Excretion balance, pharmacokinetics and metabolism of S44819 after single administration of [14C]-S44819 in young healthy male volunteers. A phase 1 monocentre open-label study.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON44446

Source
ToetsingOnline

Brief title
S 44819 - PK - Mass balance study

Condition

- Neurological disorders NEC

Synonym
stroke

Research involving
Human

Sponsors and support

Primary sponsor: Institut de Recherches Internationales Servier (I.R.I.S.)
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: 14C, S 44819

Outcome measures

Primary outcome

To assess the excretion balance of total radioactivity in urine and faeces

after administration of a single oral dose of 180 mg of S 44819 containing 1.58

MBq of [14C]-S 44819 in fasting conditions.

Secondary outcome

To assess after administration of a single oral dose of 180 mg of S 44819

containing 1.58 MBq of [14C]-S 44819 in fasting conditions:

- The pharmacokinetics of the total radioactivity in blood and plasma

- The pharmacokinetics of S 44819 in plasma

- The metabolite profile of S 44819 in plasma, urine and faeces

- The safety of S 44819

Study description

Background summary

Our motricity and cognition are significantly determined by signal transmission between nerve cells (neurons). A neuron activates other neurons by releasing molecules called neurotransmitters that bind to proteins (called receptors) on other neurons. An example of such a neurotransmitter is GABA (gamma-amino-butyric acid). The transmission of signals could be potentiated or reduced depending on levels of neurotransmitters in the brain. In certain pathological circumstances, the GABA circuit can be overexpressed. This could

happen for example following an ischemic stroke (a cerebral event caused by the occlusion of a cerebral artery and a lack of blood perfusion in the concerned brain region). As a result of this, good motor and cognitive recovery may be hindered.

S 44819 is an investigational compound that is being developed for the treatment of patients presenting neurological deficits following an ischemic stroke. S 44819 is being developed to improve the recovery of the brain after such an event. S 44819 is a molecule that blocks some GABA receptors. As a result, it decreases activity of the GABA circuit and could be beneficial to enhance cognitive and motor recovery of patients suffering from stroke.

S 44819 is in development and is not registered as a drug but has been given to humans before. So far, how quickly and to what extent S 44819 is absorbed, distributed, metabolized (broken down) and excreted from the body (also called pharmacokinetics) as well as the safety of S 44819 have already been studied after a single oral administration at doses ranging from 10 mg to 800 mg in healthy young volunteers and after 10-day repeated oral administrations at doses ranging from 20 mg twice a day to 450 mg twice a day in healthy young and elderly volunteers. S 44819 has already been administered to 133 healthy volunteers; 88.7% were healthy male volunteers and 11.3% healthy female volunteers; 25% of participants were aged >= 65 years. The treatment was well tolerated.

Study objective

The purpose of the study is to investigate the pharmacokinetics of S 44819. S 44819 is labeled with 14-Carbon (14C) and is thus radioactive (also called radiolabeled). In this way, S 44819 and its metabolites can be traced in blood, urine and feces. It will also be investigated to what extent S 44819 is safe and tolerated.

Study design

The actual study will consist of 1 period during which the volunteer will stay in the clinical research center for a minimum of 8 days (7 nights) to a maximum of 15 days (14 nights). Thus, the volunteer will stay from the morning of Day -1 (1 day before administration of the study compound; also called admission) until at least Day 7.

Day 1 is the day of administration of study compound. The volunteer is expected at the clinical research center in the morning of the day (Day -1) prior to the day of administration of the study compound. The volunteer will be required not to have consumed any food or drinks (with the exception of water) during the 10 hours prior to arrival in the clinical research center.

After administration of the study compound on Day 1, all of the volunteers urine and feces will be collected during the entire research. The total amount of radioactivity excreted in his urine and feces will be measured daily. From Day 7 onwards, if the radioactivity levels in the volunteers urine and feces are below pre-defined levels and/or if more than a pre-defined amount of radioactivity has been excreted from his body, he will be allowed to leave the clinical research center. The volunteer will leave the clinical research center at the latest on Day 14. If the criteria for radioactivity as described above are still not met on Day 14, he will have to continue the collection of all of his urine and feces at home and return these to the clinical research center every 2 days until Day 28 at the latest. These ambulatory visits are planned on Days 16, 18, 20, 22, 24, 26, and 28 and will only take place if needed if the criteria for radioactivity as described above are still not met.

The post-study screening will be planned within 3 to 5 days after the volunteer has left the clinical research center, or within 3 to 5 days after he has visited the clinical research center for the last time to return your urine and feces, if this is necessary, or on Day 28 if the last ambulatory visit to return his urine and feces is planned on that day. The appointment for the post-study screening will be made with the volunteer as soon as it is known when the study will end for him.

The participation to the entire study, from pre-study screening until the post-study screening, will be a maximum of 50 days.

Back-up volunteer replacing a volunteer discontinued on Day 1
If the volunteer is a back-up volunteer and a volunteer that has received the study compound discontinues on Day 1, he may be chosen to replace this discontinued volunteer. In that case, he will be asked to stay in the clinical research center for the rest of the day. The volunteer will then receive the study compound the next day; that day will be the actual Day 1. As a result, his stay in the clinical research center will last 1 day longer than described above. Further, the volunteers participation to the entire study, from pre study screening until the post-study screening, will be a maximum of 51 days.

The volunteer will receive a single dose of 180 mg radiolabeled S 44819 as an oral suspension in sitting position. This will be immediately followed by the ingestion of 150 milliliters (mL) of water.

Intervention

The volunteer will receive a single dose of 180 milligrams (mg) radiolabeled S 44819 as an oral suspension; the suspension is a liquid with undissolved powder.

Study burden and risks

All potential drugs cause adverse effects; the extent to which this occurs differs. Three clinical studies have been conducted in healthy volunteers with S 44819 in which single doses up to 800 mg (79 healthy volunteers) and repeated doses up to 450 mg (54 healthy volunteers) were well tolerated. A total of 133 healthy volunteers received S 44819. No severe side effect was reported by investigators. The most frequently observed side effect was headache, which was reported by 3.3% of the subjects followed by dyspepsia (2.0%) and diarrhea (2.0%).

The volunteer should be aware that the aforementioned adverse effects and possibly other, still unknown adverse effects, may occur during the study. However, with the doses used in this study no serious adverse effects are expected.

In this study radiolabeled S 44819 will be used. The amount of radioactivity in this dose will be approximately 1.58 MBq (MBq = megaBecquerel, this is a unit to express the amount of radioactivity in the study compound). The average environmental background radiation burden in The Netherlands is approximately 2 mSv per year (mSv = milliSievert, this unit indicates the burden on the human body; thus the effect on the human body of the amount of radioactivity administered). The additional radiation burden in this study due to the administration of approximately 1.58 MBq radiolabeled S 44819 is calculated to be 0.5 mSv. This is approximately 25% of the average annual radiation burden.

Procedures: pain, minor bleeding, bruising, possible infection

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- healthy male caucasian participants aged between 18-45 years inclusively
- 18.5 kg/m²<=BMI<= 30.0 kg/m²
- Body weight >= 50 kg
- Be a non-smoker (or having not smoked for at least 6 months prior to the selection visit)

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 90 days before the start of this study. Donation of blood derivates or loss of more than 50 mL of blood within the 90 days before the day of selection, during the study and 3 months following completion of the study.

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):	20-07-2017
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO Date:	22-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2017
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	EUCTR2016-002982-68-NL
CCMO	NL62189.056.17