Multiple dose safety, tolerability, plasma and cerebrospinal-fluid pharmacokinetic study of oral doses of CORT113176

Published: 05-06-2021
Last updated: 17-01-2025

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Ethical review	Approved WMO
Status	Completed
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON51110

Source
ToetsingOnline

Brief title
Safety, tolerability, plasma- and CSF-PK of CORT113176

Condition

- Spinal cord and nerve root disorders

Synonym
amyotrophic lateral sclerosis (ALS)

Research involving
Human

Sponsors and support

Primary sponsor: Corcept Therapeutics Incorporated
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: ALS, CORT113176, CSF

Outcome measures

Primary outcome

Safety: AEs, clinical laboratory tests, vital signs, 12-lead ECGS, physical

examinations

Pharmacokinetics: Plasma CORT113176 concentrations and PK parameters, CSF

CORT113176 concentrations

Exploratory: Concentration of cortisol in serum.

Secondary outcome

N/A

Study description

Background summary

CORT113176 is a new compound that may potentially be used for the treatment of amyotrophic lateral sclerosis (ALS). In ALS, nerve cells involved in movements degenerate. This results in decreasing control over muscles and ends in paralysis. One of the possible mechanisms causing ALS is an increased level of cortisol in the brain. CORT113176 inhibits the activity of cortisol and thus may help to improve the mobility of the patients.

Study objective

In this study we will investigate how safe the new compound CORT113176 is and how well it is tolerated when it is used by healthy participants.

We also investigate how quickly and to what extent CORT113176 is absorbed, transported, eliminated from the body and to what extent it enters the CNS.

We compare the effects of CORT113176 with the effects of a placebo. A placebo is a compound without any active ingredient.

CORT113176 has been used by humans before. In addition, it has been extensively tested in the laboratory and on animals. CORT113176 will be tested at various dose levels.

Study design

For the study it is necessary that the volunteers stay in the research center for 1 period of 18 days (17 nights).

Day 1 is the first day when the volunteer will receive the study compound. He is expected at the research center the day before the day of first administration of the study compound. The volunteer has to be at the research center at 14:00 hrs in the afternoon. The time of entry may be changed. The volunteer will leave the research center on Day 17 of the study.

Intervention

The planned dose levels for the study are as follows:

Group 1 - Day 1 to 14 - Treatment: CORT113176 150 mg or placebo - How often: once daily (14 times in total)
Group 2 - Day 1 to 14 - Treatment: CORT113176 300 mg or placebo - How often: once daily (14 times in total)
Group 3 - Day 1 to 14 - Treatment: CORT113176 450 mg or placebo - How often: once daily (14 times in total)

Group 3 is optional.

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, sweating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about 210 milliliters of blood from the volunteer.

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

Sampling of cerebrospinal fluid
Insertion of the needle for the collection of cerebrospinal fluid may be painful. Removing the needle is painless. Usually no complications occur during

a lumbar puncture. Sometimes, during the puncture, a nerve can be hit. Then the volunteer will feel an electric pulse or a shooting pain in their leg. This can be painful, but is not harmful.

This method has been performed with humans before and was generally well tolerated. A number of complaints and complications related to the procedure are already known from previous studies:
• headache
• back pain and neck pain
• discomfort during the procedure
• hypersensitivity reaction to the lidocaine, the risk is very small
• pain at the location of the spinal catheter
• dizziness
• fainting
• inflammation or infection (1% of the cases with multiple cerebrospinal fluid sampling via a catheter); in rare cases this may result in meningitis
• bleeding and nerve damage; this risk is very small

The risks of abovementioned complaints are limited, but the volunteers may suffer from these or other, still unknown, complications. To keep the risks as low as possible, their health will be monitored continuously during the study.

Post-lumbar puncture headache is the most frequently occurring side effect and can occur sometimes up to 5 days later. The headache is characterized by the fact that it worsens with sitting and standing up or walking and improves when lying down. It can also be associated with severe nausea, double or blurry vision and disturbances in hearing. Post-lumbar puncture headaches are caused by leakage of cerebrospinal fluid through the puncture hole in the tough membrane (dura mater) that surrounds the spinal cord. This leakage decreases the pressure exerted by the spinal fluid on the brain and spinal cord, which leads to headache. The chance of a post-lumbar puncture headache developing depends on different factors such as age, weight and size of the needle used for sampling the CSF. Usually, the headache goes away by itself with resting on the bed and drinking plenty of fluids, including coffee containing caffeine. Therefore, if needed, as judged by the responsible doctor, the volunteers are allowed to drink coffee containing caffeine and/or will receive caffeine tablets.

If the volunteer do not respond to the standard *treatment* of bed rest, fluid intake and time, the responsible doctor may decide to perform an *epidural blood patch*. During this procedure a small volume of the volunteer own blood (approximately 15-20 mL that will be drawn from a vein in the arm) will be injected in the epidural space of the spinal cord (space just outside the meninges around the spinal cord) using an epidural needle. This will be performed by an anesthesiologist under sterile conditions. The volunteer will have to be in a sitting position with the legs held against each other. Relief of headache usually occurs swiftly after this procedure, sometimes directly

after administration of the blood patch. In some instances more than 1 attempt may be required for relief of headache.

After the procedure the volunteers have to lie down on their back for 1.5 - 2 hours, this is to decrease the risk of leakage of cerebrospinal fluid.
To limit the chance of headaches it is important that the volunteers drinks plenty of liquids (minimal 1.5 liters a day, from 1 day prior to the puncture [Day 6] until 1 day thereafter [Day 8]). During the lumbar puncture and the 1.5 to 2 hours thereafter fluid will be administered using an intravenous infusion.

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

Contacts

Public
Corcept Therapeutics Incorporated

Commonwealth Drive 149
Menlo Park CA 94025
US
Scientific
Corcept Therapeutics Incorporated

Commonwealth Drive 149
Menlo Park CA 94025
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Healthy male subjects.
2. Age 18 to 65 years inclusive at the time of signing informed consent (ICF).
3. Body mass index (BMI) of >=18.0 to <=30.0 kg/m2.
4. Weight of <= 100 kg.
5. Subjects who will undergo CSF sampling have to show a platelet count >=200,000/µL; international normalized ratio (INR) and activated partial thromboplastin time (aPTT) within normal laboratory ranges at screening and Day -1. The other subjects must show a platelet count above the lower limit of the normal laboratory range at screening and Day -1.
6. Must be willing and able to communicate with the study personnel, and participate in the whole study.
7. Willing and able to provide an ICF.

Exclusion criteria

1. Subjects who have received any IMP in a clinical research study within the 90 days before the first dose in this study.
2. Unable to swallow a test medicine of the size of the CORT113176 capsules
3. Subjects who are CRU or sponsor employees, or immediate family members of a CRU or sponsor employee.
4. Subjects who have previously been enrolled in this study. Subjects are only allowed to take part in one study part.
5. History of alcohol abuse or drug addiction (including soft drugs like cannabis products).

Study design

Design

Study type:	Interventional
Intervention model:	Other

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-07-2021
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	05-06-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2021

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	EUCTR2021-002456-36-NL
CCMO	NL77931.056.21

Study results

Date completed:	30-09-2021
Results posted:	04-05-2022

First publication
21-04-2022