An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Published: 09-11-2016
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* To assess the long-term safety and tolerability of ZX008.

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

Summary

ID

NL-OMON49270

Source
ToetsingOnline

Brief title
Zogenix 1503

Condition

- Seizures (incl subtypes)

Synonym
Epilepsy, SMEI

Research involving
Human

Sponsors and support

Primary sponsor: Syneos Health Netherlands BV.
Source(s) of monetary or material Support: the pharmaceutical industry.

Intervention

Keyword: Children, Dravet syndrome, Epilepsy, ZX008

Outcome measures

Primary outcome

Frequency of convulsive seizures

Secondary outcome

Safety:

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. The BRIEF will be administered to track cognitive function.

Effectiveness:

* Number of seizures by type

* Convulsive seizure-free interval

* Clinical Global Impression * Improvement as assessed by parent/caregiver

* Clinical Global Impression * Improvement as assessed by principal investigator

* QOLCE to measure changes in quality of life of the subject

* PedsQL to measure changes in quality of life of the subject

* PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver

* QoL of parent/caregiver using the EQ-5D-5L scale

* Affective symptoms of parent/caregiver using the HADS (in parents/caregivers from core studies ZX008-1501 and ZX008-1502 only)

* Duration of prolonged seizures (seizure type that, during pre-ZX008 baseline, had duration >2 minutes)

* Number of episodes of status epilepticus

* Number of instances of rescue medication use and number of doses

* Number of inpatient hospital admissions due to seizures

Exploratory (in subjects from core study ZX008-1504 only):

* Health and social care resource use, including GP visits, speech and language, occupational and physical therapy, in addition to acute hospital and institutional length of stay, loss of work, etc

* Sleep quality

* Mealtime behavior

* Karolinska Sleepiness Scale to measure the effect of study medication on sleepiness

Study description

Background summary

DS, also known as severe myoclonic epilepsy of infancy (SMEI), is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet 1978). The condition most commonly appears during the first year of life as frequent febrile seizures. As the condition progresses, other types of seizures typically occur, including myoclonic seizures and status epilepticus (Dravet 1978). Following the appearance of these seizures, affected children

develop several co-morbid conditions including psychomotor regression, ataxia, sleep disturbance, and cognitive impairment. Intellectual impairment begins to become apparent around age 2 years due to lack of intellectual/behavioral progression. Dravet children often have a lack of coordination, poor development of language, hyperactivity, and difficulty relating to others (Dravet 1978; Hurst 1990). The degree of cognitive impairment appears to correlate, at least in part, with the frequency of seizures, and might be a result of repeated cerebral hypoxia. Children with DS also encounter a higher incidence of Sudden Unexpected Death in Epilepsy (SUDEP; Nashef 2012) than other populations with epilepsy. Indirect evidence has linked SUDEP to several possible etiologies, including seizure-induced apnea, pulmonary edema, dysregulation of cerebral circulation, and cardiac arrhythmias (Shorvon 2011), although the actual etiology remains unknown and other mechanisms have not been ruled out. The vast majority of patients who survive to adulthood are wholly dependent on around-the-clock caregivers and eventually live in institutional care homes. DS is a highly treatment-resistant and refractory epilepsy syndrome. Establishment of a seizure-free condition in affected children, even with anticonvulsant drug polypharmacy, is extremely rare, since all seizure types in DS appear to be drug resistant, with minimal improvement on currently available anticonvulsant drug therapies. Since there are no treatments specifically approved for the treatment of DS in the USA, and only 1 treatment approved in Canada and Europe, there remains an unmet need for an approved treatment for children with DS. The rationale for conducting this open-label extension study is primarily to evaluate the long-term safety of ZX008 in DS. This protocol also provides the opportunity for continued treatment for subjects responding to treatment from the core study, and an opportunity for initial treatment with ZX008 for subjects randomized to placebo in the core study.

Study objective

* To assess the long-term safety and tolerability of ZX008.

Study design

This is an international, multicenter, open-label, long-term safety study

Intervention

ZX008 is supplied as an oral solution in a concentration of 2.5 mg/mL. Subjects will be titrated to an effective dose beginning with 0.2 mg/kg/day (maximum: 30 mg/day). Study medication will be administered twice a day (BID) in equally divided doses with food.

Study burden and risks

In reference to the risks: As described in more detail in the protocol, enfluramine has been used successfully for up to 27 years in some DS patients to control seizures, without emergence of clinical valvulopathy or pulmonary hypertension. Fenfluramine was administered to over 500 children with neurobehavioral conditions, including autism and ADHD with good safety and tolerability, most often at a 1 mg/kg dose.
The pharmacologic and toxicological profile for the active pharmaceutical ingredient, fenfluramine, following oral administration is well established (see ZX008 IB 2016).
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 DS 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 to the burden of the patient: The patient wil have to undergo several procedures, complete questionnaires and keep a diary as described in E4. Questionnaires and the diary can be done partly by the parents if applicable. Still, the burden for the patient can be seen as quite high. On the other hand, the consequences of frequent childhood seizure activity can be severe, therefore, the benefit of better seizure regulation with the use of fenfluramine can be viewed as high.

The available information suggests that the present clinical study has an acceptable risk-benefit ratio.

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 aged 2 to 18 years inclusive, as of the day of the core study Screening Visit. ;2. Subject has satisfactorily completed the core study in the opinion of the investigator and the sponsor.
NOTE: Those subjects who do not complete the 12-week Maintenance Period of the core study 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 open-label extension study participation resides solely with the sponsor, who may consult with the site investigator, the IPCAB and/or the IDSMC.;3. Subject is male or non-pregnant, non-lactating female. 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 last dose of study drug.;4. Subject has documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures are not completely controlled by current antiepileptic drugs.;5. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.;6. Subject has provided assent in accordance with IRB/IEC requirements, if capable.;7. Subject*s caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.;8. Subject*s parent/caregiver has been compliant with diary completion during the core study, in the opinion of the investigator (eg, at least 90% compliant).;9. Subjects entering from study ZX008-1504 must be receiving a therapeutically relevant and stable dose of clobazam, (CLB) and/or valproic acid, and stiripentol (Cohort 1 Dose Regimen 3 and Cohort 2 only) for at least 4 weeks prior to screening and are expected to remain stable throughout the study.

10. Subjects who are >18 to *35 years of age at the time of screening and did not participate in one of the core studies must meet criteria 3 to 7 above and the following criteria below in order to be considered for participation. Participation is at the discretion of the Sponsor:
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 MRI without cortical brain malformation.
e. Lack of alternative diagnosis.
f. Meets one of the following 3 confirmatory diagnostic criteria:
i. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal has developed after the first seizure type.
ii. 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.
iii. 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.)
g. Subject has been approved for study inclusion by the Epilepsy Study Consortium.
h. 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:
i. Mild or greater mitral or aortic valve regurgitation in subjects >18 yrs of age
ii. Possible signs of pulmonary hypertension with abnormal or greaterthan upper limit of normal values
iii. Evidence of diastolic dysfunction
i. Subject must have had *4 convulsive seizures (tonic, tonic atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.
j. 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.
11. Subject's parent/caregiver is willing and able to be compliant with diary completion, 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 or past history of cardiovascular or cerebrovascular disease, myocardial infarction or stroke.;3.Subject from one of the core studies with current cardiac valvulopathy or pulmonary hypertension that the investigator, parent, IPCAB, IDSMC,

or sponsor deems clinically significant and warrants discontinuation of study medication.;4. For de novo subjects: possible signs of pulmonary hypertension with abnormal or greater than upper limit of normal values.;5. 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.;6. 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.;7. Subject has a current or past history of glaucoma.;8. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3 x upper limited 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.;9. 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; atomoxetine, or other centrally-acting noradrenergic agonist; cyproheptadine, and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates (see Appendix 1 of the protocol). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.);10. Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.;11. For subjects entering from core studies ZX008-1501, ZX008-1502, or ZX008-1504 (Cohort 1/Dose Regimens 1 & 2): Subject is currently receiving or has received stiripentol in the past 21 days prior to core study Visit 1.;12. Subject is unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with Visit 1 and throughout the study.;13. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at Visit 1.;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 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.
16. Subject has participated in another clinical trial within the past 30 days (ie, the last visit of the previous study was in the past 30 days), with the exception of one of the core studies.

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):	08-06-2017
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fenfluramine hydrochloride
Generic name:	Fenfluramine hydrochloride

Ethics review

Approved WMO Date:	09-11-2016
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	04-04-2017
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-05-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-08-2017

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:	25-05-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	03-12-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-04-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	28-01-2021

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	EUCTR2016-002804-14-NL
ClinicalTrials.gov	NCT02682927
CCMO	NL59112.075.16