A Two-Part Study of ZX008 in Children and Adults with Lennox-Gastaut Syndrome (LGS); Part 1: A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS, Followed by Part 2: An Open-label Extension to Assess Long-Term Safety of ZX008 in Children and Adults with LGS.

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The primary objective of Part 1 is the primary objective of the entire study.Part 1The primary objective of Part 1 is:* To evaluate the effect of ZX008 0.8 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in...

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

Summary

ID

NL-OMON48657

Source
ToetsingOnline

Brief title
ZX008-1601

Condition

- Seizures (incl subtypes)

Synonym
Epilepsy

Research involving
Human

Sponsors and support

Primary sponsor: Zogenix International Limited
Source(s) of monetary or material Support: the pharmaceutical industry.

Intervention

Keyword: Children, Epilepsy, Fenfluramine, Lennox-Gastaut Syndrome

Outcome measures

Primary outcome

* Number, frequency, and duration of countable seizures that result in drops

Secondary outcome

-The frequency of rescue medication usage

-Number of seizure-free days

-The incidence of medical services used to treat seizures

-The incidence of status epilepticus

-frequency of all countable seizures

-frequency of all countable motor seizures

-Clinical Global Impression * Improvement rating, as assessed by the principal

investigator

-Clinical Global Impression * Improvement rating, as assessed by the

parent/caregiver

-Behavior Rating Inventory of Executive Function (BRIEF)

-Vineland Adaptive Behavior Scale (VABS)

-Quality of Life in Childhood Epilepsy (QOLCE) Assessment

-Affective symptoms of the parent/caregiver using the HADS.

-Zarit Caregiver Burden Inventory

-the PK of ZX008

AEs, laboratory safety parameters (hematology, chemistry, urinalysis), vital

signs (blood pressure, heart rate, temperature, and

respiratory rate), physical examination, neurological examination, 12 lead

ECGs, Doppler ECHOs, and body weight

Study description

Background summary

LGS is a rare epileptic encephalopathy. Onset of LGS usually occurs most commonly before age 11, with a peak between 3 and 5 years of age. Patients with LGS account for 5*10% of children with seizures Nearly all LGS patients have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: 5% of children die, 80* 90% continue having seizures into adulthood, and nearly all have cognitive and behavioral problems. Children and adults with LGS have an enormous impact on their families, and efforts to improve the quality of life for these patients are complex.

Zogenix is developing a new formulation of fenfluramine hydrochloride, ZX008, for the adjunctive treatment of seizures associated with LGS.
Fenfluramine was introduced in the USA in 1973 for the treatment of obesity in adults. Products containing fenfluramine and Dfenfluramine were withdrawn from all markets between 1997 and 2000 after reports of heart valve disease and pulmonary hypertension. While the risk/benefit relationship for fenfluramine is considered unfavorable for the treatment of obesity in adults, establishing seizure control in LGS or any of the refractory catastrophic childhood epilepsies might lead to a more acceptable risk/benefit profile for

fenfluramine, especially if lower doses can be used successfully. As a result of this previous extensive use of fenfluramine, there is a large body of information in the public domain concerning its pharmacology, toxicology and use in the treatment of obesity.

There have been several published reports of fenfluramine*s successful treatment of refractory childhood epilepsy in the 1980s (Aicardi and Gaustaut, 1985; Aicardi et al., 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel and Casaer, 1996).

Currently, a cohort of refractory LGS patients in Belgium are being treated in a Phase 2 open-label, pilot, dose-finding trial of fenfluramine as an add-on therapy to conventional therapy. Seven of the 13 patients (54%) achieved at least a 50% reduction in the number of convulsive seizures during the study at doses of 0.2mg/kg (3 patients), 0.4mg/kg (3 patients) and 0.6mg/kg (1 patient).

Study objective

The primary objective of Part 1 is the primary objective of the entire study.

Part 1
The primary objective of Part 1 is:
* To evaluate the effect of ZX008 0.8 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with Lennox-Gastaut syndrome (LGS) based on the change in frequency of seizures that result in drops between baseline and the combined Titration and Maintenance Periods (T+M)

The key secondary objectives of Part 1 are:
* To evaluate the effect of ZX008 0.2 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with LGS based on the change in frequency of seizures that result in drops between baseline and T+M
* To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the following endpoints:
- The proportion of subjects who achieve a *50% reduction from baseline in the frequency of seizures that result in drops
- Change in the frequency of all countable motor seizures between baseline and T+M (countable seizures include: generalized tonic-clonic seizures [GTC], tonic seizures [TS], clonic seizures [CS], atonic seizures [AS], tonic/atonic seizures [TA], clearly recognizable focal seizures [FS], and myoclonic seizures [MS] that result in a drop).

Part 2
The primary objective of Part 2 is:
* To assess the long-term safety and tolerability of ZX008 in children and

adults with LGS with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, suicidality, cognition (BRIEF), vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), body weight, and BMI.

The secondary objectives of Part 2 are:

To assess the effect of ZX008 relative to the baseline on the following effectiveness measures:
- The change in the frequency of seizures that result in drops
- The change in the frequency of all countable motor seizures (GTC, TS, CS, AS, TA, FS, MS with a drop)
- The change in the frequency of all countable seizures
- The proportion of subjects who achieve a *25%, *50%, *75%, and 100% reduction in frequency of all countable seizures that result in drops, countable motor seizures that do not result in drops, all countable motor seizures, all countable seizures, and all countable seizures that do not result in drops
- Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops

* To determine the incidence of the following on subjects receiving ZX008:
- The incidence of medical services used to treat seizures
- The incidence of status epilepticus
- The use of rescue medication

Study design

Part 1: A Randomized, Double-blind, Placebocontrolled Trial of Two Fixed Doses of ZX008

Part 2: An Openlabel Extension

Intervention

Part 1: subjects will be divided in 3 groups:
-dose of ZX008 of 0.2 mg/kg/day
-dose of ZX008 of 0.8 mg/kg/day
-placebo

Part 2: all subjects will be treated with an initial dose of ZX008 of 0.2 mg/kg/day. After 1 month the dose may be adjusted up in increments of 0.2mg/kg/day to a maximum of 0.8mg/kg/day.

Study burden and risks

As described in more detail in the protocol, fenfluramine has been used

successfully for up to 27 years in Belgium in refractory pediatric epilepsy patients, including those with LGS and DS. The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. No patients experienced emergence of clinical valvulopathy or pulmonary hypertension. Fenfluramine has also been administered to over 500 children with neurobehavioral conditions, including autism and ADHD with good safety and tolerability, at doses in the range of 0.65 to 3.6 mg/kg/day.

In addition, ZX008 demonstrated a statistically significant and clinically meaningful reduction in monthly convulsive seizure frequency in Study 1 for DS patients and was generally well tolerated. There was no clinical or echocardiographic evidence of cardiac valvulopathy or pulmonary hypertension in Study 1 and no patient discontinued participation or required a change in monitoring in the study due to cardiac factors.

The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect expected and unexpected treatment-emergent adverse events. While the risk/benefit relationship for fenfluramine is thus considered unfavorable for the treatment of obesity in adults, establishing seizure control in LGS or any of the refractory catastrophic childhood epilepsies might lead to a more acceptable risk/benefit profile for fenfluramine, especially if lower doses can be used successfully.

As to the burden of the patient: The patient will have to undergo several procedures, have multiple blood draws, complete questionnaires and keep a diary as described in E4. The questionnaires and the diary can be done partly by the parents/caregivers if applicable. Still, the burden for the patient can be seen as quite high. On the other hand, the consequences of frequent seizure activity can be severe, therefore, the
benefit of better seizure regulation with the use of fenfluramine can be viewed as high.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is male or non-pregnant, non-lactating female, age 2 to 35 years, inclusive as of the day of the Screening Visit. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative urine pregnancy test at screening. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control (see Section 4.4), which includes abstinence, while being treated on this study and for 90 days after the last dose of study drug.;2.Subject must have a diagnosis of Lennox-Gastaut syndrome, where seizures that result in drops are not completely controlled by current antiepileptic treatments. (Subjects without a formal diagnosis may still be enrolled at sponsor discretion if all other criteria are met.);3.Subjects must meet all of the following 4 criteria for Lennox-Gastaut syndrome, as defined in this protocol:;a. Onset of seizures at 11 years of age or younger.;b. Multiple seizure types (must include TS or TA), including countable motor seizures that result in drops. Countable motor seizure types eligible for inclusion are: GTC, TS, CS, AS, FS with observable motor symptoms and MS with a drop. ;c. Abnormal cognitive development.;d. Evidence of EEG in the medical history that shows abnormal background activity accompanied by slow spike and wave pattern <2.5 Hz. (Acceptable evidence includes a copy of the EEG trace, EEG report, or physician note that appropriately describes the EEG findings.);4. Subject must have had at least 8 drop seizures in the last 4 weeks prior to inclusion (minimum of 4 drop seizures in the first two weeks and 4 in the last two weeks before baseline), by parent/guardian report to investigator or investigator medical notes;5. Receiving at least 1 concomitant AED and up to 4 concomitant AEDs, inclusive. KD and VNS are permitted but do not count towards the total number of AEDs. Rescue medications for seizures are not counted towards the total

number of AEDs.;6. All medications or interventions for epilepsy (including KD and VNS) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.;7. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.;8. Subject has provided assent in accordance with Institutional Review Board (IRB)/Ethics Committee requirements, if capable.;9. Subject*s parent/caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.;Randomization Inclusion Criteria: Subjects must meet all of the inclusion criteria and none of the exclusion criteria above and meet the following criteria in order to be randomized:;1. Subject has been approved for study inclusion by the Epilepsy Study Consortium.;2. Subject does not have an exclusionary cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination and is approved for entry by the central cardiac reader. Exclusionary abnormalities include, but are not limited to:;a. Trace or greater mitral or aortic valve regurgitation in subjects *18 years of age;b. Mild or greater mitral or aortic valve regurgitation in subjects >18 yrs of age;c. Possible signs of pulmonary hypertension with abnormal or greater than upper range of normal values;d. Evidence of left ventricular dysfunction (systolic or diastolic);3. Subject demonstrates a stable baseline with * 2 seizures per week resulting in drops during the 4-week Baseline Period.;4. Subject*s parent/caregiver has been compliant with diary completion during the Baseline Period, in the opinion of the investigator and sponsor.;Selection Criteria for Part 2;To be included in Part 2 all subjects must continue to meet the Selection Criteria for Part 1 (except for criteria related to seizure frequency). If a subject entering Part 2 does not meet Randomization Criteria 2 regarding cardiovascular abnormalities, Section 8.9.1 Follow-up of Cardiovascular Findings will be applied to determine eligibility to continue into Part 2.;1. All subjects must have satisfactorily completed Part 1 of the study in the opinion of the investigator and the sponsor.;2. Those subjects who do not complete the 12-week Maintenance Period of Part 1 may, on a case-by-case basis, be eligible for entrance after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit participation in Part 2 for subjects who do not complete Part 1 resides solely with the sponsor, who may consult with the site investigator, the ICAB and/or the IDSMC.

Exclusion criteria

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.;2. Subject*s etiology of seizures is a degenerative neurological disease. ;3. Subject has a history of hemiclonic seizures in the first year of life.;4. Subject only has drop seizures in clusters, where individual seizures cannot be counted reliably.;5. Subject has pulmonary arterial hypertension.;6. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke, or clinically significant structural cardiac abnormality, including but not limited to mitral valve prolapse, atrial or ventricular septal defects, patent ductus arteriosis (note: Patent Foramen Ovale or a bicuspid valve are not considered exclusionary).;7. Subject has current or recent history of Anorexia Nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month.;8. Subject

has a current or past history of glaucoma.;9. Subject has had an anoxic episode requiring resuscitation within 6 months of the Screening Visit.;10. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes <3x ULN and/or elevated bilirubin <2x ULN) may be entered into the study after review and approval by the Medical Monitor in conjunction with the sponsor, in consideration of comorbidities and concomitant medications.;11. Subject has severe renal impairment (estimated glomerlular filtration rate <30mL/min/1.73m2);12. Subject is receiving concomitant therapy with any of the following: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; other centrally-acting noradrenergic agonists, including atomexetine; or cyproheptadine (see Appendix 1 for a complete list of prohibited medications). (Note: Short-term medication requirements for prohibted medications will be handled on a per case basis by the Medical Monitor.);13. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at the Screening Visit.;14. Subject is taking felbamate for less than 1 year prior to screening and/or does not have stable liver function and hematology laboratory tests, and/or the dose has not been stable for at least 60 days prior to the Screening Visit.;15. Subject is known to be human immunodeficiency virus (HIV) positive.;16. Subject is known to have active viral hepatitis (B or C) ;17. Subject is currently receiving an investigational product.;18. Subject has participated in another clinical trial within the past 30 days (calculated from that study*s last scheduled visit). Participation in non-treatment trials will be reviewed by the medical monitor. ;19. Subject is at imminent risk of self-harm or harm to others, in the investigator*s opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal behavior in the past 6 months as measured by the C-SSRS at Screening or Baseline, which includes suicidal ideation with intent and plan (Item #5). If a subject reports suicidal ideation on Item 4 without specific plan, and the investigator feels that the subject is appropriate for the study considering the potential risks, the investigator must document appropriateness for inclusion, and discuss with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.;20. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions. ;21. Subject is institutionalized in a general nursing home (ie, in a facility that does not provide skilled epilepsy care).;22. Subject does not have a reliable caregiver who can provide seizure diary information throughout the study.;23. Subject has a clinically significant condition, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to the Screening Visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-11-2017
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ZX008
Generic name:	Fenfluramine Hydrochloride

Ethics review

Approved WMO Date:	06-06-2018
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	24-09-2018
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-04-2019
Application type:	Amendment

Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2017-002628-26-NL
Other	IND 132604
CCMO	NL64769.075.18