An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

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Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54815

Source
ToetsingOnline

Brief title
Fenfluramine Hydrochloride Safety Study with Rare Seizure Disorders

Condition

- Other condition

Synonym
Dravet syndrome and Lennox-Gastaut syndrome, seizures

Health condition

seizures associated with Dravet syndrome and Lennox-Gastaut syndrome.

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Rare Seizure Disorders - Epileptic Encephalopathies - Dravet Syndrome - Lennox - Gastaut Syndrome - Fenfluramine Hydrochloride

Outcome measures

Primary outcome

The primary objective of the study is:

• To assess the long-term safety and tolerability of ZX008

Secondary outcome

The secondary objectives of the study are: • To assess the effect of ZX008 on

the following effectiveness measures: - Investigator assessment of convulsive

seizure response (<25%, >=25%, >=50%, >=75%, or 100% [ie, seizure-free]

improvement) - Clinical Global Impression - Improvement (CGI-I) rating, as

assessed by the investigator - CGI-I rating, as assessed by the

parent/caregiver - Symptomatic CGI-I for cognition, behavior, motor abilities,

as assessed by the investigator - Symptomatic CGI-I for cognition, behavior,

motor abilities, as assessed by the parent/caregiver

Study description

Background summary

This is an international, multicenter, open-label, long-term safety study of ZX008 in patients with rare seizure disorders, epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study ZX008 1503, or those with LGS who have successfully completed Study ZX008-1601-Part 2, and are candidates for continued treatment with ZX008 for an extended period of time, or those with Dravet syndrome, Lennox-Gastaut syndrome, or another epileptic encephalopathy who have completed participation in a Zogenix-sponsored study and have been invited to participate in this study.

Study objective

Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

Study design

Subject will be eligible to participate in this trial for up to 36-months, or until ZX008 is approved in a subject*s country of residence and listed on a patient*s health plan formulary. Thus, the maximum duration for participation is 36 months.

Subjects entering this OLE study who have participated in 1503 or 1601 will receive ZX008 initially at the dose prescribed at the last visit in Study 1503 or Study 1601 Part 2. Dose increases, to a maximum of 0.8 mg/kg/day (maximum 30 mg/day) for subjects not receiving concomitant stiripentol (STP) or 0.5 mg/kg/day (maximum 20 mg/day) for subjects receiving concomitant stiripentol (STP), during this OLE study should not occur more frequently than every 7 days in dose increments of not more than 0.2 mg/kg/day. Dose increases may only occur after a review of reported adverse events (AEs), and if, in the investigator*s opinion, seizure frequency, severity, or duration indicates a change in medication regimen is warranted. Dose decreases for tolerability or safety concerns can occur at the investigator*s discretion, in dose amounts and frequency appropriate for the clinical situation. ZX008 dose adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation. Changes in dosage of concomitant AEDs may be implemented as clinically necessary, and concomitant AEDs may be withdrawn completely, but all subjects must remain on a minimum of 1 concomitant AED plus ZX008 unless it is

deemed clinically appropriate by the investigator (after discussion with the Medical Monitor) to dose as monotherapy. New concomitant AEDs or anti-epileptic treatments may be introduced at the investigator*s discretion, as would be typically indicated in clinical practice. Clinical worsening leading to a change in medication must be documented in the source notes and case report form (CRF) and all medication dose changes must be documented with a clinical explanation and justification. Any medication dosage change or addition of a new AED must be discussed with the Medical Monitor prior to implementation.
Echocardiograms (ECHO) and other safety assessments detailed in the schedule of assessments (SoA) will be conducted every 6 months, unless more frequent follow-up is clinically indicated or required by the Sponsor or IDSMC.
Follow-up cardiac safety assessments will be performed after study drug discontinuation for subjects who do not transition to commercially available ZX008.
Caregivers will be asked to use a diary to record the number/type of seizures to support investigator determination of treatment benefit; however, diary data collection is not mandatory, nor will it be collected in the database.

Intervention

Participation for subjects will be up to 36 months or until ZX008 is approved in a subject*s country of residence and listed on a patient*s health plan formulary, whichever occurs first.

Study burden and risks

Safety:
AEs, vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination, neurological examination, Doppler ECHOs, and body height/weight will be assessed at each visit. Laboratory safety parameters (hematology, chemistry), 12 lead ECGs, EEGs (in Italy only), and chest-x-ray (in France and Netherlands only), will be assessed as clinically indicated.
Effectiveness (assessed at each visit):
• CGI-I as assessed by parent/caregiver
• CGI-I as assessed by investigator (or designee)
• Symptomatic CGI-I for cognition, behavior, motor abilities, as assessed by the investigator (or designee)
• Symptomatic CGI-I for cognition, behavior, motor abilities, as assessed by parent/caregiver
• Percent improvement in seizure burden as assessed by the investigator (or designee)
Assessments by the investigator (or designee) should be performed by the same rater for each subject whenever possible. If the rater changes permanently, a new baseline should be established (see Section 7.1).
The same parent/caregiver should perform each assessment. If the same parent/caregiver is not available, the assessment should be skipped.

External Committees: The ZX008 clinical program will employ an Independent Data and Safety Monitoring Committee (IDSMC) that will be responsible for safety oversight. A separate International Cardiology Advisory Board (ICAB) will monitor the cardiac safety of the ZX008 clinical trials. ECHOs will be centrally read (ERT, Inc.) and interpreted using pre-specified criteria, and if necessary, with review by the ICAB.

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)

Inclusion criteria

1. Subject is currently enrolled in core Study ZX008-1503
ORSubject has successfully completed core Study ZX008-1601-Part 2

OR
Subject with a rare seizure disorder, such as epileptic encephalopathy, that has successfully completed another Zogenix-sponsored clinical trial with ZX008, and has been invited to participate in this study by the Sponsor.
2. Subjects must, in the medical opinion of the Investigator, be candidates for continued treatment for an extended period of time with ZX008 (ie, subject has demonstrated a clinically meaningful benefit with ZX008 in the prior trial, and benefits of continued treatment outweigh potential risks).
3. Subject is male or a nonpregnant, nonlactating female. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative pregnancy test prior to study entry. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control, which includes abstinence, while being treated on this study and for 90 days after the last dose of study drug.
4. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
5. Subject has provided assent in accordance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements, if capable.
6. Subject*s caregiver is willing and able to be compliant with study procedures, visit schedule and study drug accountability.

Exclusion criteria

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication. 2. Subject has current cardiac valvulopathy or pulmonary hypertension that the investigator, ICAB, IDSMC, or Sponsor deems reason for exclusion. 3. 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 as measured by the C SSRS Since Last Visit, 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. 4. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x upper limit of normal [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. 5. Administration of monoamine oxidase inhibitors, serotonin agonists, serotonin antagonists, and serotonin reuptake inhibitors within 14 days of receiving ZX008. 6. Subject is unwilling or unable to comply with scheduled visits, drug administration plan,

laboratory tests, other study procedures, and study restrictions. 7. Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness at Visit 1, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension. 8. Subject has participated in another clinical treatment trial within the past 30 days (ie, the last visit of the previous study was in the past 30 days), with the exception of a ZX008 clinical study.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-09-2020
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fenfluramine Hydrochloride Oral Solution
Generic name:	Fenfluramine Hydrochloride Oral Solution
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	04-02-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-03-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	14-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2019-001331-31-NL
ClinicalTrials.gov	NCT03936777
CCMO	NL72209.075.19