Interventional, randomised, partial double-blind, placebo- and positive controlled, multiple-dose, 4-way-cross-over trial Investigating the effect of arimoclomol on cardiac repolarization in healthy men.

Published: 17-03-2020
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Primary Objectives:* To evaluate the effects of therapeutic and supratherapeutic plasma levels of arimoclomol on the heart rate-corrected QT interval (QTc).Secondary Objectives:* To evaluate the effect of arimoclomol on other ECG parameters: heart...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49378

Source
ToetsingOnline

Brief title
CS0344 Orphazyme TQT

Condition

- Other condition

Synonym
protein aggregation and protein misfolding diseases (lysosomal storage diseases and neuromuscular disorders such as ALS

Health condition

protein aggregation and protein misfolding diseases (lysosomal storage diseases and neuromuscular disorders such as ALS

Research involving
Human

Sponsors and support

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

Intervention

Keyword: 4-way-cross-over, arimoclomol, cardiac repolarization, multiple dose

Outcome measures

Primary outcome

Primary Endpoint:

* Placebo-corrected change-from-baseline QTcF (**QTcF).

Pharmacokinetic Endpoints:

The pharmacokinetic parameters calculated for arimoclomol, M2 and M105 in

plasma are:

* AUC0-inf: area under the arimoclomol, M2 and M105 plasma-concentration-time

curves from zero to infinity

* AUC0-t: area under the arimoclomol, M2 and M105 plasma-concentration-time

curves from zero to last quantifiable plasma concentration

* AUC0-8: area under the arimoclomol, M2 and M105 plasma-concentration-time

curves from zero to 8 hours post-dose (Day 1 only)

* AUC%extrap: percent extrapolated of total AUC0-inf

* Cmax: maximum observed plasma concentration of arimoclomol, M2 and M105

* Tmax: time at which maximum observed plasma concentrations of arimoclomol, M2 and M105 occurred (Day 1 only)

* t*: terminal elimination half-life for arimoclomol, M2 and M105

* CL/F (oral clearance) (for arimoclomol only)

* Vz/F: apparent volume of distribution for arimoclomol

* MR (metabolic ratio, defined as AUCmetabolite/AUCarimoclomol)

Safety Endpoints:

* Adverse events

* Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and ECG parameter values

* Potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values

Secondary outcome

Secondary Endpoints:

* Change-from-baseline QTcF, HR, PR, QRS intervals (*QTcF, *HR, *PR, and *QRS)

* Placebo-corrected change-from-baseline HR, PR, and QRS (**HR, **PR, **QRS)

* Categorical outliers for QTcF, HR, PR, and QRS

* Frequency of treatment-emergent changes of T-wave morphology and U-waves presence

Study description

Background summary

Arimoclomol is an orally available small molecule that crosses the blood brain barrier and amplifies the cellular production of HSPs, in particular HSP70, through the activation of heat shock factor-1 (HSF-1), the major regulator of HSP gene transcription (Kieran et al., 2004; Neef, Jaeger, & Thiele, 2011). Heat shock proteins are part of a natural defence system and function by preventing protein misfolding under cellular stress and promoting proper lysosomal homeostasis. Thus, arimoclomol has a novel mechanism of action and may be used to treat conditions that involve misfolded proteins and/or dysfunctional lysosomes, such as LSDs (e.g. NPC and GD) and neuromuscular disorders (e.g. ALS and sIBM) (Ingemann & Kirkegaard, 2014; Kalmar & Greensmith, 2017).

Study objective

Primary Objectives:
* To evaluate the effects of therapeutic and supratherapeutic plasma levels of arimoclomol on the heart rate-corrected QT interval (QTc).
Secondary Objectives:
* To evaluate the effect of arimoclomol on other ECG parameters: heart rate (HR), PR and QRS interval and
T-wave morphology.
* To demonstrate sensitivity of the trial to detect a small QT effect using moxifloxacin as a positive control.
Safety Objectives:
* To evaluate the safety and tolerability of multiple therapeutic 124 (200) mg t.i.d. (372 (600) mg/day) and supratherapeutic 372 (600) mg t.i.d. (1116 (1800) doses of arimoclomol in healthy subjects.
Pharmacokinetic Objectives:
* To assess the PK of arimoclomol and metabolites M2 and M105 following administration of multiple therapeutic and supratherapeutic doses of arimoclomol.

Study design

This is a randomised, partial double-blind trial in healthy subjects, which will be conducted as a placebo- and positive-controlled, multiple dose, 4-way crossover trial using moxifloxacin as a positive control. Arimoclomol will be studied at both a therapeutic and a supratherapeutic dose level. The treatment with arimoclomol and placebo will be double-blinded, whereas the treatment with moxifloacin will be open-labeled.
See chapter 4 Trial Design of the CSP

Intervention

Thirty-two (32) subjects will be randomised to ensure 26 evaluable subjects per group. Subjects participating in the trial will attend the clinical trial site for screening, 4 in-house periods (Treatment Periods 1-4) and a follow-up visit, i.e. 6 visits in total, see Figure 4 1 of the CSP. The total trial duration will be between 12 to 20 weeks.

Each treatment period will consist of dosing 3 times a day (t.i.d) for 2 days on Days 1-2 and a single dosing in the morning on Day 3. Each treatment period will be separated by 17 (+2) days.
The subjects will be allocated to the following four treatments in separate periods in a randomised sequence:
* Treatment A: Arimoclomol, therapeutic dose level (124 (200) mg t.i.d)
* Treatment B: Arimoclomol, supratherapeutic dose level (372 (600) mg t.i.d)
* Treatment C: Placebo
* Treatment D: Moxifloxacin (positive control)
Subjects will be randomised in an equal ratio to one of 12 treatment sequences. Each treatment sequence will comprise all 4 treatments:
* ABCD, BADC, CDAB, DCBA, ACDB, BDCA, CABD, DBAC, ADBC, BCAD, CBDA, DACB

Study burden and risks

Since the study is being executed in healthy volunteers, there are no anticipated benefits of the IMP. Please see the IMPD for further information.

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. The subject is able to read and understand the Subject Information Sheet and Informed Consent Form.
2. The subject has signed the trial-specific Informed Consent Form.
3. The subject is a man
4. The subject must:
a. remain sexually abstinent, when this is in line with his preferred and usual lifestyle OR
b. engage exclusively in same-sex relationships OR
c. agree to avoid impregnating his partner from the Screening Visit until 2 weeks after the last dose of IMP, AND
d. agree to use highly effective contraception methods as described in Appendix 4 from the Screening Visit until 2 weeks after dosing if his female partner is of childbearing potential
e. not donate sperm until *3 months after the last dose of IMP

Exclusion criteria

1. The subject has taken any prescription or non-prescription medication <1 week prior to the first IMP dosing or *5 half-lives prior to the Screening Visit for any medication taken.
2. The subject has significant alcohol consumption, defined as an alcohol intake >21 units per week, or substance use (excluding nicotine or caffeine) deemed significant by the investigator, or a history of substance abuse (DSM-5® criteria) <12 months prior to the Screening Visit. A unit of alcohol is defined as 250 mL of lager/beer, 100 mL of wine, or 25 mL of spirits
3. The subject has taken any investigational medicinal product within 3 months prior to the first IMP dosing.

4. The subject has taken any nutritional or dietary supplements, herbal preparations, or vitamins within 7 days prior to the first IMP dosing.
5. The subject has previously been dosed with arimoclomol.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-06-2020
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	arimoclomol
Generic name:	arimoclomol

Ethics review

Approved WMO

Date:	17-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	25-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-05-2020
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	EUCTR2020-000415-68-NL
CCMO	NL73001.056.20