A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2)

Published: 30-03-2016
Last updated: 17-04-2024

The primary efficacy objectives of this two-cohort study are:o To demonstrate that ZX008 is superior to placebo as adjunctive therapy in the treatment of symptoms of Dravet syndrome in children and young adults based on change in the frequency of…

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

Summary

ID

NL-OMON46127

Source
ToetsingOnline

Brief title
ZX008-1504

Condition

- Other condition
- Seizures (incl subtypes)

Synonym
Dravet Syndrome; SMEI

Health condition

Dravet Syndrome, Epilepsy, SMEI

Research involving
Human

Sponsors and support

Primary sponsor: Zogenix International Limited, a Wholly Owned Subsidiary of Zogenix, Inc.
Source(s) of monetary or material Support: Zogenix International Limited;a wholly owned subsidiary of Zogenix;Inc.

Intervention

Keyword: Dravet, Dravet Syndrome, Epilepsy, SMEI (severe mycolonus epilepsy of infancy)

Outcome measures

Primary outcome

The primary efficacy endpoint is the change in the mean convulsive seizure

frequency (MCSF) per 28 days between the Baseline and T+M periods. The MCSF

will be calculated from all available data collected during the Baseline or T+M

Periods.

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA)

model with treatment group (ZX008 or placebo) and age group (< 6 years, *6

years) as factors, and with baseline frequency as a covariate. The primary

analysis will compare the ZX008 group to the placebo group using a two-sided test at the *=0.05 level of significance.

Since the ANCOVA used in the primary analysis relies on assumptions of normality, the primary endpoint will also be analyzed using a nonparametric method that does not require as stringent assumptions. A nonparametric test such as the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the nonparametric test will be used to assess the primary objective.

An additional analysis will be performed to assess the sensitivity of the primary analysis to changes in dose or type of concomitant AED medications that may occur during the course of the trial, which are protocol violations. Specifically, the primary analysis will be repeated with a factor added to indicate whether a subject had a change in prescribed dose or type of concomitant AED medication during the T+M period. Further exploratory analyses may be conducted if changes in concomitant AED medication appear to have a significant impact on the primary outcome.

Additional analyses will compare the percentage changes between the baseline MCSF and the MCSF measured independently during the Titration Period alone and the Maintenance Period alone.

Secondary outcome

The key secondary efficacy objectives of the study are related to Cohort 2 and include:

To demonstrate that ZX008 is superior to placebo on the following endpoints:

- The proportion of subjects who achieve a *40% reduction from baseline in

convulsive seizure frequency.

- The proportion of subjects who achieve a *50% reduction from baseline in

convulsive seizure frequency.

- The longest convulsive seizure-free interval.

Study description

Background summary

Zogenix has developed an oral solution formulation of fenfluramine hydrochloride, ZX008, for the adjunctive treatment of seizures in Dravet syndrome. In addition, the effects of ZX008 on a composite of symptoms that negatively impact quality of life and intellectual development will be explored. Fenfluramine is an amphetamine analogue that was approved in a large number of countries and widely prescribed as an appetite suppressant for the treatment of adult obesity.
Products containing fenfluramine and the D-enantiomer were withdrawn from the market globally after reports of heart valve disease and pulmonary hypertension in the late 1990*s (Connolly 1997; CDC 1997; Wong 1998). While the risk/benefit relationship for fenfluramine is thus considered unfavorable for the treatment of obesity in adults, establishing seizure control in Dravet syndrome or any of the 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 (ZX008 IB 2016). There is also a large body of information concerning its clinical safety profile.

Study objective

The primary efficacy objectives of this two-cohort study are:
o To demonstrate that ZX008 is superior to placebo as adjunctive therapy in the treatment of symptoms of Dravet syndrome in children and young adults based on change in the frequency of convulsive seizures between baseline and the combined Titration and Maintenance Periods (T+M) in Cohort 2.
The key secondary efficacy objectives of the study are related to Cohort 2 and

include:
o To demonstrate that ZX008 is superior to placebo on the following endpoints:
* The proportion of subjects who achieve a *40% reduction from baseline in convulsive seizure frequency.
* The proportion of subjects who achieve a *50% reduction from baseline in convulsive seizure frequency.
* The longest convulsive seizure-free interval.

Additional secondary efficacy objectives of the study (Cohort 2) are:
o To demonstrate that the ZX008 is superior to placebo on the following endpoints:
* The number of convulsive seizure-free days.
* The proportion of subjects who achieve *75% reductions from baseline in convulsive seizure frequency.
* The change from baseline in non-convulsive seizure frequency.
* The change from baseline in convulsive + non-convulsive seizure frequency.
* The incidence of rescue medication usage.
* The incidence of hospitalization to treat seizures.
* The incidence of status epilepticus.
* Change from baseline in subjects* quality of life measured using the QOLCE
* The change from baseline in health related quality of life (HRQOL) measured using the Pediatric Quality of Life Inventory* (PedsQL) Generic Core Scale.
* The change from baseline in the HRQOL of the parent/caregiver using the EQ-5D-5L scale.
* The change from baseline on the impacts of the condition on parents and the family using the PedsQL family impact module.

Pharmacokinetic objectives of this study include:
o To assess the PK profile of ZX008 administered as a single oral dose with clobazam (CLB) + valproate (VPA) and with CLB + VPA + stiripentol [STP] in subjects aged 2-18 years of age with Dravet syndrom (Cohort 1)
o Model PK of ZX008 in single and multiple dose regimens using fenfluramine/nor-fenfluramine concentration-time data from subjects in Cohorts 1 and 2

Exploratory objectives of this study (Cohort 2) include:
o To assess the change from baseline in health and social care resource use. These measures include planned and unplanned hospital visits, use of ambulances, general practitioner (GP) visits, speech and language therapy utilization, occupational and physical therapy utilization.
o Clinical Global Impression * Improvement rating, as assessed by the principal investigator.
o Clinical Global Impression * Improvement rating, as assessed by the parent/caregiver.
o Change from baseline in sleep quality.
o Change from baseline in mealtime behavior.
o Effect of study medication on sleepiness (Karolinska Sleepiness Scale).

o Assessment of a Dravet syndrome composite endpoint, which will include core objective (eg, seizure frequency) and subjective (eg, behavior, sleepiness, etc) patient-relevant outcome measures.

The safety objectives of the study are:
o Cohort 1: To evaluate the safety and tolerability of ZX008 as a single dose when added to standard of care treatment for Dravet syndrome (CLB + VPA; CLB + VPA + STP).
o Cohort 2: To compare the safety and tolerability of ZX008 to placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), body weight and cognitive function (using age-appropriate versions of the Brief Rating Inventory Executive Function [BRIEF]).

Study design

This is a multicenter, two-cohort trial to assess the pharmacokinetic and safety profile of a single dose of ZX008 (fenfluramine hydrochloride) oral solution when added to Dravet syndrome treatment regimen containing VPA and CLB, with or without STP (Cohort 1), followed by a randomized, double-blind, placebo-controlled parallel group evaluation of the efficacy, safety, and tolerability of ZX008 as adjunctive therapy for seizures in children and young adults with Dravet syndrome (Cohort 2). Cohort 2 will not be dosed until the PK and safety data from Cohort 1 have been collected and evaluated. The PK and safety data from Cohort 1 will inform the dose of ZX008 to be used in Cohort 2. Approximately 2-3 sites in France and the Netherlands will be involved in the pharmacokinetic portion of the trial (Cohort 1). Approximately 10 study sites in France and the Netherlands will enroll participants for Cohort 2.
Cohort 1: Subjects will attend the CRU for a screening visit up to 14 days before dosing. Eligible subjects will return to CRU on Study Day *1 for an outpatient visit. Inclusion and exclusion criteria will be confirmed, and physical exam, medical history, body weight/BMI, vital signs, urine pregnancy test, urine THC, and whole blood CBD will be obtained. The subject will be discharged from the unit or allowed to stay overnight, as required. After dinner and a light snack prior to bedtime, subjects will be fasted until the next morning. On the following day (Study Day 1), a parent/caregiver will bring the fasted subject to the CRU between 6 AM and 7 AM.
Following blood collection for clinical labs, and vital sign measurements and weight, subjects will be given a light, low fat breakfast, followed by administration of their usual epilepsy medications. Based on the assigned treatment allocation, each subject will then receive the appropriate dose of study medication (ZX008). Subjects receiving CLB and VA at screening will be stratified by age group (< 6 years of age; >6 of age) and randomly allocated to Dosing Regimen 1 (ZX008 0.2 mg/kg + CLB + VPA) or Regimen 2 (ZX008 0.4mg/kg + CLB + VPA). At least two subjects from each pre-specified age group are to be assigned to Regimen 1; and at least 2 subjects from each group are to be

assigned to Regimen 2. Subjects receiving CLB and VA and STP at screening, will be assigned to Regimen 3 (ZX008 0.2 mg/kg + CLB + VPA + STP). Approximately 5 subjects from each age group (<6 years; >6 years) should be enrolled in dosing Regimen 3.

Blood samples for PK assessment will be obtained from all subjects through 12-hours post-dose. After the last Study Day 1 blood draw (12 hours post-dose), subjects will be discharged. Twenty-four to thirty-six hours following dosing the subjects will return to the research unit for assessment of vital signs, a final PK sample and to record any adverse events that may have occurred since leaving the CRU. A seizure diary will be provided to record seizure activity between Study Day 2 and the follow-up safety visit (Study Day 15). On Study Day 15, subjects and/or caregivers will return to the CRU for follow-up, including review of diary data. At the conclusion of this portion of the study, eligible subjects from Cohort 1 will be offered enrollment in a separate open-label extension study and will begin transitioning to study medication (ZX008, 0.2 mg/kg/day), diary data will continue to be captured and the exploratory composite endpoint components will be administered prior to commencement of transitional treatment. A schedule of assessments is provided in Table 1.
Cohort 2: A 6-week Baseline Period will consist of the establishment of initial eligibility during a screening visit followed by an observation period where subjects will be assessed for baseline seizure activity based on recordings of daily seizure activity entered into a diary. Upon completion of the Baseline Period, subjects who qualify for the study will be randomized (1:1) in a double-blind manner to receive ZX008 (at a dose determined by results from Cohort 1 in this study; maximum dose: 30 mg/day) or placebo. Randomization will be stratified by age group (<6 years, *6 years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group. All subjects will be titrated to their randomized dose during the Titration Period (titration will occur in 7-day increments starting with a 0.2 mg/kg/day dose of ZX008). The duration of the titration period will be determined following evaluation of the data from Cohort 1, and will have a maximum of 28 days.
Following titration subjects will continue treatment at their randomly assigned dose of ZX008 or placebo over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is a maximum of 16 weeks. Parents/caregivers will use a diary daily to record the number/type of seizures, dosing, and use of rescue medication. A schedule of assessments is provided in Table 2.
At the end of the Maintenance Period (or early discontinuation), subjects who will not be entering the open-label extension will undergo a taper of up to 21 days (duration to depend on dose chosen based on results of Cohort 1). Subjects who will be enrolled in the separate open-label extension study will enter a transition period (duration to depend on dose of ZX008 used in Cohort 2).
For Cohort 2 subjects, a follow-up ECHO, ECG, and possibly physical examination

will be performed 3-6 months after study drug discontinuation with early termination, or for those subjects who complete the study but do not enter the open-label extension study.

Intervention

NA

Study burden and risks

NA

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Subject is male or non-pregnant, non-lactating female, age 2 to 18 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. 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 dose of study drug.
2. Subject must have documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures are not completely controlled by current antiepileptic drugs (AEDs).
3. Subjects must meet all of the following 5 criteria:
a. Onset of seizures in the first year of life in an otherwise healthy infant.
b. A history of seizures that are either generalized tonic-clonic or unilateral clonic or bilateral clonic, and are prolonged.
c. Initial development is normal.
d. History of normal brain magnetic resonance imaging (MRI) without cortical brain malformation.
e. Lack of alternative diagnosis.
4. Subjects must meet at least one of the following 3 criteria:
a. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal has developed after the first seizure type.
b. Prolonged exposure to warm temperatures induces seizures and/or seizures are associated with fevers due to illness or vaccines, hot baths, high levels of activity and sudden temperature changes and/or seizures are induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.
c. Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis.)
5. Subject must have had *4 convulsive seizures (tonic-clonic, tonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes [Cohort 2 only].
6. All medications or interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulation [VNS]) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
7. Subject must be receiving a therapeutically relevant and stable dose of CLB, VPA, and STP for at least 4 weeks prior to screening and are expected to remain stable throughout the study [Cohort 2 only]. (In some cases, subjects who are conraindicated for VPA or CLB may be enrolled in Cohort 2. Subjects in these cases must be receiving a therapeutically relevant and stable dose of STP and VPA [if contraindicated for CLB] or STP and CLB [if contraindicated for VPA]. Each subject must be reviewed with the Medical Monitor and sponsor before initiating screening. The decision to allow enrollment of these subjects is at the sole discretion of the sponsor.)
8. Subject must be receiving a stable dose of CLB and VPA, administered twice daily (BID), to be eligible for Dose Regimen 1 and 2 or subject must be receiving a stable dose of CLB, VPA, and STP, administered BID, to be eligible for Dose Regimen 3 [Cohort 1 only].

9. Subject agrees to provide a buccal swab sample for CYP2D6 (cytochrome P450 2D6) genotyping.
10. Subject has been informed of the nature of the study and informed consent has been obtained
from the legally responsible parent/guardian.
11. Subject has provided assent in accordance with Institutional Review Board (IRB)/Independant Ethics Committee (IEC) requirements, if capable.
12. Subject*s parent/caregiver is willing and able to be compliant with all study requirements and
visit schedule. Subject*s parent/caregiver must also be willing and able to be compliant with diary completion and study drug accountability [Cohort 2 only].

Exclusion criteria

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.
2. Subject has pulmonary arterial hypertension.
3. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac
valvulopathy, myocardial infarction or stroke.
4. 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.
5. Subject has a current or past history of glaucoma.
6. Subject has moderate or severe hepatic impairment.
a. Asymptomatic subjects with mild hepatic impairment (aspartate aminotransferase [AST] and
alanine aminotransferase [ALT] < 2x the upper limit of normal (ULN) and no elevations of gamma-glutamyltransferase [GGT], alkaline phosphatase, or total bilirubin indicative of more than mild hepatic impairment), 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 [Cohort 1 only].
b.Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes <3x the 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 [Cohort 2 only].
7. Subject is receiving concomitant therapy with: 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; triptans, atomoxetine, or

other centrally-acting noradrenergic agonist; or cyproheptadine, and/or cytochrome P450 (CYP)
2D6/3A4/2B6 inhibitors/substrates (see Appendix 1). (Note: Short-term medication requirements
will be handled on a per case basis by the Medical Monitor.)
8. Subject is currently receiving or has received STP in the past 21 days prior to Screening (only for
Cohort 1 subjects allocated to Dose Regimen 1 or 2).
9. Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or
phenytoin, or has taken any of these within the past 30 days as maintenance therapy.
10. Subject is unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges,
and their juices beginning with the Baseline Period and throughout the study.
11. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at the Screening Visit.
12. Subject has participated in another clinical trial within the past 30 days.
13. Subject is currently receiving an investigational product.
14. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
15. Subject has a clinically significant condition, 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):	07-12-2016
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ZX008
Generic name:	fenfluramine hydrochloride

Ethics review

Approved WMO Date:	30-03-2016
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	28-07-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-09-2016
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	31-03-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	24-04-2017
Application type:	Amendment

Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	03-08-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	16-01-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	09-04-2018
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	EUCTR2016-000474-38-NL
CCMO	NL56818.075.16