A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, Multicenter Study to Examine the Efficacy and Safety of ZX008 in Subjects with CDKL5 Deficiency Disorder Followed by an Open-Label Extension

Published: 31-03-2022
Last updated: 02-12-2024

This study has been transitioned to CTIS with ID 2023-506269-78-00 check the CTIS register for the current data. Objectives for Part 1: Primary (Efficacy): To demonstrate that the efficacy of fenfluramine (ZX008) 0.8 mg/kg/day is superior to placebo...

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

Summary

ID

NL-OMON56446

Source
ToetsingOnline

Brief title
ZX008-2103(EP0216)

Condition

- Seizures (incl subtypes)

Synonym
CDKL5 Deficiency Disorder; CDD

Research involving

Human

Sponsors and support

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

Intervention

Keyword: CDKL5 Deficiency Disorder, Incapacitated, Minors and adults, ZX008

Outcome measures

Primary outcome

Part 1:

Efficacy

Percentage Change from Baseline in CMSF during T+M

Part 2:

Safety

Treatment emergent adverse events (TEAEs)

Abnormal physical examination findings

Abnormal neurological examination findings

Positive response to self-harm question

Increase in valvular regurgitation from baseline (except absent to trace)

Pulmonary arterial hypertension (PASP > 35 mmHg) at any time during treatment

on repeat testing

Change from Baseline at end of OLE Period in Laboratory parameters (hematology,

hormones, chemistry, urinalysis)

Change from Baseline at end of OLE Period in Vital signs (blood pressure, heart

rate, temperature, and respiratory rate)

Change from Baseline at end of OLE Period in Body weight

Change from Baseline at end of OLE Period in Tanner Staging

Secondary outcome

Part 1

Efficacy:

Key secondary

Achievement of a >= 50% reduction from Baseline in CMSF during T+M

Achievement of a CGI-I rating of much or very much improved as assessed by the Investigator at the end of T+M

Percentage change from Baseline in monthly GTC seizure frequency during T+M

Additional secondary

Achievement of Categorized Percentage change in seizures from Baseline in CMSF during T+M Periods (no reduction or worsening, >= 25%, >= 75%, or 100% reduction)

Achievement of *near seizure freedom* (0 or 1 seizures) during T+M

Achievement of a CGI-I rating of much or very much improved as assessed by the parent/caregiver at the end of T+M

Achievement of improvement (minimal, much, or very much improved) in the CGI-I rating as assessed, independently, by the Investigator at the end of T+M

Achievement of improvement (minimal, much, or very much improved) in the CGI-I rating as assessed, independently, by the parent/caregiver at the end of T+M

Percentage change from Baseline in the monthly frequency of all seizures during

T+M

Change from Baseline in the monthly frequency of CMS-free days during T+M

Exploratory

Percentage change from Baseline in the monthly frequency of all seizure types not included as CMS (ie, *non-CMS* seizures) during T+M

The longest CMS-free interval (in days) during T+M

Change from Baseline in subject quality of life as measured using the Quality-of-Life Inventory-Disability (QI Disability)

Change from Baseline in parent/caregiver quality of life as measured by EQ-5D-5L

Change from Baseline in subject*s sleep behavior as measured by CGI-I by parent/caregiver

Safety

Treatment emergent adverse events (TEAEs)

Abnormal physical examination findings

Abnormal neurological examination findings

Positive response to self-harm question

Increase in valvular regurgitation from baseline (except absent to trace)

Pulmonary arterial hypertension (PASP > 35 mmHg) at any time during treatment on repeat testing

Change from Baseline in Laboratory parameters (hematology, hormones, chemistry, urinalysis)

Change from Baseline in Vital signs (blood pressure, heart rate, temperature, and respiratory rate)

Change from Baseline in Body weight

Change from Baseline in Tanner Staging

Part 2

Effectiveness

Percentage change from Baseline in CMSF during the OLE Treatment Period

Achievement of Categorized Percentage change in seizures from Baseline in CMSF during OLE Treatment Period (no reduction or worsening, >= 25%, >= 50%, >= 75%, or 100% reduction)

Achievement of *near seizure freedom* (0 or 1 seizures) during T+M

Achievement of a CGI-I rating of much or very much improved as assessed by the Investigator and by the parent/caregiver at the end of the OLE Treatment Period

Achievement of improvement (minimal, much, or very much improved) in the CGI-I rating as assessed by the Investigator at the end of the OLE Treatment Period

Achievement of improvement (minimal, much, or very much improved) in the CGI-I rating as assessed by the Parent/Caregiver at the end of the OLE Treatment Period

Percentage change from Baseline in monthly GTC seizure frequency during the OLE Treatment Period

Change from Baseline in the monthly frequency of CMS-free days during the OLE Treatment Period

Exploratory

Percentage change from Baseline in the monthly frequency of non-CMS seizures

The longest CMS-free interval (in days) during the OLE Treatment Period

Change from Baseline at end of OLE Treatment Period in subject quality of life as measured using the Quality-of-Life Inventory-Disability (QI Disability)

Change from Baseline at end of OLE Treatment Period in parent/caregiver quality of life as measured by EQ-5D-5L

Change from Baseline at the end of OLE Treatment Period in subject*s sleep behavior as measured by CGI-I by parent/caregiver

Study description

Background summary

5.1 Overview of Disease and Disease Burden
CDKL5 deficiency disorder (CDD) is a rare genetic disorder that is caused by a mutation in the cyclin-dependent kinase-like 5 (CDKL5) gene, located on the X chromosome. The CDKL5 protein is a serine-threonine kinase, that is implicated in normal brain development and function (Olson 2019). CDD is a debilitating developmental disease with severe sequelae including frequent seizures that cause multisystemic abnormalities. Increased seizure frequency and intensity are often associated with catastrophic consequences of interfering with intellectual and psychomotor development (Jakimiec 2020).
It is estimated that CDD affects 1 in 40,000 to 60,000 live births (Demarest 2019, Jakimiec 2020). The majority of patients with CDD are female (ie, the female/male ratio is estimated to be 4:1) (Fehr 2015; Jakimiec 2020; Mirzaa 2013). In general, a CDD diagnosis is made on the basis of a patient*s history, symptoms, physical examination, and genetic testing. Additionally, there are proposed minimal criteria for diagnosis, including a pathogenic or likely pathogenic variant in the CDKL5 gene, epilepsy with onset in the first year of life, and motor and cognitive developmental delays (Olson 2019). The disorder encompasses a wide array of clinical symptoms that range from mild to severe across multiple systems. Male patients tend to have more severe symptoms than female patients (Jakimiec 2020). The majority of patients with CDD have treatment-resistant and long-term epilepsy (Olson 2019). Additional symptoms of CDD include cortical visual impairment, hypotonia, gastrointestinal dysfunction, gross motor impairment, sleep disturbances, respiratory ailments, and feeding difficulties. The comorbidities associated with the disorder not only severely impact the patients themselves, but also the caregivers.
Of the numerous symptoms that are associated with the manifestation of CDD, early onset epilepsy is the initial symptom to occur within the first 3 months of life (Olson 2019). Seizures in patients with CDD are more severe and begin

at a much younger age when compared with other epileptic encephalopathies (Cutri French 2020). Epileptic spasms are one of the most common seizure types during disease onset; however, this type of seizure can manifest at any time throughout the course of a patient*s life (Demarest 2019; Olson 2019). Other presenting seizure types include tonic seizures, generalized tonic-clonic (GTC), hypermotor tonic spams, myoclonic seizures, and atonic seizures (Cutri French 2020; Demarest 2019). A unique feature of CDD is that the epileptic episodes may have diverse morphology (Jakimiec 2020). Some patients with CDD can experience several seizure types during their lifetime (Demarest 2019), and seizure types vary/change with age. Children and adults with CDD are functionally impaired due to the debilitating symptoms including severe cognitive and motor development delays, which significantly impact their daily lives.

5.1.1 Current Management of CDKL5 Deficiency Disorder

One proposed mechanistic approach to treating CDD is reduction of seizure burden. Accordingly, early intervention with an effective antiepileptic treatment (AET) could be crucial for improved disease outcomes. Antiepileptic treatment regimens include antiseizure medications (ASMs), vagus nerve stimulation (VNS), responsive neurostimulation (RNS), ketogenic diet (KD), surgery, and other non-pharmacological interventions.

Antiseizure medications have the potential to reduce the frequency, severity, and duration of seizures associated with CDD. The effectiveness of many ASMs tend to follow a pattern, which includes a period of high efficacy in the first 3 months but gradually declines over the course of a year (Müller 2016). Antiseizure medications typically used in CDD include sodium valproate, levetiracetam, lamotrigine, vigabatrin, clobazam, zonisamide, felbamate, and steroids (Müller 2016; Amin 2017; Olson 2019). In addition, ganaxolone was recently approved in the US for the treatment of CDD. Patients continue to experience inadequate seizure control despite the usage of numerous ASMs; early susceptibility to drug-resistance remains a hurdle for drug development. Clinicians continue to need to consider each patient individually, considering the potential benefit of each therapy weighed against the risk of adverse effects.

Study objective

This study has been transitioned to CTIS with ID 2023-506269-78-00 check the CTIS register for the current data.

Objectives for Part 1:

Primary (Efficacy): To demonstrate that the efficacy of fenfluramine (ZX008) 0.8 mg/kg/day is superior to placebo as an adjunctive therapy for pediatric and adult subjects with CDD

Secondary (Safety): To characterize the safety and tolerability of fenfluramine (ZX008) in pediatric and adult subjects with CDD

Objectives for Part 2:
Primary (Safety)
To characterize the long-term safety and tolerability of fenfluramine (ZX008) in pediatric and adult subjects with CDD
Secondary (Effectiveness)
To assess long-term effectiveness of fenfluramine (ZX008) as an adjunctive therapy for pediatric and adult subjects with CDD

Study design

Methodology:
This is a 2-part multicenter trial. Part 1 is a 20-week randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study to examine the efficacy and safety of fenfluramine (ZX008) as an adjunctive therapy (to existing concomitant treatment with antiepileptic treatments [AETs]) in subjects 1 to 35 years of age with a CDD diagnosis and uncontrolled seizures. The primary study analysis to evaluate the efficacy and safety of fenfluramine (ZX008) in subjects with CDD will be based on Part 1 data in all randomized subjects.
Part 1 of the study is 20 weeks in duration and will consist of the following stages: Baseline Period (ie, Baseline; 4 weeks including the Screening Visit and Baseline observation), Titration Period (ie, Titration; 2 weeks), Maintenance Period (ie, Maintenance; 12 weeks), and a 2-week Transition Period (ie, Transition; 2 weeks) to the open-label starting dose.
Part 2 is a 54-week, open-label, flexible-dose, long term extension for subjects who complete Part 1. Part 2 includes an Open-Label Extension (OLE) Treatment Period (52 weeks) with a Taper Period (ie, Taper; 2 weeks). A cardiac follow-up visit will be conducted 6 months after the last dose of study drug.

Intervention

Investigational product, dosage, and mode of administration:
Fenfluramine (ZX008) is supplied as an oral solution in concentrations of 1.25, 2.5, and 5 mg/mL. In Part 1, subjects will be randomized to receive either fenfluramine (ZX008) 0.8 mg/kg/day or placebo. Subjects receiving concomitant STP and randomized to fenfluramine (ZX008) 0.8 mg/kg/day will receive fenfluramine (ZX008) 0.5 mg/kg/day. In Part 2, open-label fenfluramine (ZX008) will be administered using a flexible dosing regimen, up to fenfluramine (ZX008) 0.8 mg/kg/day. The maximum dose of fenfluramine (ZX008) allowed during the study is 30 mg/day (or 20 mg/day for those receiving concomitant STP). Study drug will be administered twice a day (BID) in equally divided doses with or without food.

Study burden and risks

5.4 Risk-Benefit Assessment

The clinical benefit of fenfluramine (ZX008) in subjects who participated in 3 positive, adequate, and well controlled, randomized, double-blind, placebo-controlled trials for Dravet syndrome, Study 1, Study 2 Cohort 2, and Study 3 demonstrated a statistically significant and clinically meaningful reduction in monthly convulsive seizure frequency and was generally well tolerated. Moreover, the Phase 3, randomized placebo-controlled trial for LGS Study 1601 also demonstrated clinically meaningful reduction in monthly drop seizures. No subject had valvular heart disease or pulmonary arterial hypertension in any study.

Fenfluramine (ZX008) was additionally evaluated in an Investigator-initiated trial in subjects 2 to 35 years of age with CDD (Devinsky 2020). The trial demonstrated that fenfluramine provided a clinically meaningful reduction in both GTCs (90%) and tonic seizures (55%) in patients with CDD.

Fenfluramine has been used successfully for up to 30 years in Belgium in refractory pediatric epilepsy patients, including those with Dravet syndrome (Boel 1996; Ceulemans 2012; Schoonjans 2015; Schoonjans 2017). The doses used in this study (ZX008-2103/EP0216) are based on data from the patients being successfully treated in Belgium discussed above, and from four fenfluramine (ZX008) studies (Study 1, Study 2 Cohort 2, Study 3 in Dravet syndrome and Study 1601 in LGS). Fenfluramine (ZX008) 0.8 mg/kg/day dose is believed to be a likely therapeutic dose, which could provide sufficient antiepileptic effect for a sustained period of time during this study.

In summary, considering the clinical activity and well-tolerated safety profile with fenfluramine (ZX008) as a treatment for seizures associated with Dravet syndrome and with LGS, as well as the clinical benefit seen in an Investigator-initiated study in patients with CDD, there is a positive benefit risk assessment and strong scientific and clinical rationale for the broad development of fenfluramine (ZX008) in a population of subjects with CDD.

5.4.1 Risk/Benefit Assessment for Minors or Cognitively Disabled

For minors or persons of legal age not capable of understanding the nature, significance, and implications of the clinical trial and expressing their wishes accordingly, the degree of burden and risk threshold should be monitored carefully. Section 5.2.3 and the IB (please see the current effective ZX008 IB) list the AEs that have been commonly reported in several ongoing and completed clinical trials of fenfluramine (ZX008) for the treatment of seizures in epileptic encephalopathies. The burden of these AEs should be monitored and weighed against the benefits of seizure reduction or other improvements of the CDD condition that the participant may be experiencing. Section 8.4 addresses criteria for withdrawal from the study in cases in which the risk threshold for these participants may be reached.

Contacts

Public

Zogenix International Limited

West Street The Pearce Building
Maidenhead, Berkshire SL6 1RL
GB
Scientific
Zogenix International Limited

West Street The Pearce Building
Maidenhead, Berkshire SL6 1RL
GB

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)
Babies and toddlers (28 days-23 months)

Inclusion criteria

To be eligible to enroll in this study, subjects must meet the following inclusion criteria:
1. Subject has a confirmed pathogenic or likely pathogenic mutation in the CDKL5 gene and a clinical diagnosis of CDD with epilepsy onset in the first year of life, plus motor and developmental delays.
2. Subject is male or female, aged 1 to 35 years, inclusive, as of the day of the Screening Visit. Subjects aged 1 to < 2 years will ONLY be permitted to enroll in the trial AFTER the DSMB has determined that it is appropriate to do so based on a planned unblinded interim safety review to be conducted after approximately 40 subjects aged >= 2 to 35 years have completed Visit 6.
3. Subject must have failed to achieve seizure control despite previous or current use of 2 or more AETs.
4. Subject is currently receiving at least 1 concomitant antiseizure treatment:

antiseizure medication (ASM), vagus nerve stimulation (VNS), responsive neurostimulation (RNS), or ketogenic diet (KD). During the trial, rescue medications (may include ASMs) or interventions for rescue treatment of seizures will not be counted towards the total number of antiseizure treatments established at Baseline.
5. All medications or interventions for epilepsy (including VNS, RNS, and KD) must be stable prior to screening and are expected to remain stable throughout the study. In order to establish stability at Baseline, duration of treatment with medications or interventions for epilepsy prior to the Screening visit must be as follows: VNS and RNS: >= 6 months duration; ASMs or KD: >= 4 weeks duration.
6. At the Screening Visit, parent/caregiver reports that subject has >= 4 countable motor seizures (CMS) per week. CMS include distinct seizures of the generalized tonic-clonic [GTC], bilateral clonic, bilateral tonic, atonic (drop), bilateral tonic/atonic (drop), or focal to bilateral tonic-clonic type lasting approximately 3 seconds or longer, to distinguish from short-clustered seizures, spasms, or jerks.
7. Subject (and/or subject*s parent[s]/legal guardian[s]) has provided written informed consent (and assent if applicable).
8. Subject (and/or subject*s parent/caregiver) is willing and able to comply with study requirements (including diary completion, visit schedule, and study drug accountability).

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from enrollment in this study:
1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study drug.
2. Subject has a diagnosis of pulmonary arterial hypertension.
3. Subject has a clinically significant medical condition, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension, or has had clinically relevant symptoms or a clinically significant illness currently or 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.
4. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke, severe ventricular arrhythmias, or clinically significant structural cardiac abnormality, including but not limited to mitral valve prolapse, atrial or ventricular septal defects, patent ductus arteriosus, and patent foramen ovale with reversal of shunt. (Note: Patent foramen ovale or a bicuspid aortic valve are not considered exclusionary.)
5. Subject has current eating disorder that suggests anorexia nervosa or bulimia.

6. Subject has a current or past history of glaucoma.
7. Subject is taking > 4 concomitant ASMs. Rescue medications are not included in the count.
8. Subject is receiving concomitant treatment with cannabidiol (CBD) other than Epidiolex/Epidyolex or is being actively treated with tetrahydrocannabinol (THC) or any marijuana product for any condition. Disallowed medications are subject to wash-out requirements.
9. Subject has moderate to severe hepatic impairment, assessed based on the Child-Pugh system (Appendix 1).
10. Subject has moderate to severe renal impairment (estimated glomerular filtration rate < 50 mL/min/1.73 m2 calculated with the Isotope Dilution Mass Spectrometry [IDMS] Traceable Schwartz equation for children and the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation for adults, using actual body weight).
11. 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 atomoxetine; or cyproheptadine (see Appendix 2 for a list of prohibited medications). (Note: Short-term requirements for prohibited medications will be handled on a per case basis by the study physician or delegate.)
12. Subject is currently receiving another investigational product(s) or has received another investigational product within 30 days or within < 5 times the half-lives of the investigational product, whichever is longer, prior to the Screening Visit.
13. Female subjects of childbearing potential must not be pregnant or breastfeeding. Female subjects of childbearing potential must have a negative urine or serum pregnancy test at Screening. Subjects of childbearing or child-fathering potential must be willing to use an approved method of highly effective contraception, which includes abstinence, while participating in this study and for 90 days after the last dose of study drug.
14. Subject is known to be human immunodeficiency virus positive.
15. Subject is known to have active viral hepatitis B or C.
16. Subject is institutionalized in a facility that does not provide skilled epilepsy care.
17. Subject has previously been treated with Fintepla® (fenfluramine) prior to the Screening Visit.

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:	Recruiting
Start date (anticipated):	28-12-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Fintepla
Generic name:	Fenfluramine hydrochloride

Ethics review

Approved WMO Date:	31-03-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-08-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-09-2022

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-01-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
EU-CTR	CTIS2023-506269-78-00
EudraCT	EUCTR2021-003222-76-NL
CCMO	NL80928.028.22