Multicenter, open-label, single arm study to evaluate long-term safety, tolerability, and effectiveness of 10mg/kg olesoxime in patients with SMA

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Main objective: The main objective of this open-label, single arm study is to further characterize the safety, tolerability and effectiveness profile of olesoxime in SMAThe primary safety objective for this study is as follows:To evaluate the safety...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON43897

Source
ToetsingOnline

Brief title
BN29854

Condition

- Musculoskeletal and connective tissue disorders congenital
- Muscle disorders
- Neuromuscular disorders

Synonym
Disease of muscles and nerves

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: Olesoxime, Spinal Muscular Atrophy, Treatment

Outcome measures

Primary outcome

Due to progressive proximal muscle weakness, study TRO19622CLEQ1275-1 considered the MFM D1 + D2 score as the most appropriate measure in patients with SMA Type 2 and non-ambulatory Type 3 and as such it was used as the primary endpoint in the study. As this open-label study aims to provide further clinical information and complement the results of study TRO19622CLEQ1275-1 consistency in primary endpoint is appropriate. The primary endpoint is therefore MFM D1 + D2.

Secondary outcome

Although MFM D1+D2 is considered to be the most appropriate measure for the study population and defined as primary efficacy endpoint in study TRO19622CLEQ1275-1 and in this study, it is important to evaluate the Total MFM score that includes D3 reflecting distal motor function. The Total MFM, D1+D2+D3 score and the HFMS score are therefore included as secondary efficacy measures.

An additional secondary efficacy measure is the proportion of patients with disease associated medical complications and procedures. An effective treatment for SMA is expected to reduce the incidence of comorbidities and thus the need

for medical interventions and procedures.

Consistent with TRO19622CLEQ1275-1, this study will use Forced Vital Capacity (FVC) to assess pulmonary function as an exploratory outcome. Pulmonary measures have been validated in SMA in a previous study and the FVC was the most reliable measure (Iannaccone et al., 2003).

Study description

Background summary

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder clinically characterized by progressive muscular weakness and atrophy. In most patients the disease results from homozygous deletion or mutation of the survival motor neuron protein (SMN) gene SMN1 (Lefebvre 1995). Clinical severity is inversely correlated with SMN2 gene copy number (Kolb and Kissel 2011).
SMA leads to predominantly proximal muscle atrophy and weakness and the potential for medical complications. There is no effective pharmacological treatment for SMA (Lewelt et al., 2012). Treatment is supportive with the goals being to improve the patient*s quality of life and to minimize disability (Wang et al., 2007).
Olesoxime (RO7090919, cholest-4en-3-one, oxime), is a cholesterol-like compound identified through its survival-promoting activity on trophic factor deprived motor neurons in culture. Olesoxime showed neuroprotective effects in four animal models of motor nerve degeneration as well as anti-nociceptive and neuroprotective effects in experimental models of painful peripheral neuropathies induced by diabetes or chemotherapy. Olesoxime binds to proteins that have been implicated in the formation or modulation of the mitochondrial permeability transition pore complex. By binding to these proteins, olesoxime may preserve essential mitochondrial functions such as calcium buffering in stressed neurons, thereby reducing neuronal degeneration and death (Bordet et al., 2010).
Seventeen clinical Phase 1, 2 and 2/3 studies were performed with olesoxime including one Phase 2/3 double-blind study in SMA (Study TRO19622CLEQ1275-1): 849 healthy subjects and patients have been exposed to olesoxime.
Information on non-clinical pharmacology, non-clinical safety and clinical experience can be found in the Olesoxime Investigator's Brochure (IB).

Study objective

Main objective:
The main objective of this open-label, single arm study is to further characterize the safety, tolerability and effectiveness profile of olesoxime in SMA

The primary safety objective for this study is as follows:
To evaluate the safety of olesoxime in patients with SMA, focusing on the nature, frequency, and severity of adverse events, as well as effects on laboratory values, vital signs and electrocardiogram (ECG) parameters

The secondary objectives for this study are as follows:
To evaluate effectiveness of olesoxime compared to the natural history of disease in patients with SMA, as measured by MFM D1+D2 and MFM Total scores, and HFMS score.
To evaluate the disease associated medical complications and procedures in olesoxime treated patients compared to the natural history of disease, focusing on their nature, frequency of occurrence, and severity
To evaluate the disease course between last visit of the studies TRO19622CLEQ1275-1 and TRO19622CLEQ1115-1, and baseline assessment in this study, as measured by motor functional scales (e.g. MFM) and as measured by nature, frequency, and severity of medical procedures.

The pharmacokinetic (PK) objectives for this study are as follows:
To investigate the pharmacokinetics of olesoxime in the target population using Bayesian feedback analysis based on a population pharmacokinetic model (as appropriate and permitted by the data).

The patient-reported outcome (PRO) objectives for this study are as follows:
To compare changes in Health Related Quality of Life and the relationship to other measures of disease status (such as motor function scales), following treatment with olesoxime versus the natural history of disease in patients with SMA, as measured by PedsQL core, and neuromuscular sub-scales.
To assess health-related quality of life and conduct economic modeling using the EQ-5D-5L.

CAREGIVER-REPORTED OUTCOME OBJECTIVES
The exploratory objectives for this study are as follows:
To assess caregiver related quality of life and conduct economic modeling using the Caregiver resource use: Work Productivity and Activity Impairment: Caregiver (WPAI:CG) and Caregiver generic health related quality of Life (Short Form-36 questionnaire)

The exploratory objectives for this study are as follows:
To explore olesoxime treatment response of FVC in patients with SMA.
To evaluate the percentage of responders in patients with SMA, defined as patients who did not have a decrease from baseline in MFM scores.
To investigate the impact of SMN2 copy number genes, transcripts and protein

involved in pathological pathways of SMA in patients with SMA on the safety, pharmacokinetics, pharmacodynamics, and efficacy of olesoxime.
To explore olesoxime treatment response to levels of SMN2 mRNA and SMN protein in blood.

Study design

This is an open-label, single arm study to further evaluate long-term tolerability, safety and efficacy outcomes in patients with SMA who previously participated in one of the following two clinical studies:
* Open-label Phase Ib, dose-ranged, single and multiple dose study to assess safety and pharmacokinetics of olesoxime in 6-25 year old Spinal Motor Atrophy (SMA) patients (TRO19622CLEQ1115-1), and
* Phase II/III, multicenter, randomized, adaptive, double-blind, placebo controlled study to assess safety and efficacy of olesoxime in 3-25 year old Spinal Muscular Atrophy (SMA) patients (TRO19622CLEQ1275-1).

The study will consist of Historical Data Collection, screening, treatment, and safety follow up periods. The study will occur in approximately 23 sites in 7 countries in Europe. All patients who participated in the studies mentioned above will be invited to participate in this study. The maximum number of patients in this study will be 171.

Historical Data Collection
All patients who participated in TRO19622CLEQ1115-1 or TRO19622CLEQ1275-1 will be asked to provide medical history and information of all relevant medical procedures that occurred between the patient*s last study visit of TRO19622CLEQ1115-1 or TRO19622CLEQ1275-1 studies and the screening visit of this current study, including:
* Motor Function Assessment using any SMA validated motor function scale, such as the MFM and HFMS;
* patient disability status as assessed during routine clinical visits, such as Brooke or Vignos scales;
* any documented medical procedures and therapies related to the natural course of SMA disease according to the opinion of the treating investigator.
The request to provide detailed medical history information will be documented in a separate Informed Consent Form (please refer to Appendix 2 of the protocol).
Patients (or their legal representatives) who decline to provide detailed medical history information are still eligible to participate in the treatment phase of the study.

Intervention

Olesoxime will be given as 100 mg/mL oral suspension. The drug will be administrated at 10 mg/kg once a day with food in the evening, throughout the

study, either orally or via gastric tube with food.

The clinical formulation is a powder and solvent for preparation of an oral suspension. The drug product will be supplied by Roche. Final investigational medicinal product (IMP) kits will be delivered as one box containing one amber glass bottle containing 7.5 g olesoxime powder and one amber glass bottle containing sesame oil. The powder will be constituted on first use to yield a homogeneous suspension containing 100 mg/mL of olesoxime in sesame oil. IMP will be administered in mL at a dose of 10 mg/kg with suitable oral devices. For more information please refer to the Investigator*s Brochure, the pharmacy manual, and the patient*s instruction for use.

Study burden and risks

During clinical development of olesoxime, 849 healthy volunteers and patients have been exposed to study drug. Olesoxime has shown to be well tolerated at all tested dose regimens including co-administration with riluzole or beta-interferons. To date, there are no identified risks with olesoxime therapy. Based on efficacy data from the completed trials and based on the safety findings observed to date, the sponsor considers the benefit-risk balance to have remained positive for the continuation of the development program with olesoxime.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

* Participation in the previous studies (TRO19622CLEQ11150-1 or TRO19622CLEQ1275-1)
* Able to comply with the study protocol, in the investigator*s judgment, including ability to take study treatment and perform study visits
* For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 28 days after last dose of olesoxime.

Exclusion criteria

* Patients who, in the opinion of the investigator, are not suitable to participate in this open label study
* Patients who have developed study drug hypersensitivity to olesoxime or one of the formulation excipients, including sesame oil
* Concomitant or previous participation in any other investigational drug or device study within 90 days prior to screening
* Concomitant or previous participation in a survival motor neuron protein gene (SMN2) targeting antisense oligonucleotide study within 6 months prior to screening
* Pregnant or lactating, or intending to become pregnant during the study.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-07-2016
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Olesoxime
Generic name:	Olesoxime

Ethics review

Approved WMO Date:	07-10-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-04-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	09-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Not approved Date:	29-08-2018
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	EUCTR2015-001589-25-NL
CCMO	NL54816.041.15
Other	nog niet bekend