PROTOCOL SUMMARY

TITLE OF THE STUDY

A Prospective Multicentre Study to Evaluate the Consistency of the IHS Diagnostic Criteria, the Usefulness of Brain MRI for the Diagnosis, Follow Up and Treatment Management, and the Outcome after High Dosage 6-Methylprednisolone Therapy, in Subjects with Tolosa Hunt Syndrome.

STUDY TYPE/PHASE

Multicentre Prospective study

STUDY OBJECTIVES

The three main objectives of this study, not listed in order of relevance, are the following:

1. to acknowledge the clinical and MRI characteristics of the THS at presentation, for diagnostic purpose.

2. to acknowledge the outcome after a determined steroid treatment in the THS by describing:

   - the time to pain resolution after the starting of the steroid treatment;
   
   - the time to symptom resolution after the starting of the steroid treatment;
   
   - the time to neurological sign resolution after the starting of the steroid treatment;
   
   - the time to pathological tissue disappearance at MRI after the starting of the steroid treatment;
   
   - the occurrence of relapses after the discontinuation of the steroid treatment;
   
   - the effect on the outcome of the site of the lesion.
3. to evaluate the consistency of the ICHD II diagnostic criteria for THS; specifically regarding:

- the time to pain resolution after the starting of the steroid treatment;
- the time to symptom resolution after the starting of the steroid treatment;
- the time to neurological sign resolution after the starting of the steroid treatment;

**Hypothesis**

The hypothesis is that the time to the symptoms and signs disappearance after the starting of the steroid treatment may be more than 72 hours, that the time to the disappearance of the pathological tissue at MRI outlasts the time to pain and symptoms disappearance, and that the discontinuation of the steroid treatment only after the disappearance of the pathological tissue at MRI will avoid the occurrence of short-term relapses. Thus the IHS diagnostic criteria may lack of consistency regarding the above mentioned points, and the diagnostic procedure and treatment management might take advantage by MRI follow-up.

**STUDY VARIABLES**

**Diagnostic Variables**

The diagnostic variables are:

a) the detection of the pathological tissue by means of MRI.

b) the site of the pathological tissue (*MRI*)

c) the involved structures as implied from the presentation (*neurological examination, SOE or HLT*)

d) the pain characteristics (*pain questionnaire*)

**Outcome Variables**
The primary outcome variable is the time to pain and the time to sign resolution after the starting of the steroid treatment, assessed by means of:

   e) Pain resolution: *pain questionnaire and subject diaries*

   f) Signs resolution: *subject diaries, SOE or HLT, neurological examination*

The secondary outcome variables are:

   g) the time to pathological tissue disappearance at *MRI* during the 6-month maintenance phase

   h) the relapses occurrence after steroid treatment discontinuation, assessed by means of *MRI, SOE or HLT and neurological examination* every month for 6 months from the starting of the taper phase.

All the outcome variables will be measured over the maintenance period and the follow up period.

**STUDY ENDPOINTS**

To describe the clinical and MRI characteristics of the THS at presentation and after a determined steroid treatment (objectives number 1, and 2) we will perform descriptive analyses of the diagnostic and of the outcome variables by means of survival analyses.

If allowed by the number of the patients:

   - a probability analyses will be performed for each diagnostic and outcome variable;

   - each diagnostic variable will be correlated with the outcome variables to evaluate the possible effects on the outcome of the clinical and MRI characteristics at presentation.

In order to evaluate the consistency of the ICHD II diagnostic criteria (objective number 3), the endpoints will be:
- the percentage of pain-free subjects after 72 hours from the starting of the steroid treatment, and the time to pain resolution for the 95% of subjects;

- the percentage of symptom-free subjects after 72 hours from the starting of the steroid treatment, and the time to symptoms resolution for the 95% of subjects;

- the percentage of neurological sign-free subjects after 72 hours from the starting of the steroid treatment, and the time to neurological signs resolution for the 95% of subjects.

SAFETY EVALUATIONS

Safety will be evaluated by the monitoring of the frequency, severity, and timing of AEs, clinical laboratory test values, vital signs measurements, physical and neurologic examinations.

STUDY DESIGN

This is a prospective multicenter study. Formal approval of local ethic committee is needed prior the enrolling phase of the study. After obtaining informed consent, subjects will have a screening visit to determine study eligibility. Subjects who met the inclusion criteria may enter the 6-day high treatment period during which they will maintain the prescribed stable dosage.

After completion of the high dosage treatment period, subjects will continue to the maintenance period of the oral treatment phase. At baseline as well as at each visit, a pain questionnaire will be assessed and a neurological examination will be performed together with an SOE or HLT and an MRI.

Starting after a 1-month maintenance period the subjects will undergo to an MRI study to assess the disappearance of the pathological tissue, and will have the opportunity to:

- enter immediately the taper phase, if the disappearance of the pathological tissue is assessed, starting tapering the oral steroid treatment until suspension.
or

- continue with the maintenance phase, if the pathological tissue is still identifiable at MRI. The subject will undergo a brain MRI scan monthly, until the disappearance of the pathological tissue, at which point he will enter the taper phase.

The taper phase will last about 2 months depending on the dose taken by the subject throughout the maintenance phase.

From the third month after the starting of the taper phase, the subjects will enter the follow-up phase during which they will undergo a visit and an MRI scan after 5 and 8 months from the starting of the taper phase.

The typical total study period for each subject will varies from 9 to 20 months during which each subject will undergo to a minimum of 5 and a maximum of 16 MRI.

The subjects who will not achieve the disappearance of the pathological tissue at the end of the 12-month maintenance period, will be assigned to one of the following options on the basis of each subject’s symptoms, signs, and adverse events:

Option A

The subject enter the taper and the follow-up phase.

Option B

The subject undergo to a biopsy of the pathological tissue. If the diagnosis of THS is confirmed the subjects can be switched to either Option A or C.

Option C

The subject continue with the oral steroid treatment and repeat the MRI after 3 months.
The decision about which alternative option is the more suitable for a determined subject will be taken by the Investigator; the Study Medical Team of the Coordinator Centre will be available to contribute to the Investigator’s decision.

Data from the subjects assigned to the Options A, B or C will be recorded in the dedicated section of the CRF.

Relapses

The subjects who will experience pain and/or symptoms exacerbation persisting for more than 12 hours during the maintenance, the taper or the follow-up phase, will undergo an unscheduled visit and an MRI scan, the results of which will be discussed by the Investigator with the Study Medical Team of the Coordinator Centre in order to establish the best diagnostic procedures and treatment options.

**PLANNED STUDY PERIOD**

The study will start during 2010 (first subject visit) and subjects will be enrolled for a 24 month period; accordingly the study is expected to be completed during 2014 (last subject last visit).

**STUDY DURATION PER SUBJECT**

The typical total duration of the study will be up to 20 months by subject with a maximum of a 12 month exposure to steroid treatment before tapering.

- Baseline period (1 week) S1-D2
- Treatment period:
  - High dosage period (1 week) D2-HD3
  - Maintenance period (3 weeks to 12 months) HD3-M4
- Taper phase (2 months) M4-T5

- Follow-up period (6 months) T5-F(6-7)

**PLANNED NUMBER OF SUBJECTS AND SITES**

The Centres that will accept to participate to the study will be asked to make a forecast about the subjects they will be able to enrol in a 24-month period. If the total forecast from all the centres will be less of 20 the study will not start. The same will apply if less than 10 Centres will be available to participate to the study. To be eligible the subjects must meet all of the inclusion and none of the exclusion criteria.

**MAIN INCLUSION AND EXCLUSION CRITERIA**

**Inclusion Criteria**

Subjects must satisfy the following criteria to be enrolled in the study:

- Male or Female aged 14 years or older

- An episode of painful ophthalmoplegia with onset in the last month, whose clinical characteristics fulfil the IHS diagnostic criteria for THS*

- Willing to adhere to the prohibitions and restrictions as specified in section 10, Prohibitions and Restrictions

- Must have signed an informed consent form document (subjects or they legally acceptable representatives) indicating that they understand the purpose and the procedures required for the study and are willing to participate in the study. Assent is also required of adolescents as described in section 16, Informed Consent. (Assent applies to adolescent only. Adult not competent to consent will not be allowed into study.)
• For adolescent (as defined by local regulations), a responsible person must be available to accompany the subject to the study centre at each visit, to provide reliable information for the safety and efficacy evaluations, and to accurately and reliably dispense the drug as directed, if in the opinion of the investigator, the subject cannot otherwise be compliant with study procedures and study drug.

* The symptoms and signs at presentation must be compatible with the IHS diagnostic criteria for the THS (see attachment A), with the exception of the criteria at point D, that concerns with the time to pain, symptoms and signs resolution after the starting of the steroid treatment.

**Exclusion Criteria**

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

• Currently taking steroid or immunosuppressive treatment.

• History of any medical condition that could potentially disqualify the subject for medical or safety reasons, in particular: immunodeficiency, infections, uncontrolled hypertension, myocardial infarction, congestive heart failure, hepatic failure, renal insufficiency, diabetes mellitus, osteoporosis, glaucoma, cataract, corneal perforation, psychosis, epilepsy, peptic ulcer, hypotiroidism, steroid myopathy.

• Clinically relevant abnormalities for laboratory test values at screening

• Woman who are pregnant

• Unable to meet or perform study requirements

In addition, subjects should be excluded if in the opinion of the investigator they should not be enrolled in the study because of the precautions, warnings or contraindications outlined in the local 6-methilprednisolone and/or local prednisone package insert.
TREATMENT DOSAGE AND ADMINISTRATION

High dosage steroid treatment phase

6-Methylprednisolone 1000 mg i.v. die x 7 days

Maintenance treatment period

Prednisone 1 mg/Kg p.o. die up to a maximum of 100 mg/die, until MRI normalization.

Taper phase

10 mg decrease every 7 days, until suspension.

STATISTICAL METHODS

We will perform descriptive analyses of the diagnostic and of the outcome variables by means of survival analyses.

If allowed by the number of the patients:

- a probability analyses will be performed for each diagnostic and outcome variable;

- each diagnostic variable will be correlated with the outcome variables to evaluate the possible effects on the outcome of the clinical and MRI characteristics at presentation.

Sample size calculation

The sample size can not be forecast since THS is a rare disease, and no incidence data are available. Until now there are no multicenter studies on THS, accordingly we expect that the sample size of our study will be larger than any other already available.
# TIME AND EVENTS SCHEDULE

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<th>Phase:</th>
<th>Screening</th>
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<th>Maintenance</th>
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<td>HD3</td>
<td>M4</td>
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* subjects suitable for the Option A, B, or C will continue with the oral steroid treatment and repeat the MRI on the basis of the assigned option.