjects)/more than 1.0 liter of blood (for female subjects) in the 10 months prior to the first drug administration in the current study.
10. Significant and/or acute illness within 5 days prior to the first drug administration that may impact safety assessments, in the opinion of the Investigator.
11. Unsuitable peripheral veins for infusion or blood sampling.
12. Participation in another ADME study with a radiation burden >0.1 mSv in the period of 1 year prior to screening.
13. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton [excluding spinal column]), during work, or during participation in a clinical study in the period of 1 year prior to screening.
14. Irregular defecation pattern (less than once per 2 days).

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):	20-02-2019
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO Date:	05-02-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2019
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	EUCTR2018-004366-33-NL
CCMO	NL68882.056.19