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"RILUZOLE (GLENTEK) IN PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 7: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT TRIAL WITH A LEAD IN PHASE".

Version n. 2.0, dated 28/09/2020
Study phase: IIb

GENERAL INFORMATION

Name and addresses of the clinical laboratories and other institutions involved in the trial

- Institute of Neurology of Catholic University of Sacred Heart of Rome, Prof. Gabriella Silvestri, gabriella.silvestri@rm.unicatt.it;
- Clinical Paediatric, Medical Sciences Department at University of Ferrara, Prof. Agnese Suppiej, agnese.suppiej@unife.it;
- National Rare Diseases Centre (CNMR) of National Institute of Health directed by Dr. Domenica Taruscio (it will be involved in the enrollment process, publicizing the trial through the National Associations for Ataxic Syndromes).
- Complex Diseases Group of National Centre of Epidemiology, Surveillance and Health Prom otion of National Institute of Health, Dr. Nicola Vanacore (statistical analysis unit).
- Morsani College of Medicine of University of South Florida (USF), Tampa, FL, USA.

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INVESTIGATOR'S AGREEMENT

"RILUZOLE (GLENTEK) IN PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 7: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT TRIAL WITH A LEAD IN PHASE".

Protocol code AIFA-2016-02365063

Sponsor Rappresentative

_____ _____

Prof. Maurizio Barbara — Date
NESMOS Department
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Giovanni Ristori — Date

TABLE OF CONTENTS

Abstract

Spinocerebellar ataxia type 7 (SCA7) belongs to the dominant forms of inherited cerebellar ataxias (CA), being one of the rarest form. SCA7 has no therapeutic options, so that the relentless course, the important visual deficit that accompanies CA, and the possibility of disease development in childhood are pressing unmet needs. We published encouraging data on riluzole in inherited CA other than SCA7. These results prompted off-label use of riluzole in single cases of SCA7 in Italy and United States, suggesting possible efficacy of the drug in this condition. We propose a clinical trial in SCA7 patients performing a serial evaluation of riluzole (Glentek) effects on stringent outcome measures: ophthalmological metrics, scale for the assessment and rating of ataxia (SARA) scores, and safety biomarkers.

The study design will be a randomized, double-blind, placebo-controlled pilot trial with a lead-in phase. The design will include a run-in phase of 6 months for all the participants, assessing ophthalmological metrics and SARA scores at the month 0, 3, and 6. Then one arm will undergo riluzole (Glentek) for other 12 months, while the other will take placebo for 6 months, and riluzole (Glentek) for the following 6 months; from both groups the same evaluations will be obtained at the month 12, 15 and 18 of the study.

Thirty-four patients will be enrolled at 4 clinical Centers (3 in Italy and one in U.S.). The clinical epidemiology aspects (design of the study, statistical analysis and enrollment process) will be followed by National Rare Diseases Centre and Complex Diseases Group of National Centre of Epidemiology, Surveillance and Health Promotion of National Institute of Health.

Eligible subjects for this study are patients (at least 7-year old) with positive genetic test for SCA7. Serious systemic illnesses or conditions (cardiac, haematologic and hepatic diseases) known for enhancing the side effects of riluzole (Glentek), pregnancy or breastfeeding will be exclusion criteria.

Participants will be randomly assigned (1:1) to riluzole (Glentek) (50 mg twice daily) or placebo. In pre-pubertal subjects the dosage will be adjusted on a mg/m^2 basis according to the recommended human daily dose (100 mg).

At baseline and after 3, 6, 12, 15 and 18 months, symptoms, physical and neurological signs, and SARA score will be recorded. At the same time points the following quantitative ophthalmologic assessments will be performed:

- Corrected visual acuity (right eye and left eye measurements) expressed as logMAR units with the ETDRS chart (either back-illuminated or projected).

- Color vision via a Farnsworth D15 Arrangement Test.

- Visual evoked potential are elicited using transient Pattern Reversal stimuli and monocular stimulation.

- Electroretinography

- Optical Coherence tomography with macular map of both eyes.

- Computerized visual field examination by standard automated perimetry and kinetic perimetry

Every three months electrocardiogram and a laboratory profile will be obtained for drug safety.

The co-primary endpoints will be the proportion of patients with stability of SARA score and visual acuity (in log MAR units) at 18 months, compared to the mean values of t0-t3-t6 evaluations.

A sample size of 17 patients per group (a total of 34 patients) had 80% power and an α value of 10% to detect a difference between the two groups of 35% in the co-primary end points. This calculation took into account published data on riluzole in CA.

Data will be expressed as mean (SD) for continuous variables and as proportions for categorical variables. Comparisons between riluzole (Glentek) and placebo group will be assessed using the t test for unpaired data for continuous variables and odds ratio with a relative 95% CI for categorical data. An intention-to-treat analysis will be done adopting a last observation carried forward method. A logistic regression model will be done at 18 months to adjust the results for the main baseline characteristics; p values less than 0.05 will be considered significant.

1. BACKGROUND INFORMATION AND TRIAL RATIONALE

1.1 Background

The hereditary ataxias are a group of genetic disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements. Frequently, atrophy of the cerebellum occurs. Hereditary ataxias can be divided into autosomal dominant cerebellar ataxias (ADCAs), autosomal recessive cerebellar ataxias (ARCAs), X-linked, and mitochondrial on the basis of mode of inheritance. ADCAs may also have diverse associated neurological features including retinopathy, optic atrophy, extrapyramidal or pyramidal signs, peripheral neuropathy, cognitive impairment, or epilepsy (1).

Spinocerebellar ataxia type 7 (SCA7) belongs to the dominant forms. It is caused by the expansion of a CAG repeat within the ataxin 7 (ATXN7) gene on chromosome 3p12-p21.1, leading to a pathogenic polyglutamine tract within the ataxin 7 protein. SCA7 is considered to be one of the rarest forms of ADCAs. In several studies SCA7 represented 2-4% of all SCAs, though higher frequencies were also observed (until 11,6%; 2,3). The mean prevalence is less than 1:100,000; however, founder effects have been reported in South Africa, Scandinavia, Venezuela and Mexico, where the prevalence is higher and SCA7 may be the most common form of SCAs (4-7). SCA7 is severe in its course, especially for the important ocular complications. It is also characterized by a progressive "anticipation" of the age at onset through the generations, manifesting often with visual loss during childhood. As for all the genetic forms of ataxia, SCA7 is suspected by family history, physical examination, and neuroimaging; the definite diagnosis is done through a molecular genetic test that is available in specialized laboratories.

There is no treatment option for SCA7. We reported encouraging data on riluzole effects in patients with cerebellar ataxias of different etiologies (8), and in patients with hereditary cerebellar ataxia other than SCA7 (9). The work rationale was based on experimental evidences showing a beneficial role of small-conductance potassium channels openers (including riluzole) in the pathophysiology of ataxia, a research line that is still actively underway (10-12). These works prompted an off-label use of riluzole in single cases of SCA7 followed at Department of Neurological Sciences School of Medicine -University of Padua-(one 41-year old woman), and at the Ataxia Research Center of University of South Florida, Tampa US (two siblings).

The 41-year old woman, with 40 triplets at ATXN7 gene, referred at 36 years visual deterioration and cerebellar signs with progressive course. She started riluzole in late 2014 when visual loss was overt, and SARA score was 30. After 2 years of riluzole therapy SARA score was 25: the patient reported subjective benefit after 3-4 months from beginning of treatment, while no improvement in vision occurred; she is going on under riluzole therapy without adverse events. Two female siblings (51 and 60 years-old) assessed at Tampa Center, reported visual disturbances and were evaluated for SCA7: the molecular analysis of ATXN7 gene demonstrated abnormally expanded CAG repeats in both patients (39 for the older one and 40 for the younger one) confirming the diagnosis. At the beginning motor signs were absent or unremarkable. They were followed up by ophthalmological examinations (best-corrected visional acuity, color vision - Roth 28 Hue test-, electroretinography - ERG - and optical coherence tomography – OCT -) and neurological examination (including SARA scale) for several years. In late 2010 they started riluzole when their visual acuity measured as logMAR was 0.6 and SARA score 8 (both measures indicate worsening as they increase). After one year of therapy cerebellar and visual functions improved (respectively 6 at SARA score and 0.4 at logMAR) in both siblings with comparable metrics. SARA score remained stable for 3 years and then started to increase (13 at the last evaluation - 5 years after the beginning of the treatment), while visual acuity and OCT lesions were practically stable in both siblings since they started the drug.

Overall, the published data (8, 9) as well as these preliminary results, warrant a trial aimed at verifying the effects of riluzole in SCA7. The search of at least a symptomatic approach for this rare inherited disease should be considered a pressing unmet need: the relentless course, the important visual deficit, the possibility of disease development in childhood are all good reasons to add results coming from an informative clinical trial to the available evidences.

Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS). The recommended daily dose is 100 mg (50 mg every 12 hours). Repositioning this approach in cerebellar ataxia seems promising (8,9), although the mechanism of action of riluzole in this condition is not fully understood.

The action of small-conductance potassium channel openers is a plausible working hypothesis that is being investigated (10-12). An additional pleiotropic neuroprotective effect was described: the drug enhances the uptake of glutamate by astrocytes and reduces the release of glutamate from

active synapses, counteracting damage by excitotoxicity; it also enhances activity of the TWIK-related potassium channel-1 (TREK-1) and intracellular expression of heat shock proteins that have a neuroprotective role and counteract blood–brain barrier dysfunction (13,14).

1.2 Scientific Rationale

Considering published data on riluzole in cerebellar ataxia (8, 9), as well as preliminary results on single SCA7 cases, we propose an a randomized, double-blind, placebo-controlled pilot trial with a lead in phase, aimed at verifying the effects of the drug in an informative number of SCA7 families. The impact on study population is of potential great relevance being the therapeutic options for SCA7 virtually nil. An effectiveness of riluzole, even as a symptomatic approach, may be important for the life quality of these people. The potential impact on the National Health Service (NHS), and on the Health Service of other countries as well, deals with the heavy direct and indirect costs that this condition implies, and that may be, at least in part, relieved by a therapy of some efficacy. A clinical trial has never been tried before in SCA7; however, our previous studies in cerebellar ataxias proved to be encouraging, and the benefit/risk ratio of the attempt seems acceptable.

1.3 Objectives of the study

The objective of the trial will be to evaluate riluzole (Glentek) effects on cerebellar ataxia, visual impairment, and safety biomarkers. Our working hypothesis is that riluzole (Glentek) is superior to the current pragmatic approaches that have minimal, if any, effect on disease progression. In the section 2 of the protocol the primary and secondary objectives of the study are detailed.

1.4 Risk/benefit evaluation

Riluzole (Glentek) resulted beneficial in patients with cerebellar ataxias of different etiologies (8), and in patients with hereditary cerebellar ataxia (9). The only observed adverse event was a reversible increase of liver enzymes.

Considering these data, the use of riluzole at the same therapeutic regimen as ALS in cerebellar ataxia seemed handy and devoid of specific adverse events, that proved to be within the expected safety profile (especially reversible increase of liver enzymes).

2. TRIAL OBJECTIVES

2.1 Primary Objective

The co-primary objective will be to compare the two study arms for the proportion of patients who remain stable at SARA (15) score and visual acuity at 18 months respect to run-in.

2.2 Secondary Objective

The secondary objective will the effect of riluzole (Glentek) on visual function using quantitative ophthalmologic assessments and on SARA score, as continuous values, assessing changes at 18 months compared to run-in. The wide panel of ophthalmological exams should warrant the clinical relevance of the possible drug effects.

2.3 Safety Objectives

To investigate the overall safety and tolerability of riluzole (Glentek) administered in SCA 7 patients.

3. INVESTIGATIONAL PLAN

3.1 Trial Design and Plan

Small clinical trials are necessary when there are difficulties in recruiting enough patients for conventional statistical analyses to provide an appropriate answer. These trials are often necessary for the study of rare diseases as well as specific study populations (e.g. paediatric, geriatric, individually tailored therapies, regional subpopulations). In these settings the issue of small sample size has to be faced. The European Medicines Agency guidelines on clinical trials in small populations (CHMP/EWP/83561/2005) considers the problems associated with clinical trials when there are limited number of patients available to study and clearly defines the field of application.

To choose the trial design we used the algorithm performed by Cornu t el al. (16). We opted for a randomized, double-blind, placebo-controlled pilot trial with a lead-in phase. Moreover, the patients to be included in the placebo arm will receive riluzole (Glentek) during the last 6 months of study, so that all patients will undergo the active drug in the last phase of the study (figure 1). The lead-in phase will allow to define for each patient the pre-treatment values of co-primary end

points. This study design will provide also an estimate of individual effectiveness (personalized medicine). Overall, the design will include a run-in phase of 6 months for all the participants, during which the baseline characteristics of the patients, as well as an ophthalmological evaluation and neurological scales will be obtained at the month 0, 3, and 6. Then one arm will undergo riluzole (Glentek) for other 12 months, while the other will take placebo for 6 months, and riluzole (Glentek) for the following 6 months; from both groups the same evaluations will be obtained at the month 12, 15 and 18 of the study.

3.2 Study population

Thirty-four patients meeting inclusion criteria will be enrolled at the following Centers: UOC Neurologia – NESMOS Department -Sapienza, University of Rome, S. Andrea Hospital; Institute of Neurology of Catholic University of Sacred Heart of Rome; Child Neurology and Clinical Neurophysiology Paediatric, and Institute of Neurology at University of Padua; Morsani College of Medicine of University of South Florida (USF), Tampa, FL, USA.

3.3 Inclusion criteria

1. Male and female of any race and > 6 years old
2. Positive genetic test for SCA7.
3. Signed Informed Consent. (in case of minors, written informed consent must be obtained by parents or legal representative)

3.4 Exclusion criteria

1. Female subjects: pregnant or lactating women cannot participate in the study. Women of childbearing potential cannot participate unless willing to use highly effective contraception methods as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study drug. Periodic abstinence (e.g., calendar, ovulation,

symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

2. Subjects with a clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation. Such conditions may include cardiovascular, pulmonary, hepatic, renal, severe systemic mycotic infections, metabolic diseases or malignancies.
3. Hepatic diseases with serum values of alanine aminotransferase, aspartate aminotransferase or bilirubin > 1·5 times above normal limit
4. Any medical or psychiatric condition that may affect the subject ability to give informed consent, or to complete the study, or if the subject is considered by the treating neurologist to be, for any other reason, an unsuitable candidate for this study.
5. Known hypersensitivity to any component of riluzole (Glentek).

4. TRIAL TREATMENT

4.1 Investigational Medicinal Products

Participants will be randomly assigned (1:1) to riluzole (Glentek) or placebo. Study drug will be orally dispensed in doses of 50 mg twice daily for 12 months in the treated group and for 6 months in the comparison group. In pre-pubertal subjects the dosage will be adjusted on a mg/m^2 basis according to the recommended human daily dose (RHDD; 100 mg). The investigational medical products will be prepared (packaging and labeling) by an independent Contract Research Organization (CRO).

4.2 Delivery, Handling and Storage

Study drugs will be supplied by the Sponsor after the completion of all the Ethical and Administrative procedures. At receipt the drug conditions will be checked for the adequacy.

The study drug shall be carefully stored in the study site, in a safe area and apart from other drugs.

The Principal Investigator shall maintain records of the study drug delivery to the study site, of the inventory at the study site, and of the use by each subject.

After study conclusion, all drugs not used, partially used or not at all used shall be returned to the Sponsor.

Numbered kits, one per subject, will be provided.

Study medication will be delivered to clinical sites in blocks, according to the randomization list. Each clinical site will be then re-supplied when the study medication has been almost totally allocated to enrolled subjects. Re-supplies will follow the rate of recruitment at each clinical site.

4.3 Packaging and Labeling

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

The drug labels will be written in the language of the Country where the study takes place (Italy).

4.4 Drug Accountability

The investigators will maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by coordinator unit during site visits or remotely and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and packaging at scheduled visit, at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the coordinator unit.

4.5 Concomitant and permitted therapy

There is no therapy for SCA7. The patients usually take supplements or carry out protocols of physical therapy. The participants' treatments at recruitment will be maintained all over the trial to prevent bias or status changes due to the switch in symptomatic approaches (especially the physical therapy).

4.6 Prohibited Therapy and interaction with other medicinal products and other forms of interaction

There have been no clinical studies to evaluate the interactions of riluzole with other medicinal products. In vitro studies using human liver microsomal preparations suggest that CYP 1A2 is the

principal isozyme involved in the initial oxidative metabolism of riluzole. Inhibitors of CYP 1A2 (e.g. caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones) could potentially decrease the rate of riluzole elimination, while inducers of CYP 1A2 (e.g. cigarette smoke, rifampicin and omeprazole) could increase the rate of riluzole elimination.

Consuming low doses of caffeine and nicotine is required during the study.

If previous medications are used during the trial, the subject will drop-out the study.

5. TRIAL CONDUCT

Participants will be randomly assigned (1:1) to riluzole (Glentek) or placebo. Riluzole (Glentek) 50 mg or placebo was given orally every 12 h for 12 months in the treated group and 6 months in the comparison group. The investigational medical product will be prepared (packaging and labeling) by an independent Contract Research Organization (CRO).

A list of randomization numbers and corresponding treatment numbers will be computer-generated by the National Institute of Health before the start of the study. A centralized randomization system will be organized at the Centre for Experimental Neurological Therapies (CENTERS). The assignment of the patient to the treatment or placebo group will be determined ensuring that each clinical centers will include patients in both arms of the trial. All subjects who will sign the informed consent and receive a screening code will be entered into a screening and enrolment log. The Investigator will record the date of birth, date of consent, and date of randomization, if applicable, or reason for not being randomized.

Participants and assessing neurologists and ophthalmologists will be masked to treatment allocation. A two-physician treating and assessing model will be used; the treating physician will be as responsible for supervision, drug administration, recording of adverse events, and safety assessments. The assessing neurologists and ophthalmologists will be exclusively responsible for ophthalmologic and neurological assessments. All patients included in the trail will be followed for 18 months.

Baseline evaluation will include history, electrocardiogram, clinical and neurological assessment us ing SARA and ophthalmological exams (see below). Blood will be sampled for routine laboratory ev aluation. After 3, 6, 12, 15 and 18 months, symptoms, physical and neurological signs, and SARA sc

ore will be recorded. At the same time points the following quantitative ophthalmologic assessme nts will be performed:

- Best corrected visual acuity (right eye and left eye measurements) expressed as logMAR un its: Visual acuity is affected in SCA7 and will therefore be measured longitudinally. This test it to be applied with the ETDRS chart (either back-illuminated or projected) with the patient's correction for distance.
- Color vision: SCA7 is often characterized by cone-rod dystrophy affecting color vision. Therefore, color vision will be assessed longitudinally via a Farnsworth D15 Arrangement Test.
- Visual evoked potentials are elicited using transient Pattern Reversal stimuli and monocular stimulation. The checkerboard is displayed on a television screen subtending a visual angle of 15°. Contrast is 99%, spatial frequencies equivalent to three visual angles of 60 and 15 minutes are separately presented.
- Electroretinography: photopic and scotopic paradigms following the international guideline , modified for children, are used, with recording skin electrodes (17,18) Scotopic ERG is obt ained after at least 20 min of adaptation in a fully darkened room with dim blue light flashe s delivered at 2 sec interstimulus interval (ISI). Photopic responses are recorded after 10 mi n light adaptation. Responses are also obtained with 30 Hz flickering white light. The wavef orms obtained from the average of 100 responses to each stimulus condition.
- Optical Coherence tomography: macular map of both eyes.
- Computerized visual field examination: standard automated perimetry (30.2 threshold exa m) and kinetic perimetry

Every three months electrocardiogram and a laboratory profile (CBC, liver enzymes including AST, ALT, GGT, bilirubin and creatinine) will be obtained for drug safety.

All the data will be recorded on paper case record form (CRF). The participating Centers will sendtt to the coordinator the CRF at each time point's assessment (within one week from the neurologica l and ophthalmological evaluations). The expected estimate of subjects lost to follow up will be about 5%.

5.1 Trial Visit Schedule

See Flow Chart.

5.2 Trial Procedures by Visit

Prior to performing any trial assessments, the Investigator will ensure that the subjects have provided written informed.

Seven visits per subject are planned:

Visit 1 – from day -3 to day +1 Baseline, Randomization, Treatment

Visit 2 – 3 months (±7 days) Follow-up visit

Visit 3 – 6 months (±7 days) Follow-up visit

Visit 4 – 9 months (±7 days) Follow-up visit

Visit 5 – 12 months (±7 days) Follow up visit

Visit 6 – 15 months (±7 days) Follow-up visit

Visit 7 – 18 months (±7 days) End of study visit

Visit 1 – from day -3 to day +1: Screening, Randomization, Treatment start

- Informed Consent collection
- Evaluation of inclusion and exclusion criteria
- Demographic data collection
- Evaluation of concomitant medications
- Physical examination and neurological examination
- Collection of the medical history
- Evaluation of concomitant medications
- Physical examination and neurological examination
- Ophthalmological assessment
- SARA scale
- Hematology and Blood Chemistry (and pregnancy test if female)
- Electrocardiogram

Visit 2 – 3 months (±7 days);

The following assessments will be done at visits:

- Evaluation of concomitant medications

- Physical examination and neurological examination
- Collection of the medical history
- Evaluation of concomitant medications
- Physical examination and neurological examination
- Ophthalmological assessment
- SARA scale
- Hematology and Blood Chemistry (and pregnancy test if female)
- Electrocardiogram

Visit 3 – 6 months (±7 days); Visit 4 – 9 months (±7 days); Visit 5 – 12 months (±7 days); Visit 6 - 15 months (±7 days); Visit 7 – 18 months (±7 days) End of Study

The following assessments will be done at visits:

- Evaluation of concomitant medications
- Physical examination and neurological examination
- Collection of the medical history
- Evaluation of concomitant medications
- Physical examination and neurological examination
- Ophthalmological assessment
- SARA scale
- Hematology and Blood Chemistry (and pregnancy test if female)
- Electrocardiogram

5.3 Biosamples

Biosamples will be collected and analized only for safety issues. Samples will be not stored and used for other purposes.

5.4 Compliance

The Investigator will promote compliance by instructing the patient to take the study medication exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient will be instructed to contact the Investigator if he/she is unable

for any reason to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or study personnel at each visit using capsule counts. This information should be captured in the source document at each visit.

The patients will record information concerning their home study drug administrations in a diary provided for the study. The Investigator will review the diary with the patient at each visit and record the information on the relevant CRFs.

A monitor will perform and document drug accountability during site visits and at the end of the study. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

5.5 Emergency breaking of assigned treatment code

The study is designed as a double-blind study and neither the patient nor the clinical site personnel (Investigator, sub-Investigator, study nurse, pharmacist) will know which treatment is being administered. The identity of the treatments can't be revealed except in an emergency under the discretion of the Investigator.

The Principal Investigator will receive a study treatment identification key in the form of sealed envelopes containing the kit number and the corresponding treatment.

The envelope can be opened only in case of an emergency presenting the need to disclose the identification of the study treatment assigned to the patient, for the purpose of establishing the appropriate therapy. Once the code is broken for a patient, this patient shall be withdrawn from the study, with the completion of the final study evaluation, indicating the specific reason of the patient withdrawal.

Sponsor must be notified immediately by the Investigator of any emergency unblinding; the date and time, along with the reason for the unblinding, will be noted. Treatment codes will not be freely available to the Investigator until after the study completion and database lock.

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition.

After an emergency treatment code break, the patient should discontinue study drug.

5.6 Definition of Completion

A subject will be defined as "completed" if he/she completes Visit 7 of the trial. Termination at a different time point will be considered as discontinuation.

Project completion will be the date of the Last Visit Last Subject (LVLS).

5.7 Study Discontinuation

Subjects may be discontinued at any time from the trial for any of the following reasons:

- An AE occurs that, in the opinion of the Investigator, makes it unsafe for the subject to continue in the trial, included laboratory test abnormalities evaluation Riluzole should be discontinued if the ALT levels increase to 5 times the upper limit of the normal range
- The subject is lost to follow-up
- The subject dies
- The subject withdraws consent
- The Investigator, for any reason, terminates the entire trial, or terminates the trial for that subject or the attending physician requests that the subject is withdrawn for any medical reason.
- The Sponsor or the Regulatory Authority or the Ethics Committee(s), for any reason, terminates the entire trial or terminates the trial for this trial site or this particular subject.

If a subject is discontinued from the trial, the Investigator will complete the end of trial visit CRF pages. The Investigator should try to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights.

5.8 Study Interruption

The Sponsor may consider trial closure at a clinical site if the following occurs:

- serious and/or persistent non-compliance with the protocol;
- inadequate collaboration of site personnel with Sponsor

- administrative reasons
- non-compliance with GCP, SOPs or regulatory requirements
- lack of confidentiality and/or non-compliance with the contract spread with the Sponsor.

6. METHODS OF ASSESSMENT

6.1 Efficacy Endpoints

The co-primary endpoints will be the proportion of patients with stable SARA score and visual acuity expressed as log MAR units [the metric to quantify the best corrected visual acuity, by applying the ETDRS chart (either back-illuminated or projected) with the patient's correction for distance] at 18 months, in comparison with the same parameters calculated for each patient as mean of t0-t3-t6 evaluations (lead-in period). The measure of visual acuity by log MAR units is commonly used in serial study and is related to subjective visual function (19). Concerning SARA scores, the scale is a validated, widely accepted, end point in studies on cerebellar ataxic syndromes (15). Moreover, our group has already used this outcome measure and described its relationships with daily living in a previous study (9).

6.2 Secondary endpoints

The secondary endpoint will be quantitative ophthalmologic assessments (via a Farnsworth D15 Arrangement Test, Visual evoked, Electroretinography, Optical Coherence tomography, Computerized visual field examination) and SARA score as continuous values at 18 months, in comparison with the same parameters calculated for each patient as mean of t0-t3-t6 evaluations (lead-in period).

The wide panel of ophthalmological exams should warrant the clinical relevance of the possible drug effects.

6.3 Safety Endpoints

The safety profile will be assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events, physical examination findings including laboratory tests.

Trial site personnel will report any adverse event (AE), whether observed by the Investigator or reported by the subject.

6.4 Adverse Events

6.4.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse events observed during all periods of a clinical trial are to be recorded, since the first dose of study treatment injection.

Within the scope of this trial, such untoward medical occurrences would be considered as "AEs" even if the subject was not yet administered the investigational medical product (IMP) but had already signed the Informed Consent Form.

Adverse Drug Reaction (ADR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (SADR)

Any untoward medical occurrence or effect that at any dose:

- Results in death. This includes any death that occurs during the conduct of a clinical trial, including deaths that appear to be completely unrelated to the IMPs (e.g., car accident).
- Is life-threatening. This includes any AE during which the subject is, in the view of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include events that may have caused death if they had occurred in a more severe form.
- Requires subject hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Other medical events that based upon appropriate medical judgment are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Note: Planned hospitalization due to a pre-existing condition (corrective procedure, etc.) will not be regarded as a SAE for these trials.

Clinically significant findings at screening (e.g. laboratory findings) are not considered an AE/SAE.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information.

6.4.2 Classification of Adverse Events

The Investigator will classify AEs based on their intensity and relationship to the trial drug/placebo**.**

Intensity

For this trial, the intensity of an AE will be rated according to the following definitions:

Mild — Symptom barely noticeable to subject; does not influence performance or functioning. Prescription medication is not ordinarily needed for relief of symptom but may be given because of the personality of a subject.

Moderate — Symptom of a sufficient intensity to make a subject uncomfortable; performance of daily activities influenced; subject is able to continue the trial; treatment for symptom may be needed.

Severe — Symptom causes severe discomfort. May be of such intensity that a subject cannot continue the trial. Intensity may cause cessation of treatment with the IMPs; treatment for symptom may be given and/or subject hospitalized.

Relationship to Investigational Products

For this trial, an AE cause and effect relationship to the IMPs will be classified by the Investigator as follows:

Table 1: relationship between AE and IMP

Description	Definition
Certain	The AE is clearly related to the IMP
Probable	The AE is likely related to the IMP
Possible	The AE may be related to the IMP
Doubtful	The AE is doubtfully related to the IMP
None	The AE is clearly not related to the IMP
Unknown	Causality is not assessable, for one reason or another, e.g. because of insufficient evidence, conflicting data or poor documentation

6.4.3 Reporting Adverse Events

As a minimum, at each visit during the study, the Investigator or sub-Investigator will ask the subject whether he/she has experienced any health problems or symptoms since the last visit. An open style questioning will be used to avoid the possibility of influencing the subject.

During the course of the trial, all AEs (including SAEs), irrespective of the relatedness to the IMPs, will be recorded in detail in the source records and transcribed onto the AEs pages of the CRF. The Investigator will be responsible for ensuring that the correct information concerning all AEs is entered on the appropriate CRF pages.

The reporting period for AEs is the period starting from the time of the informed consent release and lasting until 36 months (± 7 days). At the end of this follow-up period, all unresolved AEs will be documented on the CRF as "ongoing".

In addition to the AE data collected on the CRF, Investigators are obliged to report SAEs that occur during the study to the Sponsor's pharmacovigilance responsible person immediately, within 24 hours, as described in the following section.

6.4.4 Reporting Serious Adverse Events (SAEs)/Serious Adverse Drug Reactions (SADRs)

All SAEs and all SADRs, occurring from the time of signing of the informed consent form until the last visit (36 months), must be reported immediately to the Sponsor's pharmacovigilance responsible person appointed for the study.

Information on the actual fax and phone numbers are provided in the Investigator file. The Investigator or designated personnel must call as well as fax or e-mail the completed Serious AEs/Serious ADRs Reporting Form to the Sponsor's pharmacovigilance responsible person within 24 hours of observation or notification of a Serious AE/ADR. All of these events must also be recorded on the appropriate CRF sections.

The Investigators should contribute to the clarification of the cause(s) of the SAE/SADR and to the assessment of potential risks by providing any relevant information obtained or requested with respect to the case and inform the Sponsor's pharmacovigilance responsible person of the outcome and other relevant follow-up information of the SAE/SADR.

Multiple independent SAEs/SADRs for the same subject which occur simultaneously should be described on the same SAE/SADR Reporting Form.

Serious Adverse Event/Serious Adverse Drug Reaction reporting to Local Ethics Committees/Competent Authority

It will be the responsibility of the Investigator to inform the Ethics Committee (EC) about SAEs/SADRs, according to local requirements. It is the responsibility of the Sponsor (or Sponsor's designee) to submit applicable SUSAR Reports to the Competent Authority and to the coordinating Ethics Committee.

6.4.5 Follow-up of Serious Adverse Events/Serious Adverse Drug Reactions

SAEs/SADRs will be followed by the Investigator until the outcome is resolved, has reached a stable condition in the Investigator's opinion, or until the subject is lost to follow-up. When the clinical site receives any new relevant information about a SAEs/SADRs, the site will fill out a new SAE/SADR Reporting Form and tick the "Follow-up" box of the SAE/SADR Reporting Form and fax or e-mail it within 24 hours to the Sponsor's pharmacovigilance responsible person.

6.4.6 Riluzole (Glentek) Undesirable Effects

Table 2: List of adverse reactions from Riluzole (Glentek).

MedDRA System Organ Classes	Undesirable effects	Frequency
Blood and lymphatic system disorders	Anaemia	Uncommon
Immune system disorders	Anaphylactoid reaction, angioedema	Uncommon
Nervous system disorders	Headache, dizziness, oral paraesthesia, somnolence	Common
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	Uncommon
Cardiac disorders	Tachycardia	Common
Gastrointestinal disorders	Nausea Diarrhoea, abdominal pain, vomiting Pancreatitis	Very Common Common Uncommon
Hepato-biliary disorders	Abnormal liver function tests	Very common
General disorders and administration site conditions	Asthenia Pain	Very common Common

The frequency has been determined according to the following criteria: very common (> 1/10), common (> 1/100, <1/10), uncommon (> 1/1 000 to <1/100), rare (> 1/10 000 to <1/1 000), very rare (<1/10 000), not known (frequency cannot be estimated from the available data).

7. STATISTICAL METHODS

7.1 Sample Size Determination

We assumed that a sample size of 17 patients per group (a total of 34 patients) had 80% power and an α value of 10% to detect a difference between the two groups of 35% in the proportion of patients with stable SARA score and visual acuity (in log MAR units) at 18 months, compared to

mean of t0-t3-t6 evaluations. This calculation took into account published data on riluzole (Glentek) in cerebellar ataxia (8, 9).

7.2 Definition of Trial Populations for Analysis

The trial results will be assessed according to an intention to treat (ITT) approach. Each subject enrolled in the study will be included in the ITT population. The opportunity of a per protocol (PP) analysis will be considered after the review of preliminary results. In this case, the PP population will exclude subjects with major protocol violations.

7.3 Efficacy Analysis

Data will be expressed as mean (SD) for continuous variables and as proportions for categorical variables. Comparisons between the riluzole (Glentek) and placebo groups will be assessed using the t test for unpaired data for continuous variables and odds ratio (OR) with a relative 95% CI for categorical data. An intention-to-treat analysis will be done adopting a last observation carried forward method. A logistic regression model will be done at 18 months to adjust the results for the main baseline characteristics; p values less than 0.05 will be considered significant.

7.4 Safety Analysis

The safety profile of each treatment will be assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events occurring during the study and laboratory tests.

Incidence, type, and severity of the adverse events will be summarized by presentation of the number of subjects with any AE, related AEs (including those possibly related, or not evaluable), and serious AEs. AEs will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs will be summarized in frequency tables according to the MedDRA terms. Chi-square test or Fisher's exact test will be used to compare the frequency of subjects with AE and the frequency and characteristics of AEs between treatment groups.

Laboratory tests will be summarized and compared in terms of frequencies for normal, abnormal non-clinically significant and abnormal clinically significant values. Chi-square test will be used, if

appropriate. In case of low number of cases with abnormal values, only individual description will be provided.

7.5 Planned Interim Analysis(es)

No interim analysis is planned.

8. DATA SAFETY MONITORING BOARD / DATA MONITORING COMMITTEE

No Data Safety Monitoring Board/Data Monitoring Committee is planned for this study.

9. ETHICAL AND REGULATORY ASPECTS

9.1 Laws and Regulations

This clinical study will be conducted in accordance with the principles contained in the Declaration of Helsinki as amended by the World Medical Association in Fortaleza, Brazil, October 2013, and in compliance with all international and national laws and regulations of the country in which the trial is performed, as well as any applicable guidelines. If there are conflicts between local laws and regulations, the more stringent requirements will be adopted.

9.2 Subject's Information Sheet and Informed Consent Form

The Investigator is responsible for and will obtain informed consent from each subject in the study, in accordance with the ICH-GCP Guidelines and the current version of the Declaration of Helsinki.

All subjects invited to participate in the clinical trial are entitled to make their decision based on all current available information provided to them by the Investigator/designee. In addition, they will be given a document in native language written in clear concise lay language for review and consideration. The document will previously have been approved by relevant Independent Ethics Committees (IECs) and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the trial.

This document will tell potentially eligible subjects about the nature of the IMP(s), their efficacy and safety profile, the route of administration, and the human experience available. It will also outline the steps of the protocol as they will apply to the individual, including the number of visits

and types of procedures/assessments/measurements to be performed so that the individual has a clear picture of the risks, inconveniences and benefits that may accrue from the trial.

The subject must be made aware that he/she may refuse to join the trial or may withdraw his/her consent at any time without prejudicing further medical care and that he/she is covered by the Sponsor's indemnity insurance in the event of a trial related injury. Contact details (mobile, pager, etc.) to report and discuss suspected trial-related injuries will be provided. Subjects must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by Regulatory Authorities and IEC and that personal information will be collected and retained in a confidential database. Conditions for ensuring the anonymity of data and the security and confidentiality of the database should be explained.

Consent will always be given in writing after the subject has had adequate time to review the information and ask questions, if need be. The subject and the Investigator conducting the informed consent discussion will both personally write the name, sign and date the consent form. Two copies of the informed consent form shall be signed. The Investigator shall provide one signed copy of the signed informed consent and one copy of the subject information sheet to the subject, and will keep the second copy of the original signed forms in the onsite study file.

The signed form will be reviewed by the study monitor.

9.3 Ethics Review and Authorization by Competent Authorities

Prior to the start of the study, the protocol, amendment(s), consent form, information sheet, Investigator's Brochure, and any written information to be provided to subjects will be submitted to the national Competent Authority (CA) and to coordinating and satellite IECs. The designated CRO will obtain a copy of the written approval by each IEC and a list of the IEC members, their titles or occupations, and their institutional affiliations and will provide originals or copies of these documents to the Sponsor. The study will be conducted in the proposed country in accordance with the respective local regulations and requirements.

All documents subject to review during the study, including any modifications made to the protocol after receipt of IEC approval, will also be submitted to the coordinating IEC and CA for approval prior to implementation, unless they cover administrative issues only. Each Investigator must also provide periodic reports as required, and promptly report important safety information (i.e., SAEs) to the IEC. The CA will be notified by the Sponsor or designee of completion of the

study (Last Visit Last Subject – LVLS) and a synopsis of study results will be provided. The Sponsor will provide study results to the IECs, too.

9.4 Protocol Amendments

Changes to the protocol may only be made by means of a written amendment, which has to be approved and signed by the authorized individuals of the Sponsor and by the Investigator.

The trial code, the title of the trial, the progressive number and the date of the amendment must be recorded on the first page of the document.

Exhaustive justifications that motivate the amendment to the protocol should clearly be addressed in the document.

All substantial protocol amendments must be submitted to IECs and to Regulatory Authority (where applicable) for review and approval unless it covers administrative issues only. In this case the IEC and the Regulatory Authorities (when applicable) will be notified of the amendment without the request to review and approve it.

The Investigator, the Sponsor and IEC, separately or together, should decide whether the subject's informed consent form needs to be changed.

The Investigator will not modify the protocol without first discussing the changes and obtaining the Sponsor's written approval.

9.5 Protocol Deviations

The Investigator is to conduct the trial in accordance with the approved current protocol. In order to obtain interpretable results, neither the Investigator nor the Sponsor will alter the trial conditions agreed upon and set out in this protocol.

In the event that an isolated, unforeseen instance resulting in a protocol deviation occurs, the Investigator is to document and explain this deviation and notify the Sponsor and the Coordinating Investigator as soon as possible, in writing.

In no instance should this increase the subject's risk.

9.6 Data Collection

During each subject's study visit, the study Investigator or a designee will collect and report study data on the relevant subject's chart, documenting all significant observations. Any contact with the subject via telephone or other means that provides significant clinical information must be documented on the source data. All information present on the source data and relevant to this clinical trial will be promptly entered in the CRFs.

A Paper Case Report Form will be used for recording subjects' trial data. The Investigator will maintain a list of all persons authorized to make entries and/or corrections on the CRFs. Data entries and corrections will be made only by the authorized persons. It is the responsibility of the Investigator to ensure that the CRFs are properly and completely filled in. The CRFs must be completed for all subjects who have been included in the trial. The Investigator will review all CRFs and sign and date them for each subject, verifying that the information is complete, true and correct. All fields on the CRF must be completed as applicable.

Checks to assess the appropriateness and consistence of data will be developed on monitoring visits. After CRF pages will be approved and signed by the Investigator, they can be reviewed on site by the monitor. Data Clarification Forms (DCF) will be generated during on site monitoring and the Investigator will have to check and resolute them. The Investigator is responsible for the review and approval of all query resolutions.

9.7 Trial Documentation and Record Retention

The Investigator must retain investigational product disposition records, copies of CRFs, and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroy any records associated with the study.

The Sponsor will notify the Investigator when the trial records are no longer needed.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed designee (e.g., another Investigator). Notice of such transfer will be given in writing to the Sponsor.

9.8 Confidentiality

The Sponsor must ensure that the Investigator keeps secret from third parties any confidential information disclosed or provided by the Sponsor and regarding the Sponsor and its trial-related

products. The Investigator agrees to use such information only to accomplish the present trial tasks and not to use it for any other purposes without the prior written consent by the Sponsor.

The Investigator of each study site must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorised parties. According to the Directive 95/46/EC (General Data Protection Regulation, GDPR), only an identification code (i.e., consists of identification number, sex and year of birth) should be recorded on any form or biological sample submitted to the laboratory, Sponsor, Competent Authorities' or Ethics Committee.

The PI must keep a screening and enrolment log showing codes and names for all patients screened and for all patients enrolled in the trial.

In compliance with the GCP-ICH the study information will be kept secure by appropriate physical, technical, organizational and other measures to safeguard study data and prevent unauthorized or unlawful processing or accidental loss or destruction. Study information will only be accessible to authorized staff and will be stored for only as long as it is needed.

Data management responsible will take appropriate steps to ensure that appropriate technical and security measures are put into place when transferring study data within data management unit, and that such data transfers are carried out in accordance with applicable local law.

9.9 Study Report and Publication Policy

The results of the clinical study will be documented in an integrated clinical study report according to ICH E3 Note for Guidance on Structure and Content of Clinical Study Reports.

The Sponsor and the Investigator(s) agree that no publications presenting or discussing data and/or results from clinical trials sponsored by the Sponsor will take place until the participating center(s) has/have completed the trial, the data have been interpreted, and the final report has been issued.

9.10 Insurance

The Sponsor will obtain liability insurance, which covers health impairments resulting from drugs and/or substances/investigational products administered in the course of this trial for which the subject has given his/her written informed consent. This liability insurance also covers health impairments resulting from trial procedures.

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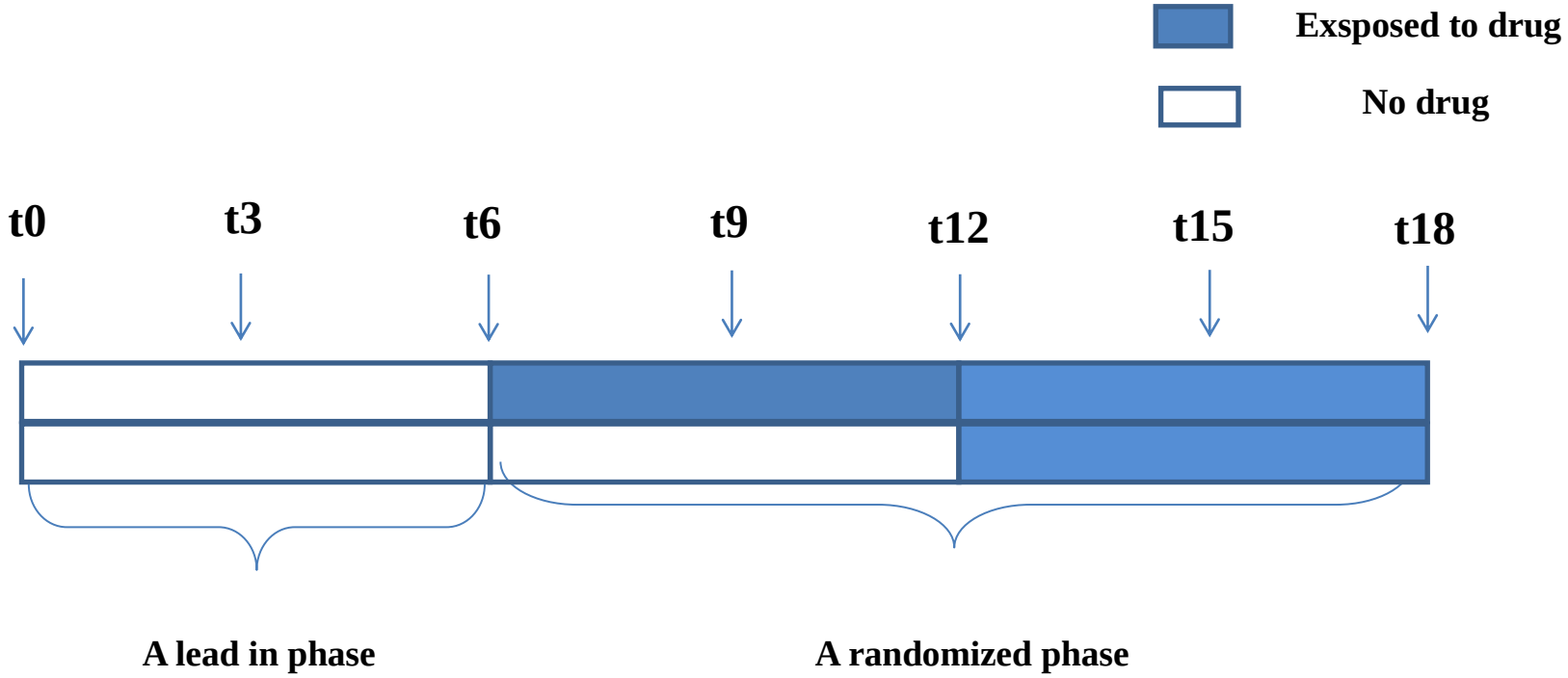
STUDY DESIGN



Flow Chart

	Visit 1		Visit 2	Visit 3-7
Activity	T0 Baseline Randomization Treatment		T3 Follow-up visit	T6-T9-T12-T15-T18 Follow-up visit
Informed Consent	x			
Inclusion / Exclusion Criteria	x			
Demographic data	x			
Medical History	x			
Concomitant medications	x		x	x
Physical examination	x		x	x
Neurological examination(SARA score)	x		x	x
Electrocardiogram	x		x	x
Ophthalmological exams	x		x	x
Hematology and Blood Chemistry	x		x	x
Randomization		x		
Study drug/placebo				x
Adverse Events			x	x