Trial Description

Title

Treatment of Established Status Epilepticus in the Elderly - a prospective, randomized, double-blind comparative effectiveness trial

Trial Acronym

ToSEE

URL of the trial

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Brief Summary in Lay Language

The study ToSEE aims to generate evidence for the treatment of the benzodiazepine-resistant (established) status epilepticus in the elderly. All subtypes of status epilepticus will be considered. The efficacy of the two frequently used drugs levetiracetam and valproat will be compared. Also the safety profile of both drugs will be investigated. ToSEE will also collect information about this disease, its complications and outcome aspects at the time of discharge or 30 days after inclusion at the latest.

Brief Summary in Scientific Language

ToSEE is a prospective, multicenter, double-blind phase IV-trial with two treatment arms (levetiracetam and valproate) for the therapy of the benzodiazepine-resistant (established)status epilepticus (BRSE) in the elderly. Four hundred and seventy-seven elderly patients (≥ 65 years old) diagnosed with BRSE will be allocated by 1:1 randomization to receive either levetiracetam (LEV) or valproate (VPA). All types of SE will be considered. For the diagnosis NCSE a verification by EEG is required. The Intervention is deemed successful if there is a stable cessation of ictal activity 15 minutes after the start of infusion persisting for the following 45 minutes of observation. To obtain data about the further treatment of SE, intrahospital complications and the functional outcome in the short term the study participants will be observed until the day of discharge or day 30 whichever is earliest.

Do you plan to share individual participant data with other researchers?

No

Description IPD sharing plan

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Organizational Data

- DRKS-ID: **DRKS00022308**
- Date of Registration in DRKS: **2020/07/03**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **153/19-ff , Ethikkommission an der Medizinischen Fakultät der Universität Leipzig**

Secondary IDs

- EudraCT-No.
  (for studies acc. to Drug Law): **2018-003917-16**

Health condition or Problem studied

- ICD10: **G41.9 - Status epilepticus, unspecified**

Interventions/Observational Groups

- Arm 1: **valproate 30mg/kg, one single infusion over 10 minutes, Maximum 3g**
- Arm 2: **levetiracetam 45 mg/kg, one single infusion over 10 minutes, Maximum 4.5g**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, investigator/therapist**
- Control: **Active control (effective treament of control group)**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **IV**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **No**

Primary Outcome

Primary endpoint is the effectiveness of intravenous valproate or levetiracetam to terminate established status epilepticus and maintain control of epileptic activity up to 60 minutes after initiation of the trial intervention.

Secondary Outcome

Secondary goals are to assess the safety profile of valproate and levetiracetam in elderly patients with eSE, and to collect observational data about the established status epilepticus.
Key secondary endpoints:
- Time from initiation of trial intervention to cessation of eSE within 60 minutes
- Neurological status (including vigilance) 60 minutes after initiation of Intervention
- Difference of blood levels of VPA and LEV before and 60 minutes after initiation of intervention
- Recurrence of seizures or nonconvulsive/ convulsive SE after initially successful intervention
- For patients who failed the primary endpoint, number of patients in whom SE cessated during 60 minutes after initiation of intervention according to the treating physician
- For NCSE patients who failed the primary endpoint, time to first cessation, as verified by EEG
- Number of patients with SE-associated ventilation until hospital discharge
- Functional outcome at discharge, defined by Barthel Index and modified Rankin Scale

Assessment of safety:
- Mortality
- Need for any emergency medication (different from allocated study drug) during 60 minutes after initiation of study intervention
- Need for ventilation (noninvasive/ invasive) during 60 minutes after initiation of intervention
- Intrahospital complications
o Incidence of delirium as diagnosed by the treating physician
o Infections requiring intravenous administration of anti-infectives
o Adverse events related to infusion/subsequent therapy with antiepileptic drug (sedation, dizziness, nausea, vomiting, thrombocytopenia, leukopenia,hypotension, new elevation of liver enzymes, hyperammonaemia, acute new liver failure or pancreatic damage, tremor, psychiatric abnormalities)

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Department of Neurology,, Leipzig**
- Medical Center **Department of Neurology, Klinikum Altenburger Land, Altenburg**
- University Medical Center **Department of Neurology, Charité Medical University , Berlin**
- University Medical Center **Department of Neurology, Erlangen**
- University Medical Center **Department of Neurology, Essen**
- University Medical Center **Department of Neurology, Frankfurt a.M.**
- University Medical Center **Department of Neurology, Greifswald**
- Medical Center **Department of Neurology, Günzburg**
- University Medical Center **Department of Neurology,, Jena**
- Medical Center **Department of Neurology, Kassel**
- Medical Center **Department of Neurology, Johannes Wesling Klinikum , Minden**
- University Medical Center **Department of Neurology and IFB, Klinikum Großhadern, München**
- Medical Center **Department of Neurology,, Osnabrück**
- University Medical Center **Department of Neurology, Tübingen**
- University Medical Center **Department of Neurology,, Ulm**
- University Medical Center **Department of Neurology,, Rostock**
- University Medical Center **Department of Neurology, Würzburg**
- Medical Center **Department of Neurology, Carl-von-Basedow-Klinikum, Merseburg**
- University Medical Center **Klinik und Poliklinik für Neurologie, Marburg**
- University Medical Center **Neurologische Klinik und Poliklinik, Mannheim**
- University Medical Center **Klinik für Neurologie und Klinische Neuropsychologie, Wuppertal**
- University Medical Center **Department of Neurology, Freiburg im Breisgau**
- Medical Center **Evangelisches Krankenhaus Oldenburg , Oldenburg**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2021/02/06**
- Target Sample Size: **477**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **65 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

Adult patients ≥ 65 years old with ongoing convulsive SE (generalized CSE/focal CSE with impaired consciousness/focal CSE without impaired consciousness), as defined by a seizure lasting ≥ 5 minutes or 2 or more convulsive seizures without full recovery of consciousness ≥ 5 minutes, or nonconvulsive SE (NCSE with coma/ NCSE without coma) defined as ongoing EEG patterns consistent with definite or possible NCSE according to the Salzburg criteria (Leitinger et al. 2016), or clinically defined NCSE non-responding to treatment with AT LEAST
Lorazepam 2 mg (i.v.)
Midazolam 5 mg (i.v., buccal, intranasal, i.m.)
Diazepam 5 mg (i.v., rectal)
Clonazepam 1 mg (i.v.)

Exclusion criteria

- Treatment of SE with other antiepileptic drugs/sedatives before enrollment
- Intravenous application of VPA or LEV in the last 24 hours before enrollment.
- Known or suspected severe liver or pancreatic disease (alcohol addiction, known liver cirrhosis or familial liver diseases, clinical signs of severe liver disease such as ascites, jaundice)
- Known concomitant treatment with one or several of the following medications: phenobarbital, phenytoin, carbamazepine, carbapenem antibiotics, rifampicin, erythromycin, cimetidine, primidone, mefloquine, fluoxetine, felbamat, lopinavir, ritonavir
- Known coagulopathy (anticoagulants allowed)
- Known porphyria, mitochondriopathy and urea cycle disorders
- Known severe kidney disease (GFR < 30ml/min)
- Known insulin dependent diabetes mellitus
- Hypoglycemia (< 3.3 mmol/l)
- Estimated weight < 45kg.
- Need for acute neurosurgical treatment.
- Known cardiopulmonary resuscitation within the last 7 days before enrollment
- Known hypersensitivity against VPA or LEV
- Known participation in other interventional trials
- Known former participation in this trial

Addresses

■ **Primary Sponsor**

Universität Leipzig
Ritterstraße 26
04109 Leipzig
Germany

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

■ **Contact for Scientific Queries**

Klinik und Poliklinik für Neurologie Universitätsklinikum Leipzig
Mr. Prof. Dr. med. Joseph Claßen
Liebigstraße 20
04103 Leipzig
Germany

Telephone: **0341/9724200**
Fax: **0341/9724209**
E-mail: **joseph.classen at medizin.uni-leipzig.de**
URL: **https://www.uniklinikum-leipzig.de/einrichtungen/neurologie**

■ **Contact for Public Queries**

Klinik und Poliklinik für NeurologieUniversitätsklinikum Leipzig
Ms. Dr. med. Annekatrin Müller
Liebigstraße 20
04103 Leipzig
Germany

Telephone: **0341/9720846**
Fax: **0341/9724209**
E-mail: **Annekatrin.Mueller at medizin.uni-leipzig.de**
URL: **https://www.uniklinikum-leipzig.de/einrichtungen/neurologie**

Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

  Bundesministerium für Bildung und Forschung Dienstsitz Bonn
  Heinemannstr. 2
  53175 Bonn
  Germany

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **www.bmbf.de**

Status

- Recruitment Status: **Recruiting ongoing**
- Reason, if "Recruitment stopped after recruiting started" or "Recruiting withdrawn before recruting started": **[---]***
- Reason, if Reason for Recruiting Stop "Other": **[---]***
- Study Closing (LPLV): **[---]***
- Number of Participants in Germany after Recruiting complete: **[---]***
- Total Number of Participants (all Sites worldwide) after Recruiting complete: **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*