A multicentre, randomised, active comparator, parallel group study to compare the effect on cognition of adjunctive therapy with zonisamide versus sodium valproate.

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Congenital and peripartum neurological conditions
Study type	Interventional

Summary

ID

NL-OMON32279

Source
ToetsingOnline

Brief title
COGZ 406

Condition

- Congenital and peripartum neurological conditions

Synonym
faling disease, Partial epilepsy

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: cognition, epilepsy, zonisamide

Outcome measures

Primary outcome

The Primary Endpoint is the change from baseline to Week 12 in the CVST

(Computerised Visual Searching Task Reaction Time) from the FePsy cognitive

battery.

Secondary outcome

The Secondary Endpoints include:

- the change from "baseline" to "Week 6" in the CVST

- the remainder of the FePsy cognitive battery at Weeks 6 and 12:

• Measures of Motor Speed

• Measures of Mental Speed

• Memory Function

- the Profile of Mood States at Weeks 6 and 12 (scale for state-dependent mood

changes)

- the ABNAS at Weeks 6 and 12 (measures subjective cognitive complaints, as

reported by the subject)

Study description

Background summary

Clinical research with zonisamide indicates a relatively benign cognitive profile. A review of cognitive side effects reported in the Columbia AED Database found no difference between patients receiving zonisamide and the overall group.
Therefore there is a need to determine the cognitive profile of zonisamide by a robust assessment of its cognitive effects in a well designed, controlled clinical study.

Study objective

Zonisamide (Zonegran) and sodium valproate (Epilim) are both medicines approved for the treatment of epilepsy. This study is intended to investigate to what extent zonisamide can affect your memory and concentration in comparison with sodium valproate.

Study design

A phase IV, multicentre, randomised study with parallel groups and active comparator (two arms).

Intervention

researchproduct regime:

Zonisamide:
Patients will be initiated on 50mg/day and increase to the minimally effective dose, the maximum tolerated dose, or 500mg/day, whichever is the lowest.
The minimum permitted maintenance dose is 200mg/day. Dosing two times a day.

Sodium valproate:
Patients will be initiated on 600mg/day and increase to the minimally effective dose, the maximum tolerated dose, or 2500mg/day, whichever is the lowest.
The minimum permitted maintenance dose is 1000mg/day. Dosing two times a day.

Study burden and risks

Possible side effects and risks of participation to the study:

• Drawing blood can cause some pain (often), a bruise (sometimes), fainting (not so often), or infection (rare).
• You will have to be available to visit the hospital and hold regular

telephone consultations with your study doctor while you participate in the study.
• As with any scientific study, it is possible that not all of the risks are known at the start.
• You will have to take the study medication according to your study doctor's instructions.
• You will have to complete the seizure diary every day.

Side effects of Zonisamide:

Frequently occurring side effects (more than 1 out of 100 patients)
• agitation, irritability, confusion, depression, sleeplessness, strange or unusual thoughts, fearful or emotional feeling.
• poor muscle coordination, dizziness, poor memory, reduced mental capacity, drowsiness, loss of concentration, speech disturbances, abnormal skin sensation (tingling), shaking.
• seeing double, involuntary eye movements.
• kidney stones.
• rash, allergic reactions, fever, fatigue, flu-like symptoms.
• ecchymosis (small bruises caused by blood leaking into the skin from the blood vessels).
• reduced appetite, weight loss, lowered blood concentration of bicarbonate (a substance that prevents your blood becoming too acidic).
• nausea, indigestion, stomach ache, diarrhoea, constipation.

Rarely occurring side effects (1 to 10 out of 1000 patients)
• rage, aggression, suicidal thoughts, suicide attempts.
• vomiting.
• gallbladder inflammation, gallstones.
• urolithiasis.
• pneumonia and urinary tract infections.
• low potassium concentration in the blood, convulsions/seizures.

Very rare side effects (fewer than 1 out of 10,000 patients)
• hallucinations, memory loss, coma, inability to move; sweating; fever; incontinence, chronic or repeated seizures.
• respiratory disorders, shortness of breath, pneumonia.
• inflammation of the pancreas (severe pain in the stomach or back).
• liver problems, renal failure, raised blood concentration of creatinine (a waste product that your kidneys would normally excrete).
• severe rash (you could also feel ill or feverish), itching.
• abnormal muscle decomposition (you could feel pain or weakness in your muscles) which can lead to kidney problems.
• swollen glands, blood disorders (reduction in the number of blood cells, which increases the risk of infection and can make you look pale, feel tired and feverish and cause you to bruise more rapidly).
• decreased sweating, overheating.

Side effects of Sodium valproate:

Problems with the nervous system;
Shaking, drowsiness, weakness, instability when walking, fatigue, confusion, hallucinations, fainting, problems with balance, deterioration of epilepsy, hearing problems, increased alertness, aggression, hyperactivity, changes in mood, worsening or bizarre behaviour.

Problems with the gastrointestinal tract;
Nausea, stomach ache, vomiting, diarrhoea, bloated feeling.

Blood problems;
Blood clotting problems, abnormal bleeding or tendency to bruise easily, inflamed or painful blood vessels, red or itching skin, changes in the ammoniac concentration on some blood tests.

Problems with the skin;
Rash, acne, red or itching skin, swelling or tight feeling in the hands and feet, blistering of the skin, hair loss, augmented hair growth.

Problems with the urogenital system;
Kidney problems, bed wetting or increased urgency.

Musculoskeletal problems;
Spastic muscle movements and cramps.

Other problems;
Severe liver dysfunction, pancreatitis, greater breast development in men, menstruation changes in women, reduced appetite, increased appetite, weight gain, allergic reactions and other immune disorders, jaundice (yellow discolouration of the skin), general unwell feeling.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Subjects with a diagnosis of non-symptomatic localisation-related epilepsy with partial onset seizures;
2) Male or female subjects aged >=18 years;
3) Subjects taking carbamazepine as monotherapy at baseline or who can be transferred to carbamazepine monotherapy in the two months before the Screening Visit;
4) Subjects requiring addition of another AED;
5) Female subjects of childbearing potential must not be pregnant.

Exclusion criteria

1) Previous treatment with valproate or zonisamide.
2) Use of an AED other than carbamazepine less than 6 weeks prior to randomisation, and other than carbamazepine, zonisamide or sodium valproate during the study.
3) Hypersensitivity to zonisamide or valproate or their respective excipients.
4) Predisposing condition potentially altering the absorption, distribution or elimination of zonisamide or valproate.
5) Sulphonamide allergy.
6) Subjects with diagnosed idiopathic/primary generalised epilepsy or with results of clinical investigations.
7) History of status epilepticus within 12 months of screening whilst complying with AED therapy
8) History of cluster seizures.
9) History of non epileptic seizures.
10) Use of benzodiazepines during the Baseline Period or during randomised treatment.

11) Regular treatment with antihistamines.
12) Use of ketogenic diet.
13) Use of acetozolamide, triamterene, vitamin C (>2g/day), regular antacids or other medicines associated with nephrolithiasis less than one month prior to randomisation or during the study.
14) Subjects with a vagal nerve stimulator implanted, or due to be implanted within the expected duration of the study.
15) Subjects expected to undergo any surgery within the expected duration of the study.
16) History of renal calculi or renal insufficiency.
17) Active psychiatric disease.
18) History of suicide attempt within last 2 years.
19) History of drug or alcohol abuse within the last 2 years.
20) History of cerebrovascular disease/stroke or transient ischemic attacks; progressive neurological disease; focal central nervous system pathology or behavioural disturbances that may impair the subject*s ability to complete the neuropsychological tests; or previous or current brain neoplasm.
21) Neoplastic disease within the last 5 years.
22) Diagnosis of HIV or Hepatitis B or C.
23) Other clinically significant organic disease.
24) Female subjects who are lactating, pregnant or intending to become pregnant.
25) Subjects with history of demonstrated non compliance with medication or an inability to maintain a seizure diary
26) Subjects considered by the Investigator not to be within normal cognitive limits.
27) Participation in clinical study within 30 days of screening.
28) Clinically significant laboratory value abnormalities at baseline.
29) Weight <40kg.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	15-04-2008
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-06-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-07-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-08-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2007-005313-19-NL
CCMO	NL22254.040.08