



Clinical trial results:

Open-Label Phase Ib, Dose-Ranged, Single and Multiple Dose Study to Assess Safety and Pharmacokinetics of TRO19622 in 6-25 Year Old Spinal Muscular Atrophy (SMA) Patients

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2006-006845-14 |
| Trial protocol | FR |
| Global end of trial date | 06 November 2008 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 13 February 2016 |
| First version publication date | 13 February 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WP29845 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|---------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trophos Study ID: CL E Q 1115-1 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 April 2009 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 November 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was an open-label, single and multiple dose, dose-ranged study in participants aged 6-25 years with spinal muscular atrophy (SMA) type Ib, II, or III; to assess the safety, tolerability, and pharmacokinetic of single and multiple oral doses of olesoxime.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practices (GCP) based on guidelines of the European Economic Community and French law and with the principles of the Declaration of Helsinki as revised in Edinburgh, Scotland, October 2000, "note of clarification on paragraph 29 added by the World Medical Association (WMA) General Assembly, Washington 2002" and "Note of clarification on paragraph 30 added by the WMA General Assembly, Tokyo 2004". In accordance with French law, the sponsor had subscribed an insurance that covered the liability of the sponsor, the investigator and other persons involved in the study (Gerling France Police N [1680] 90712).

In order to protect anonymity and confidentiality, a code (five digits) was assigned to each participant enrolled in the study and was composed of the participant number, the first two letters of the last name and the first two letters of the first name. All study documents bore this code.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 17 December 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | France: 8 |
| Worldwide total number of subjects | 8 |
| EEA total number of subjects | 8 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 5 |

| | |
|---------------------------|---|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 3 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study was planned to evaluate 2 doses of olesoxime: 125 milligrams (mg) once a day (QD) and 250 mg QD; however, due to difficulties in recruitment the study was stopped after the inclusion of the 8th participant. Only the first dose (125 mg QD) was studied.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------------------|
| Arm title | Olesoxime 125 mg |
|-----------|------------------|

Arm description:

Participants received single oral dose of olesoxime 125 mg capsule on Day 1 followed by olesoxime 125 mg capsule orally once a day (QD) from Day 16 to Day 25.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Olesoxime |
| Investigational medicinal product code | TRO19622 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Olesoxime 125 mg capsule with 200 milliliters (mL) of water after standard breakfast on Day 1 and with 200 mL of water just before the noon meal from Day 16 to Day 25.

| | |
|--------------------------------|------------------|
| Number of subjects in period 1 | Olesoxime 125 mg |
| Started | 8 |
| Completed | 8 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Olesoxime 125 mg |
|-----------------------|------------------|

Reporting group description:

Participants received single oral dose of olesoxime 125 mg capsule on Day 1 followed by olesoxime 125 mg capsule orally once a day (QD) from Day 16 to Day 25.

| Reporting group values | Olesoxime 125 mg | Total | |
|---|------------------|-------|--|
| Number of subjects | 8 | 8 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 13.63 ± 7.37 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 4 | 4 | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Olesoxime 125 mg |
| Reporting group description: | |
| Participants received single oral dose of olesoxime 125 mg capsule on Day 1 followed by olesoxime 125 mg capsule orally once a day (QD) from Day 16 to Day 25. | |

Primary: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1] |
|-----------------|---|

End point description:

An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as AEs. AEs included SAEs as well as non-SAEs. An SAE was any experience that suggests a significant hazard, contraindication, side effect or precaution that: resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was medically significant. Analysis was performed on all enrolled participants.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Day 65

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this single arm study.

| | | | | |
|-----------------------------|------------------|--|--|--|
| End point values | Olesoxime 125 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 | | | |
| Units: participants | | | | |
| Participants with AEs | 5 | | | |
| Participants with SAEs | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Olesoxime

| | |
|-----------------|--|
| End point title | Maximum Plasma Concentration (Cmax) of Olesoxime |
|-----------------|--|

End point description:

Analysis was performed on all enrolled participants. Among the population, 2 participants who had stopped the treatment during repeated dose period, were excluded from the analysis on Day 25. For analysis, 2 sub-populations were defined: children and adults. Participants aged less than (<) 18 years were considered as children and participants aged greater than or equal to (≥) 18 years were considered as adults.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Single dose (Day 1): Pre-dose, 4, 8, and 12 hours after post-dose on Day 1, Days 2, 3, 5, and 10, pre-dose on Day 15; Multiple dose (Day 25): pre-dose, 4, 8, and 12 hours post-dose on Day 25, Days 26, 27, 29, 34, and 65

| | | | | |
|---|------------------|--|--|--|
| End point values | Olesoxime 125 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 ^[2] | | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1, Adults (n = 3) | 209 (± 25.2) | | | |
| Day 1, Children (n = 5) | 373 (± 201) | | | |
| Day 25, Adults (n = 3) | 594 (± 149) | | | |
| Day 25, Children (n = 3) | 1190 (± 1070) | | | |

Notes:

[2] - Number of participants (n) = participants evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Curve From Administration to 24 Hours (AUC0-24) of Olesoxime

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Curve From Administration to 24 Hours (AUC0-24) of Olesoxime |
|-----------------|--|

End point description:

AUC0-24 = Area under the plasma concentration-time curve from time 0 to 24 hours post dose. Analysis was performed on all enrolled participants. Among the population, 2 participants who had stopped the treatment during repeated dose period, were excluded from the analysis on Day 25. For analysis, 2 sub-populations were defined: children and adults. Participants aged <18 years were considered as children and participants aged ≥18 years were considered as adults.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Single dose (Day 1): Pre-dose, 4, 8, and 12 hours after post-dose on Day 1, Day 2; Multiple dose (Day 25): pre-dose, 4, 8, and 12 hours post-dose on Day 25, Day 26

| | | | | |
|--|----------------------|--|--|--|
| End point values | Olesoxime 125 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 ^[3] | | | |
| Units: hour*nanograms/milliliter (h*ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1, Adults (n = 3) | 3191.85 (± 979.39) | | | |
| Day 1, Children (n = 5) | 4427.16 (± 1760.54) | | | |
| Day 25, Adults (n = 3) | 12359.69 (± 4344.54) | | | |

| | | | | |
|--------------------------|-----------------------|--|--|--|
| Day 25, Children (n = 3) | 26232.49 (± 24381.78) | | | |
|--------------------------|-----------------------|--|--|--|

Notes:

[3] - Number of participants (n) = participants evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Time Passed Since Administration at Which the Cmax Occurred (tmax) of Olesoxime

| | |
|-----------------|---|
| End point title | Time Passed Since Administration at Which the Cmax Occurred (tmax) of Olesoxime |
|-----------------|---|

End point description:

Analysis was performed on all enrolled participants. Among the population, 1 participant who had an outlier value during single dose period, was excluded from analysis on Day 1 and 2 participants who had stopped the treatment during repeated dose period, were excluded from the analysis on Day 25. For analysis, 2 sub-populations were defined: children and adults. Participants aged <18 years were considered as children and participants aged ≥18 years were considered as adults.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Single dose (Day 1): Pre-dose, 4, 8, and 12 hours after post-dose on Day 1, Days 2, 3, 5, and 10, pre-dose on Day 15; Multiple dose (Day 25): pre-dose, 4, 8, and 12 hours post-dose on Day 25, Days 26, 27, 29, 34, and 65

| | | | | |
|-------------------------------|------------------|--|--|--|
| End point values | Olesoxime 125 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 ^[4] | | | |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1, Adults (n = 3) | 12 (8 to 12) | | | |
| Day 1, Children (n = 4) | 18 (8 to 24) | | | |
| Day 25, Adults (n = 3) | 8 (8 to 12) | | | |
| Day 25, Children (n = 3) | 8 (4 to 24) | | | |

Notes:

[4] - n = participants evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration Half-Life (t1/2) of Olesoxime

| | |
|-----------------|--|
| End point title | Plasma Concentration Half-Life (t1/2) of Olesoxime |
|-----------------|--|

End point description:

Plasma concentration half-life is the time measured for the plasma concentration to decrease by one half. Analysis was performed on all enrolled participants. Among the population, 1 participant who had a bad fitting in the terminal phase during single dose period, was excluded from analysis on Day 1 and 2 participants who had stopped the treatment during repeated dose period, were excluded from the analysis on Day 25. For analysis, 2 sub-populations were defined: children and adults. Participants aged <18 years were considered as children and participants aged ≥18 years were considered as adults.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Single dose (Day 1): Pre-dose, 4, 8, and 12 hours after post-dose on Day 1, Days 2, 3, 5, and 10, pre-dose on Day 15; Multiple dose (Day 25): pre-dose, 4, 8, and 12 hours post-dose on Day 25, Days 26, 27, 29, 34, and 65 | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Olesoxime 125 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 ^[5] | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1, Adults (n = 3) | 53.79 (± 6.87) | | | |
| Day 1, Children (n = 4) | 55.74 (± 6.46) | | | |
| Day 25, Adults (n = 3) | 69.08 (± 3.79) | | | |
| Day 25, Children (n = 3) | 68.78 (± 24.2) | | | |

Notes:

[5] - n = participants evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Dose and Weight Normalized Cmax of Olesoxime

| | |
|--|--|
| End point title | Dose and Weight Normalized Cmax of Olesoxime |
| End point description: | |
| Analysis was performed on all enrolled participants. Among the population, 2 participants who had stopped the treatment during repeated dose period, were excluded from the analysis on Day 25. For analysis, 2 sub-populations were defined: children and adults. Participants aged <18 years were considered as children and participants aged ≥18 years were considered as adults. Dose and weight normalized cmax was reported in nanograms/milliliter/milligram/kilogram ([ng/mL]/mg/kg). | |
| End point type | Secondary |
| End point timeframe: | |
| Single dose (Day 1): Pre-dose, 4, 8, and 12 hours after post-dose on Day 1, Days 2, 3, 5, and 10, pre-dose on Day 15; Multiple dose (Day 25): pre-dose, 4, 8, and 12 hours post-dose on Day 25, Days 26, 27, 29, 34, and 65 | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Olesoxime 125 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 ^[6] | | | |
| Units: (ng/mL)/mg/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1, Adults (n = 3) | 87.7 (± 6.56) | | | |
| Day 1, Children (n = 5) | 96.1 (± 72) | | | |
| Day 25, Adults (n = 3) | 256 (± 88.5) | | | |
| Day 25, Children (n = 3) | 352 (± 293) | | | |

Notes:

[6] - n = participants evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Dose and Weight Normalized AUC0-24 of Olesoxime

| | |
|-----------------|---|
| End point title | Dose and Weight Normalized AUC0-24 of Olesoxime |
|-----------------|---|

End point description:

AUC0-24 = Area under the plasma concentration-time curve from time 0 to 24 hours post dose. Analysis was performed on all enrolled participants. Among the population, 2 participants who had stopped the treatment during repeated dose period, were excluded from the analysis on Day 25. For analysis, 2 sub-populations were defined: children and adults. Participants aged <18 years were considered as children and participants aged ≥18 years were considered as adults. Dose and weight normalized AUC0-24 was reported in hour*nanograms/milliliter/milligram/kilogram ([h*ng/mL]/mg/kg).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Single dose (Day 1): Pre-dose, 4, 8, and 12 hours after post-dose on Day 1, Day 2; Multiple dose (Day 25): pre-dose, 4, 8, and 12 hours post-dose on Day 25, Day 26

| End point values | Olesoxime 125 mg | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 ^[7] | | | |
| Units: (h*ng/mL)/mg/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1, Adults (n = 3) | 1315.89 (± 208.25) | | | |
| Day 1, Children (n = 5) | 1037.8 (± 461.38) | | | |
| Day 25, Adults (n = 3) | 5369.42 (± 2325.92) | | | |
| Day 25, Children (n = 3) | 7694.38 (± 6664.91) | | | |

Notes:

[7] - n = participants evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Weight Normalized Apparent Oral Clearance (CL/F) of Olesoxime

| | |
|-----------------|---|
| End point title | Weight Normalized Apparent Oral Clearance (CL/F) of Olesoxime |
|-----------------|---|

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed. Analysis was performed on all enrolled participants. Among the

population, 2 participants who had stopped the treatment during repeated dose period, were excluded from the analysis on Day 25. For analysis, 2 sub-populations were defined: children and adults. Participants aged <18 years were considered as children and participants aged ≥18 years were considered as adults.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Single dose (Day 1): Pre-dose, 4, 8, and 12 hours after post-dose on Day 1, Days 2, 3, 5, and 10, pre-dose on Day 15; Multiple dose (Day 25): pre-dose, 4, 8, and 12 hours post-dose on Day 25, Days 26, 27, 29, 34, and 65 | |

| | | | | |
|--------------------------------------|------------------|--|--|--|
| End point values | Olesoxime 125 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 ^[8] | | | |
| Units: liters/hour/kilogram (L/h/kg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1, Adults (n = 3) | 0.18 (± 0.02) | | | |
| Day 1, Children (n = 5) | 0.21 (± 0.14) | | | |
| Day 25, Adults (n = 3) | 0.22 (± 0.11) | | | |
| Day 25, Children (n = 3) | 0.22 (± 0.19) | | | |

Notes:

[8] - n = participants evaluable for specified category.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 65

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Olesoxime 125 mg |
|-----------------------|------------------|

Reporting group description:

Participants received single oral dose of olesoxime 125 mg capsule on Day 1 followed by olesoxime 125 mg capsule orally QD from Day 16 to Day 25.

| Serious adverse events | Olesoxime 125 mg | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Olesoxime 125 mg | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Pharyngolaryngeal pain subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | | |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 20 September 2007 | To recruit 2 additional sites and to modify the list of investigators. |
| 15 May 2008 | To recruit 2 additional sites and to modify the list of investigators. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported