2 SYNOPSIS

Sponsor: TROPHOS	
Name of finished product: TRO19622	
Name of active ingredient: cholest-4-en-3-one, oxime	
Title: An open-label safety extension study of TRO19622 in Amyotrophic Lateral Sclerosis (ALS) patients treated with riluzole. Report date 04 December 2014.	
Investigators & study centers 15 centers in total; France (7), Germany (4), UK (2), Spain (1), Belgium (1) Principal investigator: [redacted], France See Appendix 16.1.4 for a list of all participating investigators.	
Publication (references): None	
Study period **Date of first inclusion:** 20 October 2010 **Date of last visit for last patient:** 19 April 2012	**Clinical phase:** II/III
Objectives **Primary objective** To allow patients to be treated by olesoxime (TRO19622) in an open-label safety extension following their participation in a randomized study and to provide additional safety data on olesoxime (TRO19622).	
Methodology Multicenter, open-label safety extension study. Each patient will be treated with olesoxime (TRO19622) for a maximum duration of 15 months.	
Number of subjects (planned and analyzed) Planned: 300-350 patients Analyzed: 271	
Diagnosis and criteria for inclusion Patients completing the 18-month study of TRO19622 in ALS patients treated with riluzole (Protocol TRO19622CLEQ1015-1) were eligible and were included on the basis of previous good tolerance and other clinical grounds. Patients had to provide signed informed consent. Patients with any ongoing, unresolved, clinically significant medical problem were excluded as were pregnant or breast-feeding women. All females had to use an effective method of birth control.	
Investigated Medicinal Product (IMP), dose, mode of administration, batch No. TRO19622, two soft capsules of 165 mg orally, once daily (total daily dose 330 mg QD), taken with lunch. Batch No: [redacted]	
Duration of treatment Expected overall study duration was up to ~26 months including an 11-month enrollment period and a 15-month treatment period. Individual patient study duration was up to 15 months until availability of the main outcome criteria (survival) of the double-blind randomized study.	
Reference product, dose, mode of administration, batch No. Not applicable	
Riluzole treatment All patients were to receive TRO19622 as add-on therapy to riluzole 50 mg bid orally, morning and evening on an empty stomach (at least 20 min before the meal). A marketed preparation of riluzole (not supplied by the Sponsor) as part of standard treatment for ALS was used.	
Criteria for evaluation *Primary outcome measure:* The primary outcome measure was the safety assessment. Criteria were • Occurrence of adverse events (AEs) • Clinical laboratory tests • Physical examination, including vital signs	

- Electrocardiography (ECG)

Secondary outcome measures:

- Overall survival
- Total score of the 48-point ALS Functional Rating Scale Revised (ALS FRS-R)
- Slow vital capacity (SVC) including percent predicted SVC for sites performing this as part of routine care.

Statistical methods

The sample size was based on a non-statistical estimation of the number of patients expected to complete the initial efficacy study and who would be eligible and willing to participate in the open-label extension study.

Safety

Safety analyses were performed using standard descriptive methodology.

Efficacy

Overall survival was estimated using the Kaplan-Meier method (95% confidence intervals for each 3-month period, median and quartiles) for the whole population and by site of onset.

ALS FRS-R scores (individual parameter and global) were analyzed by visit.

SVC was not analyzed due to incomplete data following the non-obligatory nature of the evaluation.

Summary and conclusions

Patient disposition

A total of 271 patients were included over an 11-month period, most in France (44.3%), Germany (22.5%) and Spain (18.8%). Of the 271 patients enrolled, 127 were in the placebo group, and the remaining 144 in the TRO19622 group in study TRO19622CLEQ1015-1. All 271 patients had at least one olesoxime intake. Patients were on study for a mean of 7.4 months ± 3.0 (range, 0.2-15.4), receiving ~6.8 months ± 2.9 of treatment. Riluzole was generally administered as planned to all patients.

As a result of the sponsor decision to prematurely terminate the study after unblinding of the initial randomized efficacy study, only three patients (1.1%) completed the study. The withdrawal rate for sponsor decision was 73.1%, 17.7% of patients withdrew due to death, 6.6% for patient decision and 1.5% for an AE.

Protocol deviations were reported in 16 patients (5.9%), 14 for unauthorized medications and 2 patients for delayed signed informed consent. In addition, 21 patients (7.7%) did not transfer directly to the extension study after completing the efficacy study.

Demographics

Male to female ratio was ~2:1 and mean age was 56.1 years ± 11.2 (range 31 to 81); 76.4% of patients were < 65 years. 229 (84.5%) out of 271 patients had spinal onset and the mean ALS FRS-R global score at study start was 27.0 ± 9.04 out of a maximum of 48 points (range 4-47).

AEs from the preceding trial which had not resolved at study start were reported in 48.3% of patients.

Clinically significant (CS) abnormalities in laboratory values were rare and not related to the study medication.

Mean vital signs and ECG parameters were mostly normal at inclusion. One patient had a CS ECG abnormality and 11.2% had abnormal NCS ECG outcomes. Median PR interval was 157 ms, median QRS was 95 ms, and median QTc interval (Bazett) was 405 ms (range 341 – 495).

All but one patient were receiving riluzole; other concomitant treatments included vitamins (55.7%), anti-depressants (44.6%), and anxiolytics/sedatives (36.9%).

Overall median treatment compliance was 99.3%, and was between 99 % and 100% for all visits other than the final visit (91.3%).

Efficacy

Overall survival: At 15 months, 48 of the 271 patients had died and Kaplan-Meier estimation of overall survival was 50.2% (95% CI, 18.8% - 75.3%).

The overall survival was higher in bulbar onset patients with 61.1%, 95% CI, 40.9% - 76.2% (13 of 42 patients had died) vs spinal onset at 50.4%, 95% CI, 17.8 - 76.2% (35 of 229 patients), however at all previous visits, an advantage was seen in the spinal group.

A significant difference in survival curves was seen between patients with bulbar versus spinal onset, with an advantage in patients with spinal onset (p=0.009).

Median survival was not reached in the overall population or in either the bulbar or spinal onset subpopulations.

ALS FRS-R global score: Mean global score decreased from 27.0 ± 9.04 at inclusion to 24.7 ± 9.41 after 6 months after which it remained relatively stable.

Safety

Adverse events

Half the patients (49.4%) had ≥ 1 TEAE. AEs included infections/infestations (18.8%), respiratory and gastrointestinal disorders (both 9.2%), and injury/ poison/ procedures (8.1%). Cardiac disorders were reported in 2.2% of patients. The most common events were respiratory/disease-related.

A total of 57 related TEAEs were reported in 12.5% of patients, 37 of which were considered possibly related. All others were unlikely related.

Most TEAEs were mild to moderate, with 18.8% of all events considered severe (12.5% of patients). Almost half of the severe events were respiratory/thoracic/mediastinal disorders (6.3% of patients) and severe respiratory-related infections were reported in four patients (1.5%).

Deaths, SAEs and withdrawals due to AE

Forty-eight patients (17.7%) died during the study, all but one due to ALS (one patient died following a pulmonary embolism).

Thirty-nine patients (14.4%) experienced at least one SAE, which were related for 11 patients (4.1%) including 4 patients with possibly related SAEs (deep vein thrombosis in 3 patients, one who also had pulmonary embolism, and one patient with myocardial infarction), while the other patients had unlikely related events. SAEs typically affected the lower respiratory tract and related SAEs were mainly cardiovascular events.

Ten patients (3.7%) had AEs resulting in death, 11 of 16 of which were respiratory/pneumonia. No deaths were considered probably or possibly related, however 2 patients had unlikely related SAEs (sudden death, pneumonia/respiratory failure) with an outcome of death.

Four patients (1.5%) withdrew from treatment due to possibly related AEs (6 events).

Laboratory events

For urea, alkaline phosphatase, sodium, creatinine, total bilirubin, and potassium, values were largely within ULN at inclusion and on study, and within 2 x ULN for cholesterol, AST, ALT, GGT and glucose. Several outliers between 2 and 4 X ULN at inclusion and/or worst value on study were seen for ALT, GGT, and creatinine kinase. Values were within ULN for most hematology parameters and within 1.5 x ULN for WBC, neutrophils, monocytes, basophils and platelets.

Overall mean values were generally stable for all parameters, although the incidence of non-significant clinical abnormalities increased over time in several parameters. Clinically significant laboratory abnormalities were rare.

Vital signs and ECG

There were no changes of note in vital signs or physical examinations. Mean weight decreased over time. Four patients had clinically significant ECG results on study. Median QTc was stable throughout the study.

Conclusions:

In this study, 271 patients received TRO19622 following completion of the initial efficacy study. Additional safety data were collected in these patients suffering from ALS treated for up to 15 months with TRO19622 330 mg QD plus riluzole 50 mg bid. No additional safety concerns were raised.