Open-label, Non-randomised Extension Trial to Assess the Long-Term Safety and Efficacy of 1200 mg/day Arimoclomol 400 mg Three Times a Day (t.i.d.) in Subjects with Amyotrophic Lateral Sclerosis (ALS) who have Completed the ORARIALS-01 Trial

Published: 29-05-2019
Last updated: 10-04-2024

Primary objective:To assess the long-term safety of arimoclomol treatment of ALS.Secondary objective:To evaluate the long-term efficacy of arimoclomol treatment of ALS.Exploratory objectives:Health-related quality of life* To evaluate the effect of...

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

Summary

ID

NL-OMON55065

Source
ToetsingOnline

Brief title
Arimoclomol in patients with amyotrophic lateral sclerosis.

Condition

- Neurological disorders NEC

Synonym
neurodegenerative disorder and Lou Gehrig's disease

Research involving
Human

Sponsors and support

Primary sponsor: Orphazyme A/S
Source(s) of monetary or material Support: by the industry/company stated in question B6/B7 (Sponsor of the study;Orphazyme A/S) in G2

Intervention

Keyword: Arimoclomol in ALS patients

Outcome measures

Primary outcome

Primary endpoints:

* Incidence and severity of TEAEs over a treatment period of 76 weeks

* Mean and change from Baseline (of the present trial) to Week 76 (or End of Trial - Treatment Period 1) in clinical safety laboratory tests and vital signs

* Incidence of potentially clinically significant abnormalities in clinical safety laboratory tests and vital signs over a treatment period of 76 weeks

* C-SSRS over a treatment period of 76 weeks

Secondary outcome

Secondary endpoints:

* Time to PAV/tracheostomy/death (for subjects entering this trial having completed 76 weeks of randomised treatment in ORARIALS-01)

* Change in ALSFRS R from Baseline (of the present trial) to week 76 (End of Trial - Treatment Period 1)

* Change in SVC from Baseline (of the present trial) to the week 76 (End of

Trial - Treatment Period 1) (for subjects who did not meet the survival

endpoint in the ORARIALS-01 trial)

Study description

Background summary

This is an open-label, non-randomised, uncontrolled extension study to the ORARIALS-01 research study. Open label means that you, your primary caregiver, your legal representative, the Sponsor of the study, the study doctor, and study staff who treat you will be aware of the treatment you receive. Non-randomised means that you will not be assigned to the study treatment by chance as all subjects will be receiving the study drug arimoclomol at the same dose. Uncontrolled means that all subjects will be given arimoclomol and followed for a period of time to assess the safety and efficacy of the study drug, without being compared against a control group (ie, a placebo group). If you are eligible to participate in this study, you will receive arimoclomol in the form of 2 × 200 mg capsules to be swallowed by mouth, 3 times a day. This gives a total daily dose of 1200 mg. If required, the capsules can be opened and dispersed in a minimum of 10 to 20 mL (ie, 1 to 2 tablespoons) of liquid (wateror apple juice) or in a tablespoon of soft food material (yogurt or apple puree). Once dispersed, the study drug can also be administered via a gastric tube (as applicable). For full administration, the tube should be flushed with 5 mL of water after administration. If your dose of arimoclomol was reduced from 1200 mg/day to 600 mg/day in the ORARIALS-01 study, you will continue on this dose during this extension study. If you were already being treated with a drug for ALS called riluzole during the ORARIALS-01 study, you will be allowed to continue to take this, as well as the study drug.

Study objective

Primary objective:
To assess the long-term safety of arimoclomol treatment of ALS.

Secondary objective:
To evaluate the long-term efficacy of arimoclomol treatment of ALS.

Exploratory objectives:
Health-related quality of life
* To evaluate the effect of arimoclomol on health-related quality of life.
Population pharmacokinetics

* To investigate plasma levels of arimoclomol following administration of 1200 mg/day arimoclomol citrate (400 mg t.i.d.)

Safety
* To assess the long-term safety of arimoclomol treatment of ALS
Efficacy
* To assess the long-term efficacy of arimoclomol treatment of ALS

Study design

This is a multicentre, non-randomised, open-label, uncontrolled, trial to evaluate the safety and efficacy of long-term treatment of 1200 mg/day arimoclomol citrate (400 mg t.i.d.).
Subjects diagnosed with ALS according to the revised EL Escorial criteria must have completed the double-blind ORARIALS-01 trial. They will either have met the survival endpoint (tracheostomy or PAV) or they will have completed the 76 weeks randomised treatment period. The end-of-treatment visit of the double-blinded ORARIALS-01 trial corresponds to the Visit 1 of the OLE trial.
All subjects will receive open-label arimoclomol treatment.

Treatment Period

The trial is divided into 2 Treatment Periods. In Treatment Period 1,subjects will attend the investigator site for an in-person visit on a 4-weekly basis for the initial 6 months of treatment (on Day 1, Weeks 4, 8, 12, 16, 20, 24, 28). Following Week 28, in-person visits will be conducted on a 12-weekly basis until Week 76 (i.e., weeks 40, 52, 64 and 76). Throughout the treatment period subjects will also have remote visits (conducted by telephone) every 4 weeks (Table 1-1). All visits should be scheduled within the visit window of ± 7 days. Every effort should be made to ensure that the in-person visits at Week 52 and Week 76 are arranged as close as possible to the scheduled time point.

In Treatment Period 2, subjects will attend the investigator site for an in-person visit every 6 months (Weeks 100, 124 and 152) with remote visits (conducted by telephone) every 3 months in the intervening period.

In the event that a subject is no longer able to attend the trial site, an in-person visit may be conducted in the subject*s home/residency.

Safety Follow Up

Subjects who discontinue treatment will be encouraged to attend all planned visits as per protocol after drug discontinuation.
Additionally, these subjects will have a remote (telephone) visit 2 weeks after the premature IMP discontinuation.

End of Trial

All subjects will attend an end of trial visit.

Intervention

N/A

Study burden and risks

Adverse Effects of Arimoclomol
The study drug is in a research stage, so it may have adverse effects that are not known in advance.
Possible side effects of treatment with Arimoclomol are listed below, grouped by how likely they are to occur.
Very common: may affect more than 1 in 10 people
* Diarhoea
* Weight decreased (for most patients, the weight decrease is temporary)

Common: may affect up to 1 in 10 people
* Decreased appetite
* Shiver (tremor)
* Vomiting
* Hives

You should not drive or use machines if you experience tremor.

Symptoms of an allergic reaction such as hives with angioedema (swelling) have been reported in clinical trials. Stop taking Arimoclomol and tell your doctor if you experience hives and swelling.

In addition, arimoclomol may lead to an increase in serum creatinine levels (a waste product from the normal breakdown of muscle tissue) in blood and a decrease in mean creatinine clearance, which are laboratory signs that show stress with the kidney. Abnormally high levels of creatinine warn us of possible malfunction or failure of the kidneys.

In 1 (one) case, an elderly subject with inclusion body myositis experienced damage to kidneys resulting in decreased function approximately 1 month after initiation of arimoclomol. Although the subject had autoimmune disease (Sjögren*s syndrome) and was treated with omeprazole, both of which may have contributed to the event, it cannot be ruled out that the event was caused by treatment with arimoclomol.
We will monitor you carefully and offer treatment if these or other problems occur during the study.

Arimoclomol may also lead to an increase in liver enzymes, which are laboratory signs that may give early signals of risk of damage to the liver. The increased

liver enzymes have been observed within the first months of treatment. If this happens, your study doctor will request closer observation, e.g. additional blood samples every 2 to 3 days until your levels stabilise. If you are not able to undergo a close observation, or if your study doctor considers your level of liver enzymes are too high, you may be asked to stop study drug or other drugs.

If during the study, your blood results return with increased levels of liver enzymes (, your study doctor may request additional virology test for hepatitis A, B, C, D or E, to rule out that you do not have an acute infection of the liver. Your study doctor may also ask you for other assessment to monitor your liver function such as an abdominal ultrasound.

A one-time blood sample will be taken and sent to be stored at the central laboratory for up to two years after the completion of the trial if increased levels of liver enzymes is seen. This blood sample is taken so that additional analysis may be made to help understand the cause of the observation. If decided that this is not needed or when the two years is reached, the sample will be discarded. After analysis, the sample will be destroyed.

Allergic Reactions
As with taking any drug, there is a risk of an allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions include an itchy rash (hives) or swelling of the throat, making it difficult to breathe.
Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms, or any other side effects, during the study.

Blood Sampling
The risks of giving blood include fainting and pain, bruising, swelling, or rarely, infection at the location where the needle was inserted. These discomforts are brief and transient.
The total volume to be collected during your participation in this research study will not exceed 250 mL (i.e., approximately 17 tablespoons). The maximum volume of blood to be drawn at a single time point, i.e., at a single visit will not exceed 30 mL

Electrocardiogram
You may experience skin irritation from the ECG electrode pads or pain when removing the pads.

Risks to an Unborn Child
Studies in animals indicate that daily treatment with arimoclomol may affect male and female fertility. It is not known if this effect on fertility in animals will persist after end of treatment with arimoclomol. No human data are available.

Unknown Risks
There may be risks to you that are currently not known or cannot be predicted.
Your condition may worsen, remain the same, or improve as a result of taking part in this research study.
Please tell the study doctor or staff about all problems, illnesses, or injuries that happen to you during the study, even if you think they are not related to your partecipation in this study.
You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

New Findings
During the study, the study doctor will inform you and your primary caregiver of all new findings that could influence the use of the study drug or its safety profile and thus your agreement to take part in the study. You will receive this information orally and in writing.

Contacts

Public
Orphazyme A/S

Ole Maaløes Vej 3, Copenhagen N Ole Maaløes Vej 3
Copenhagen N DK-2200
DK
Scientific
Orphazyme A/S

Ole Maaløes Vej 3, Copenhagen N Ole Maaløes Vej 3
Copenhagen N DK-2200
DK

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is able to comprehend and is willing to provide written informed consent and is capable and willing to comply with trial procedures or in the circumstance that the subject is incompetent, informed consent/assent is provided in accordance with local regulation and/or procedures.
2. Subject has completed the ORARIALS 01 trial (i.e., met one of the surrogate survival endpoints of tracheostomy or PAV or has completed the 76 weeks randomised treatment period).
3. Subject completed ORARIALS-01 while on treatment, where on treatment is defined as having taken the last dose of IMP within 2 weeks of the End of Trial visit. (whether at week 76 or prior).

Exclusion criteria

1. Known or suspected allergy or intolerance to the IMP (arimoclomol or constituents).
2. Exposure to any other investigational treatment, advanced therapy medicinal product (ATMP) or use of any other prohibited concomitant medications (see section 6.8)
3. Women who are lactating or pregnant, or men or women unwilling to use a highly effective method of birth control if not surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy for women; vasectomy for men) for female participants until 4 weeks after last dose and for male participants until 3 months after last dose. Pre-menopausal women must have a negative pregnancy test prior to dosing with trial medication. Acceptable methods of birth control are:

a. Hormonal methods associated with inhibition of ovulation such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject*s usual menstrual cycle period) before IMP administration.
b. Total abstinence from sexual intercourse since the last menses before IMP administration. (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence methods [calendar, symptothermal, post ovulation methods] are not acceptable methods of contraception).
c. IUD or IUS.
4. Any of the following medically significant conditions:
a. Clinically significant renal or hepatic disease OR clinical laboratory

assessment (results * 3 times the upper limit of normal [ULN] for aspartate aminotransferase and/or alanine aminotransferase, bilirubin * 2 times the ULN, or creatinine * 1.5 times the ULN).
b. Any new condition or worsening of existing condition which, in the opinion of the investigator
would put the subject at undue risk.
5. Any serious adverse event or moderate/severe adverse event from the ORARIALS-01 trial which is ongoing at the time of transitioning to ORARIALS-02 and assessed as probably related to IMP.
6. Subjects who exceed 60 days from the End of Trial Visit date of the ORARIALS-01 trial at the time of enrolment.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-02-2020
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Arimoclomol
Generic name:	Arimoclomol

Ethics review

Approved WMO Date:	29-05-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-08-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	11-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2019-000374-39-NL
ClinicalTrials.gov	NCT03836716
CCMO	NL69675.041.19

Study results

Date completed:	17-06-2021
Actual enrolment:	10

Summary results
Trial is onging in other countries