Randomized Efficacy and Safety Trial with Oral S 44819 after Recent ischemic cerebral Event
International, multi-centre, randomized, double-blind placebo-controlled phase II study.

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Efficacy and safety trial with S 44819 after recent ischemic cerebral Event

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON43310

Source
ToetsingOnline

Brief title
CL2-44819-004
RESTORE BRAIN

Condition

- Other condition

Synonym
CVA stroke

Health condition

Cerebrovascular accidents

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ischaemic stroke, mRS, recovery

Outcome measures

Primary outcome

The primary objective of the study is to demonstrate the superiority of at lest

one of the two doses of S44819 versus placebo on functional recovery from

ischaemic stroke measured with the mRS after 90 days of treatment.

Secondary outcome

The secondary objectives are:

- to assess the efficacy of two doses of S44819 in stroke recovery using

neurological evaluations (NIHSS), activities of daily living test (BI) and

cognitive performance tests (Moca, TMT)

- to assess the safety and tolerability of S44819.

Study description

Background summary

Stroke is the leading cause of acquired handicap in adult live. Ischemic stroke (cerebral infarction) accounts for more than 80% of stroke in industrialized countries.
Currently available evidence based treatments act either in the acute phase of ischemic stroke, or on primary and secondary prevention.
GABA is the main inhibitory transmitter in the human brain. It is known from

preclinical and clinical studies that an acute cerebral infarction is followed by an increased activity of GABAergic neurons. In the acute phase of such an event, this is thought to be a defense mechanism to prevent excitotoxicity by protecting cerebral neurons threatened from impaired oxygen and energy supply. However, in the post-acute phase after a cerebral infarction, this increased GABAergic activity has a negative effect on neuroplasticity, and studies in animals and in humans have shown that sustained increased activity of the GABAergic system is associated with worse functional outcome.
S 44819 is a competitive antagonist of the GABAA-*5 receptor and has shown to enhance cognitive and motor recovery in several preclinical stroke models.

Study objective

Efficacy and safety trial with S 44819 after recent ischemic cerebral Event

Study design

This study is a phase II, international, multi-centre, randomized, placebo-controlled, double-blind study with a 90 days double-blind treatment period followed by a 15 days period with no treatment.
The study is divided into a selection period, a double-blind treatment period of 90 days and a follow-up period of 15 days.

Intervention

The study treatment period is divided into 3 arms: a first one receives placebo wheras the second arm will be given 300 mg S44819 twice daily. The third arm will be allocated to 150 mg S44819 twice daily.

Study burden and risks

7 study visits are planned in this study, and one phone contact with the investigator.
For inclusion, an MRI is mandatory.
At 6 study visits, an ECG will be taken.
At selection, D30, D60, D90 and D105 bloodsamples are planned.
At D5 it is planned to take pharmacokinetics samples at 3 timepoints, whereas this is planned at D30, D60 and D90 only once.
The patient can optionally consent to give a bloodsample for pharmacogenomics analysis.
At selection, women of childbearing potential will be tested for pregnancy with a urinary or blood pregnancy test.
At D30, D60, D90 and D105, the patient will be questioned for quality of live using a visual analogue scale. At these visits, a CSSRS will also be performed.
The effect of the study medication will be evaluated by the investigator by

means of the mRS, and the NIHSS at D0 D5 D30, D60 and D90 and by the Barthell Index at D30, D60 and D90 .
At D30 and D90 the MoCA will be done and at D90 the trail making test A&B will be done.
This study is a phase II trial and possibly not all side effects of the product are known. Headache is currently the most frequently reported side effect.
The patient has the chance of 2 out of 3 to be randomised to the active medication and could in this case potentially benefit from the study. On the other hand, the patient enables the further development of the product which in turn could result in other patients benefitting from the treatment. During the study the patient can benefit from an extended medical follow-up.

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

- Patients aged between 18 and 80 years (both inclusive),
- Acute ischemic stroke (IS) that occurred at least 48 hours (2 days) and less than 144 hours (6 days) (both inclusive) before selection. If the exact stroke onset time is unknown, by convention it will be defined as the moment the patient was seen well for the last time. Those patients can be included if the time interval between last seen well and stroke discovery is less than 12 hours,
- No previous disability (neither physical nor cognitive pre-stroke impairment),
- NIHSS 7-20 (both inclusive),
- Patient clinically stable according to the investigator's judgement.
- Inclusion done between 72 hours (3 days) and 144 hours (6 days) (both inclusive) after IS onset,
- Brain MRI results available with at least DWI, T2*, FLAIR,
- Brain MRI showing an acute supratentorial cortical ischemic stroke responsible for the clinical picture of the patient.

Exclusion criteria

- Impossibility to undertake an adequate rehabilitation in a specialised centre, and / or ambulatory rehabilitation services
- Stroke due to cerebral venous thrombosis,
- Vascular surgery or endovascular treatment likely to be required during the next 3 months
- Severe co-morbid medical conditions with a life expectancy <12 months or any other disease or condition which would place a patient at undue risk by being included in the study or likely to interfere significantly with the evaluation criteria of the study (according to the investigator's opinion)
- Class III or class IV Heart failure according to the New York Heart Association (NYHA) classification,
- Chronic alcohol abuse1 or drug abuse or addiction, as judged by the investigator (excluding nicotine).
- Pre-existing psychiatric disease likely to impact the clinical evaluation during the study,
- Epileptic seizure during the last 2 years or treatment for epilepsy during the last 12 months,
- Known positive HIV serology, unresolved hepatitis B and/or C infection,
- Pre-stroke known clinically significant cognitive impairment (i.e with impact on daily activities) or known dementia,
- Known severe renal impairment:
- Severe hepatic impairment or known liver enzymes abnormalities
- Contraindication or unable to perform a MRI
- Long-term prescription of benzodiazepine (BZD) that cannot be stopped without exposing the patient to safety risk
- Pregnancy, breastfeeding or possibility of becoming pregnant during the study
- Female patients with child bearing potential and procreative male patients not willing to use effective contraception methods throughout the treatment period and at least 15 days post

last treatment intake.
- Brain MRI showing
o a severe microangiopathy,
o an acute haemorrhagic stroke or an important haemorrhagic transformation of the brain infarct ,
o an acute ischemic or haemorrhagic lesion in brain stem or cerebellum likely to contribute significantly to the clinical picture of the patient,
o acute lacunar infarction in the territory of a deep perforating artery likely to contribute significantly to the clinical picture of the patient,
o signs of a pre-existing severe cerebrovascular disease
- Follow-up showing symptomatic haemorrhagic transformation of the cerebral infarction (Symptomatic defined clinically as a worsening of at least 4 points on the NIHSS),
- Repeated demonstration of ECG QTcf > 480ms (at least 2 ECGs out of 3 with a QTcf > 480ms),

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-02-2017
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	S44819

Generic name:	NA

Ethics review

Approved WMO Date:	25-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-10-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2016-001005-16-NL
CCMO	NL57643.078.16

Study results

Date completed: 26-06-2018

Results posted: 19-11-2019

First publication
15-10-2019