

Clinical trial protocol

Title

Open-Label Phase Ib, Dose-ranged, Single and Multiple Dose Study to assess Safety and Pharmacokinetics of TRO19622 in 6-20 year old Spinal Muscular Atrophy (SMA) patients.

Inclusion criteria:

Patients between 6-25 years old with SMA type Ib, II or III, whatever onset of disease on condition that disease started before 15 years old and that diagnostic be genetically confirmed and having a MFM score > or = 12

Exclusion criteria:

Non-inclusion if patients already treated by riluzole, hepatic insufficiency or ALAT_2N, renal insufficiency, severe Cardiac insufficiency, current pneumopathy, hemostasis disorders or any acute illness.

Medications:

Allowable medications or precautions:

- Paracetamol: Incidental use of paracetamol is allowed up to 48 hours before dosing and in limited amount (up to 1 g/day) following the start of the dosing with the consent of the investigator/co-investigator.

Forbidden concomitant medications:

- Medication being investigated for the treatment of SMA in a clinical trial setting (riluzole for example).
- Use of medication that could interfere with TRO19622 absorption: ezetimibe, bile salts chelators, fibrates.

Medications other than the IMP:

- Medications other than the IMP must only be taken exceptionally and with the agreement of the investigator in order to avoid interference with study assessments.
- The need for other medication may lead to exclusion of the patient from the study.
If symptomatic medication is needed to treat adverse events related to IMP, the investigator will inform the sponsor about the concomitant medication given.

Recruitment:

Total number of subjects:
2 cohorts of 10 patients.

However depending on similarity of SMA children PK parameters with adult ones, the second dose cohort may not need to be conducted. In that case the dose planned to be used for a Phase 2/3 efficacy and safety trial will be assessed for 3 months in a separate Phase 1b study with mainly safety assessments and minimal PK assessment such as TR019622 trough PK concentration.

Studied period:

Expected first enrolment: Q1 2007. Expected completion date: Q3 2007

Study duration:

For each patient, 3 months with a 5-week treatment period. Overall study duration 5 to 12 months depending on performance of one or two cohorts.

Criteria for evaluation:

Continuous recording of adverse events and concomitant therapies, physical examination, vital signs, ECG(12-leads), haematology, blood biochemistry and urinalysis, pharmacokinetics in blood.

Trial phase

Phase Ib

Test product, dose and mode of administration:

Capsules of TRO19622 25 and 125 mg,

Two doses of TRO19622 (125 and 250 mg QD) will be evaluated, oral route.

Duration of treatment: Single dose on day 1, 10 days of repeated dosing from Day 16 to Day 25, 4-week follow-up after treatment cessation.

Objectives:

To assess the safety, the tolerability and the pharmacokinetic of single and multiple oral doses of TRO19622 in SMA type Ib, II or III patients aged 6-25 years.

Methodology:

This study is an open label, single and multiple dose, dose-ranged, monocenter study in twenty patients (2 cohorts of 10 patients) with SMA type Ib, II or III.

Study procedures:

Patients between 6-25 years old with SMA type Ib, II or III having a MFM score ≤ 12 will be screened within one month before inclusion in the study. Screening will include only standard clinical, biological and SMA status assessment which are part of the routine care of the patients. The Investigator will explain to the patients the nature of the study, its procedures, requirements and restrictions so as to obtain their written informed consent.

It is possible to conduct the screening visit and the inclusion visit on the same day provided that all required data (laboratory tests, ECG, pulmonary radiography, MFM, FVC, FIM...) be available before performing the inclusion visit.

During the single dose administration period, patients will be hospitalized during 48 hours.

Visits at home will be carried out by visiting nurses or general practitioners on Day 5 and Day 10 in order to perform ECG and pharmacokinetic measurements.

During multiple-dose administration period, the patients will have to come back for an ambulatory visit on Day 15. Visits at home will also be carried out on Day 17 and D 19 in order to perform ECG measurements. The patients will be hospitalized on D 25 (steady state) for 24 hours in order to determine the pharmacokinetic profile in blood samples of TRO19622 given in multiple oral doses. ECG and pharmacokinetics will be performed at home on D 27 and D 29.

A post-treatment visit will be performed on Day 65.

National multicenter study