A Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis

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Primary objectiveTo determine the efficacy of chronic treatment with arimoclomol 1200 mg/day (400 mg TID) compared to placebo over 76 weeks in subjects with ALS as assessed with Combined Assessment of Function and Survival (CAFS).Secondary…

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

Summary

ID

NL-OMON48938

Source
ToetsingOnline

Brief title
ORARIALS-01

Condition

- Neurological disorders NEC

Synonym
motor neuron disease and Lou Ghering disease

Research involving
Human

Sponsors and support

Primary sponsor: Orphazyme A/S
Source(s) of monetary or material Support: Orphazyme A/S

Intervention

Keyword: Arimoclomol in Amyotrophic Lateral Sclerosis

Outcome measures

Primary outcome

Primary endpoint

Combined assessment of function and survival (CAFS) over a treatment period of

76 weeks (or end-of-trial)

Secondary outcome

Secondary endpoints

* Time to PAV/tracheostomy/death

* Change from Baseline to Week 76 (or end-of-trial) in ALSFRS-R

* Change from Baseline to Week 76 (or end-of-trial) in SVC

Study description

Background summary

This is a multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of arimoclomol 1200 mg/day (400 mg TID) over a 76 weeks* treatment period.
Patients diagnosed with ALS who had first appearance of symptoms (weakness) within the previous 18 months will be eligible for screening.
In accordance with the eligibility criteria (Sections 5.2 and 5.3 of the study protocol), subjects participating in the present trial may be on a stable background treatment with riluzole. Additionally, a subset of up to 18 subjects on stable (i.e. minimum 6 months*) treatment with edaravone and who otherwise fulfil the eligibility criteria are planned for enrolment (see exclusion criterion 5 in the study protocol).
Following confirmation of eligibility during the Screening/Baseline period (Day -28 to Day 1), subjects will be randomised in a 2:1 ratio to receive either arimoclomol 1200 mg/day (400 mg TID) or placebo orally TID. Randomisation will be stratified by background riluzole use. The first post-baseline assessment will take place in-person at the investigator site 4 weeks after the Baseline

visit; subsequent assessments will consist of a combination of in-person visits and remote visits (telephone calls).
Subjects will attend the investigator site for an in-person visit on an 8-weekly basis for the initial 12 months of treatment (on Weeks 4, 12, 20, 28, 36, 44 and 52) and then for the following 6 months of treatment in-person visits are scheduled on a 12-weekly basis until the end of treatment (on weeks, 64 and 76). Assessments will include those for efficacy and safety, as well as sampling of biofluids for clinical safety laboratory tests, biomarkers, and PK according to the schedule of procedures. If a subject is no longer able to attend the site, appropriate trial site staff (e.g. nurse, sub-investigator as required) will assess the subject by conducting a home visit.
On the remaining weeks of the treatment period (Weeks 8, 16, 24, 32, 40, 48, 56, 60, 68 and 72) a remote visit will be conducted by the subject receiving a telephone call from the trial site staff. Assessments will therefore be limited to efficacy and safety evaluations according to the schedule of procedures.
All visits should be scheduled within the visit window (+/- 7 days) relative to the Baseline visit. 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.
An independent DMC will be established to monitor benefit. The DMC will act in accordance with the DMC charter and may have access to unblinded data.
At any time during the trial, the IMP may be temporarily halted for up to 4 weeks for an intolerable AE. Following re-challenge at the intended dose, de-escalation from 1200 mg/day (400 mg TID) to 600 mg/day (200 mg TID) may be considered. The subject will continue on this decreased dose for the remainder of the trial.
Subjects who discontinue treatment will be encouraged to attend all planned visits as per protocol after drug discontinuation. Additionally, these subjects will have remote visit 2 weeks after the premature IMP discontinuation.
If a subject reaches a trial survival endpoint (e.g. tracheostomy or PAV), the IMP will be permanently discontinued. The subject will be offered to participate in an open-label extension trial which will be conducted as a separate trial.
Subjects who complete 76 weeks of randomised treatment will be offered participation in a separate open-label extension which will be conducted as separate clinical trial.

Study objective

Primary objective
To determine the efficacy of chronic treatment with arimoclomol 1200 mg/day (400 mg TID) compared to placebo over 76 weeks in subjects with ALS as assessed with Combined Assessment of Function and Survival (CAFS).

Secondary objective
To evaluate the impact of arimoclomol 1200 mg/day (400 mg TID) compared to placebo on:

* Time to permanent assisted ventilation (PAV)/tracheostomy free survival
* Disease progression as measured by change from Baseline of the ALSFRS-R
* Progression of respiratory dysfunction as measured by change from Baseline of the slow vital capacity (SVC)

Safety objective
To assess the safety and tolerability of arimoclomol 1200 mg/day (400 mg TID) compared to placebo

Exploratory objectives
Efficacy
To explore the potential effect of 400 mg arimoclomol TID compared to placebo on cognitive and behavioural changes

Health-related quality of life
To evaluate the effect of 400 mg arimoclomol TID compared to placebo on health-related quality of life

Pharmacokinetics
To investigate CSF and serum levels of arimoclol following administration 400 mg arimoclomol TID

Biomarkers
To evaluate the effect of 400 mg arimoclomol TID compared to placebo on candidate biomarkers of target engagement, disease activity (markers reflecting ongoing neurodegeneration), and disease progression in blood, urine, and CSF compared to placebo.

Study design

A multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of arimoclomol 1200 mg (400 mg TID) over a 76 weeks* treatment period

Screening period
Screening may be up to 4 weeks prior to Baseline if a washout period for an investigational treatment is required. The minimum screening period is set as one week for practical reasons (to ensure all results are available to determine eligibility at Baseline).

Following confirmation of eligibility during the Screening/Baseline period (Day -28 to Day 1), subjects will be randomised in a 2:1 ratio to receive either arimoclomol 1200 mg/day (400 mg TID) or placebo orally TID. Randomisation will be stratified by background riluzole use.

Treatment period
The first post-baseline assessment will take place in-person at the

investigator site 4 weeks after the Baseline visit; subsequent assessments will consist of a combination of in-person visits and remote visits (telephone calls).

Subjects will attend the investigator site for an in-person visit on an 8-weekly basis for the initial 12 months of treatment (on Weeks 4, 12, 20, 28, 36, 44 and 52) and then for the following 6 months of treatment in-person visits are scheduled on a 12-weekly basis until the end of treatment (on Weeks 64 and 76).

On the remaining weeks of the treatment period (Weeks 8, 16, 24, 32, 40, 48, 56, 60, 68 and 72) a remote visit will be conducted by the subject receiving a telephone call from the trial site staff.

If a subject is no longer able to attend the site, appropriate trial site staff (e.g. nurse, sub-investigator as required) will assess the subject by conducting a home visit.

At any time during the trial, the IMP may be temporarily halted for up to 4 weeks for an intolerable AE. Following re-challenge at the intended dose, de-escalation from 1200 mg/day (400 mg TID) to 600 mg/day (200 mg TID) may be considered. The subject will remain on this decreased dose for the remainder of the trial.

End of treatment
Subjects who discontinue treatment will be encouraged to attend all planned visits as per protocol after drug discontinuation.

An end-of treatment visit is to be conducted 2 weeks after last administration of IMP in case of a) premature IMP discontinuation or b) subject completing trial but not continuing into open label extension trial

End of trial
All randomised subjects will attend an end of trial visit.

If a subject reaches a trial survival endpoint (e.g. tracheostomy or PAV), the IMP will be permanently discontinued. The subject will be offered to participate in an open-label extension trial which will be conducted as a separate trial.

Subjects who complete 76 weeks of randomised treatment will be offered participation in a separate open-label extension trial through means of a separate clinical trial protocol.

Intervention

Subjects found to be eligible will be randomised via the IWRS in a 2:1 ratio to one of the following treatments:
a) Arimoclomol 1200 mg/day (400 mg TID)
b) Placebo (matching)

Treatment assignment will also be stratified by background treatment with riluzole.

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, there is a risk that rare or unexpected adverse effects may occur. Arimoclomol may lead to an increase in serum creatinine levels in blood and a decrease in mean creatinine clearance, which are laboratory signs that show stress with the kidneys.
Placebo Risks
If the subject is in the group that is assigned to placebo (the medically inactive substance), the ALS symptoms may not improve or may even worsen.
Allergic Reactions
There is a risk of allergic reaction. If the subject has a very serious allergic reaction, she/he 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.
Blood Sampling
The risks of giving blood include fainting and pain, bruising, swelling, or rarely, infection where the needle was inserted. These discomforts are brief and transient.
Electrocardiogram
The subject may experience skin irritation from the ECG electrode pads or pain when removing the pads.
Lumbar Puncture
For most people, lumbar puncture does not cause any serious problems; the most common side effect is headache which is often associated with fatigue and dizziness. If this happens, the subject will be asked to lie down and drink fluids, as well as to contact the investigator. If the headache does not go away in a couple of days, it may be due to a spinal fluid leak from the puncture site. This can be treated with a *blood patch* (a small amount of your blood injected into the puncture site). Less common adverse effects include pain at the place where the needle was inserted, back, neck, or shoulder pain; these can be treated and usually improve over time. Other complications such as low blood pressure, dizziness, bleeding into the spinal canal or an infection of the spinal fluid are very uncommon, and may require treatment in the hospital. In rare cases, the subject may experience pain in the leg in connection with the sample retrieval, if the needle has hit a nerve. The study doctor will discuss any risks with the patient.
Risks to an Unborn Child

Women
The subject may not take part in this study if she is breastfeeding, are pregnant, think that she may be pregnant, or are trying to get pregnant. If she is pregnant or breastfeeding, there may be risks to her and the baby that are not known at this time. Women who can get pregnant will be tested for pregnancy before and during the study, and must have a negative pregnancy test at all clinic visits.
The subject must avoid getting pregnant in order to take part in this research study.
Men
The study drug may harm an unborn child. The subject must inform his partner of his participation in the study. The subject must agree not to have sexual intercourse or to use contraception (condom) with or without spermicide in addition to the birth control used by his partner during the study until 3 months after the last dose of the study drug.
If the subject thinks that his partner has become pregnant, he should, in agreement with his partner, tell the study doctor at once. If his partner gets pregnant during the study, he may be asked questions about the pregnancy and the baby. The study doctor will request permission from his partner to collect information regarding the pregnancy and the child.
Unknown Risks
There may be risks to the patient that are currently not known or cannot be predicted.
The subject condition may worsen, remain the same, or improve as a result of taking part in this research study.

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

1. Capable of- and willing to- provide written informed consent and comply with trial procedures.
2. Subject is male or female *18 years of age.
3. Subject meets revised El Escorial criteria for clinically possible, clinically probable / clinically probable ALS laboratory-supported, clinically definite ALS or clinically definite familial ALS laboratory-supported.
4. 18 months or less since first appearance of weakness (e.g. limb weakness, dysarthria, dysphagia, shortness of breath).
5. ALSFRS-R *35 and erect (seated) SVC % predicted * 70% at Screening.
6. Able and willing to travel to the site, and in the investigator*s opinion is likely to attend visits for at least 24 weeks.
7. All sexually active female subjects of child-bearing potential (postmenarchal)* must agree not to intend to become pregnant and use a highly effective method of contraception** during the trial through 1 month after the last dose of trial medication. If the subject is a sexually active male with female partners of child-bearing potential (postmenarchal) he must use a condom with or without spermicide in addition to the birth control used by their partners during the trial until 3 months after the last dose of trial medication.
8. Stable dose of riluzole (50 mg twice daily) for a minimum of 14 days prior to Day 1 (Baseline),or has not taken it for 14 days prior to Day 1.

Exclusion criteria

1. Tracheostomy or use of non-invasive ventilation for more than 2 hours during waking hours at the time of Screening and Baseline visits.
2. Pregnant or breast-feeding.

3. Current or anticipated use of diaphragmatic pacing during the trial.
4. Exposure to any investigational treatment within 4 weeks or <5 half-lives of the Screening visit, whichever is longest and/or advanced therapy medicinal product (ATMP), i.e. treatments based on genes, cells or tissues and/or participated in any prior ALS clinical trial receiving active drug treatment (with the exception described in exclusion criterion 5).
5. Treatment with edaravone within 4 weeks of the Baseline visit. However, up to 18 subjects on stable (i.e. minimum 6 months*) treatment with edaravone and who otherwise fulfil the eligibility criteria are planned for enrolment (limited to countries where edaravone has a marketing authorisation for treatment of ALS).
6. Any of the following medically significant conditions:
a) Neurological impairment/dysfunction or unstable psychiatric illness that in the investigator*s opinion is likely to interfere with assessment of ALS disease progression.
b) Clinically significant unstable medical condition other than ALS, which would present a risk to a subject to participate in the trial
c) Presence of dementia that impairs the ability of the subject to provide informed consent, according to the PI decision.
d) Known or suspected allergy or intolerance to the IMP (arimoclomol or constituents);
e) Chronic infection particularly HIV or Hepatitis B or C.
f) Clinically significant renal or hepatic disease
g) Aspartate aminotransferase and/or alanine aminotransferase, and/or lactate dehydrogenase *3 times the upper limit of normal [ULN], bilirubin*2 times the ULN, or creatinine *1.5 times the ULN). Laboratory tests may be repeated once at Screening. Reasons to repeat laboratory tests may include that the medication causing laboratory abnormality was suspended, any other suspected cause may no longer exist, or to rule out laboratory error.
h) Cancer that is currently under active treatment or is likely to require treatment during the trial that may alter the subject*s function and thereby interfere with assessment of ALS disease progression.
i) Any other condition that in the investigator*s opinion would present a risk to a subject to participate in the trial, interfere with the assessment of safety or has an increased risk of causing death during the trial.
* Non child-bearing potential is defined as post-menopausal (minimum of 12 months with no menses and follicle-stimulating hormone in the post-menopausal range) or sterilisation (hysterectomy, oophorectomy, or bilateral tubal ligation).** Highly effective methods of contraception include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; and vasectomised partner.According to the recommendations from the Clinical Trial Facilitation Group (CTFG, 2014), sexual abstinence is considered a highly effective birth control method only if it is defined as refraining from heterosexual

intercourse during the trial until 1 week after the last dose of trial medication (for female subjects of child-bearing potential) and for 3 months after the last dose of trial medication (for male subjects with female partners of child-bearing potential). The reliability of sexual abstinence needs to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.D29è*l*<

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-02-2019
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	18-09-2018

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-11-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-01-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2018-000137-13-NL
CCMO	NL65582.041.18

Study results

Date completed: 17-12-2020

Actual enrolment: 19

Summary results
Trial is onging in other countries