# Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy - Tuberous Sclerosis Complex.

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Seizures (incl subtypes) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON41140

**Source**
ToetsingOnline

**Brief title**
EPISTOP

### Condition

- Seizures (incl subtypes)

**Synonym**
Epilepsy, Tuberous Sclerosis Complex

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Instytut Pomnik-Centrum Zdrowia Dziecka (IPCZD)/ The Children's

Memorial Health Institute
**Source(s) of monetary or material Support:** Europese Unie.

## Intervention

**Keyword:** Biomarkers, Epilepsy, Epileptogenesis, Tuberous Sclerosis Complex

## Outcome measures

### Primary outcome

The primary parameter is the assessment of (a set of) molecular and clinical biomarkers in full analysis set of patients.

### Secondary outcome

Key secondary parameter is the efficacy and safety of preventative antiepileptic treatment in patients diagnosed with epilepsy after epileptiform discharges (group A) in comparison to patients diagnosed with epilepsy after the onset of clinical seizures (including both patients in group B as well as patients who presented with clinical seizures after inclusion but before EEG abnormalities were seen). The parameters of efficacy assessment include: the distribution of seizure free patients, proportion of patients with drug resistant seizures, proportion of patients with normalized EEG, the neurodevelopmental outcome recognized as the results in a battery of neuropsychologiscal tests performed at the age of 24 months.

# Study description

### Background summary

Despite a great progress in the management of epilepsy, still one third of patients are refractory to available medications. The incidence of epilepsy is highest in infancy and 50% of children experience epilepsy-related

comorbidities, such as developmental delay and autism. This is particularly true for patients with tuberous sclerosis complex (TSC). The development of epilepsy (epileptogenesis), extensively studied in animals, is barely studied in humans, as patients usually present AFTER the seizure onset.

**Study objective**

The primary objective of the clinical part of EPISTOP project is to identify the clinical and molecular biomarkers of epileptogenesis in a prospective clinical study of patients with TSC.
Secondary objective of the clinical part of EPISTOP is to compare the effects of standard antiepileptic treatment in patients diagnosed as having epilepsy after clinical seizures vs after electroencephalographical epileptiform discharges, in a randomized trial in TSC patients.

**Study design**

This is a prospective study of epileptogenesis in TSC infants. Biomarker analysis will be performed by a multidisciplinary, systematic approach in three clinical settings:
a) Prospective study of epilepsy development in infants with TSC, including analysis of clinical, neuroimaging, and molecular, blood-derived biomarkers at predefined time points: before the onset of seizures, at the onset of epileptiform discharges on EEG, at seizure onset and at the age of 24 months;
b) Prospective study of blood-based biomarkers in infants with TSC treated with antiepileptic drugs prior to clinical seizure onset in comparison to children treated only after clinical seizures appear.
c) Analysis of biomarkers of epileptogenesis and drug-resistant epilepsy in brain specimens obtained from TSC patients who have had epilepsy surgery and TSC autopsy cases.

A randomized controlled trial (RCT) will be undertaken to establish the most optimal moment of starting anti-epileptic drug treatment: after electroencephalographical epileptiform discharges or after clinical seizures. Patients may be enrolled in the first part of the study only, or both the follow up study and the RCT if applicable.
At baseline, all patients will undergo neuroimaging examination by means of MRI, a battery of neuropsychological tests, blood biomarker sampling and the review of medical history of the patient and the family. Blood samples for biomarker studies will be collected in all patients participating in the project (including children that only participate in the follow up study) at study entry, at the onset of epileptiform discharges on vEEG or at the age of 6 months, whichever is applicable, at the onset of clinical seizures, and at the end of follow-up (age 2 years).
At the age of 24 months, all TSC infants participating in the study will undergo neuroimaging examination by means of MRI, a battery of

neuropsychological tests, and epilepsy analysis.
Epileptogenesis in TSC infants will be tracked by means of serial vEEG recordings. In children with diagnosed epilepsy, standard therapy with recommended first line antiepileptic drug will be given.
Infants that have epileptiform discharges on vEEG and no clinical seizures will, if their parents/caregivers give consent, be randomized into two groups: group A will be diagnosed as having epilepsy after epileptiform discharges, and the patients in group B will be diagnosed with epilepsy only after clinical seizures appear.

### Intervention

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### Study burden and risks

Follow up of both medical history and ancillary investigations are part of routine daily clinical practice, therefore no risks are anticipated. The burden includes few more blood withdrawals that will be combined with necessary bloodsamples as much as possible.
With respect to the RCT, children in group A will be prescribed the recommended first line antiepileptic drug. Side effects will be monitored closely, though anti-epileptic drugs are usually well tolerated in infants.
Identification of biomarkers enables assessment of prognosis, improving monitoring children at risk of worse developmental outcome and ultimately developing new treatment strategies to improve seizure control and development in this high-risk group of patients.
Observational data has given support that preventative treatment is related to improved outcome. This study aims to find ultimate evidence for preventative treatment.

## Contacts

**Public**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Children (2-11 years)

## Inclusion criteria

- Male or female infants with a definite diagnosis of TSC (Roach criteria; Roach 1998, or DNA confirmed);
- Age up to 4 months at the moment of enrolment;
- No clinical seizures seen by caregivers or on baseline videoEEG recording;
- Written informed consent of caregivers. It is possible to give consent for the observational part of the study only. In this case, the child will not enter the RCT.

## Exclusion criteria

- Any type of seizures observed till baseline visit;
- Antiepileptic treatment at or prior to study entry;
- Contraindications to MRI;
- Any severe and/or uncontrolled medical condition that is considered by the investigator as possibly affecting the EPISTOP analyses or procedures. For example non TSC related malformation of brain development or acquired brain damage.

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |

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|---|---|
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Active |
| Primary purpose: | Basic science |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 16-12-2014 |
| Enrollment: | 10 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Keppra |
| Generic name: | Levetiracetam |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Sabril |
| Generic name: | Vigabatrin |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Tegretol |
| Generic name: | Carbamazepine |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 14-07-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 05-12-2014 |

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|---|---|
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2013-005528-40-NL |
| ClinicalTrials.gov | NCT02098759 |
| CCMO | NL48101.041.14 |