Clinical Study Results

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Study Sponsor:	UCB Biopharma SRL
Treatment Studied:	Fenfluramine
Protocol Numbers:	ZX008-1501, ZX008-1502, and ZX008-1504
Short Study Title:	A study to learn how well fenfluramine works and how safe it is in children and young adults with Dravet syndrome

Thank you

UCB thanks all the participants of these studies and their caregivers. All the participants and caregivers helped the researchers learn more about using fenfluramine hydrochloride in people with Dravet syndrome. Fenfluramine hydrochloride is also called ZX008. In the rest of this summary, fenfluramine hydrochloride will be called **fenfluramine**.

This is a summary of the main results of **3** studies: ZX008-1501, ZX008-1502, and ZX008-1504.

Studies ZX008-1501 and ZX008-1502 were two identical studies that were done at the same time in different parts of the world. The results of these studies were combined. The combined results from the first participants from those studies became known as “Study 1”. The combined results of the later participants from those studies became known as “Study 3”.

“Study 2” includes the results for the ZX008-1504 study. Study 2 had 2 parts. Part 1 of Study 2 was not designed to learn about how well fenfluramine works. So, the results from Part 1 of Study 2 are not included in this summary. Only the results from Part 2 of Study 2 are included in this summary.

So, this summary includes results from **Study 1**, **Study 3**, and **Study 2 Part 2**.

An independent, non-profit organization helped prepare this summary of the studies’ results, which included feedback from patients.

We think it is important to share the results with the participants, their caregivers, and the public. We hope this summary helps the participants and their caregivers understand their important role in medical research.

The purpose of this summary is only to share information. If you or the child you care for needs medical advice, please contact your or your child’s doctor. If you or the child in your care participated in any of these studies and has questions about the results, please speak with study staff.

Overview of this study

Why was the research needed?

Researchers are looking for a different way to treat Dravet syndrome. Before a drug is available for all patients, researchers do clinical studies to find out how well the drug works and how safe it is.

What treatments did the participants take?

The participants in these 3 studies took fenfluramine or a placebo. The placebo looked like fenfluramine but did not have any fenfluramine in it.

What were the results of the 3 studies?

The main questions the researchers wanted to answer in these 3 studies were:

- **Did fenfluramine help the participants have fewer seizures?**

  Yes. The participants who took fenfluramine had fewer seizures than the participants who took the placebo.

- **What medical problems did the study doctors report as possibly related to the study treatment?**

  The number of participants who had medical problems that the study doctors reported as possibly related to the study treatment were:

Study 1 (ZX008-1501 and ZX008-1502)	42.9% (51 out of 119 participants)
Study 3 (ZX008-1501 and ZX008-1502)	50.0% (71 out of 142 participants)
Study 2 Part 2 (ZX008-1504)	52.9% (46 out of 87 participants)

More details about the results of these 3 studies are included later in this summary.

Where can I learn more about these 3 studies?

You can find more information about these 3 studies on the websites listed on the last page. If a full report of these studies' results is available, it can also be found on those websites.

Why was the research needed?

Before a treatment is available to all patients, researchers do clinical studies to get information about how well the treatment works and about how safe it is.

The researchers in these 3 studies wanted to learn if fenfluramine helped to reduce the number of seizures in a large number of participants living with Dravet syndrome. They also wanted to learn if the participants had any medical problems during the studies.

Dravet syndrome is a rare and severe type of epilepsy that starts in young children, usually before their first birthday. It causes frequent and prolonged seizures that can be hard to control with medication. **Seizures** are a sudden burst of brain activity that causes intense discomfort and uncontrollable behaviors such as shaking, twitching, unusual thoughts or sensations, and loss of consciousness.

Children with Dravet syndrome may take longer to learn or grow and have problems with movement, balance, and speech, and have a higher risk of other health problems. Dravet syndrome is a lifelong condition that requires specialized care and treatment.

There are treatments available for Dravet syndrome, but these may not work well enough. The study drug **fenfluramine** is designed to affect specific cells in the brain that are related to seizures. So, researchers think that fenfluramine could work for treating Dravet syndrome.

This summary includes the results of 3 different studies. In each of these studies, researchers wanted to learn if fenfluramine could reduce the number of seizures in children and young adults with Dravet syndrome.

What were the main questions studied?

The main questions the researchers wanted to answer in these 3 studies were:

- Did fenfluramine help the participants have fewer seizures?
- What medical problems did the study doctors report as possibly related to the study treatment?

Who participated in the 3 studies?

There were 348 males and females with Dravet syndrome who each participated in one of the 3 studies. They were 2 to 18 years old when they joined.

The 3 studies included participants in 12 countries:

Country	Number of participants	Country	Number of participants
Australia	12	Italy	32
Belgium	8	Japan	13
Canada	14	The Netherlands	10
Denmark	10	Spain	21
France	24	The United Kingdom	30
Germany	32	The United States	142

In these 3 studies, the researchers planned to include participants diagnosed with Dravet syndrome who:

- Had seizures before they turned 1 year old
- Had seizures that could not be controlled by current treatments for epilepsy
- Had at least 4 seizures every 4 weeks during the 12 weeks prior to joining the study

Each participant in **Study 1** received treatment in the study for up to 16 weeks (about 4 months). Study 1 started in January 2016 and ended in August 2017.

Each participant in **Study 3** received treatment in the study for up to 16 weeks (about 4 months). Study 3 started in February 2017 and ended in July 2020.

Each participant in **Study 2 Part 2** received treatment in the study for up to 17 weeks (about 4 months). Part 2 of Study 2 started in January 2017 and ended in June 2018.

What treatments did the participants take?

The participants in these studies took fenfluramine or a placebo as a liquid by mouth. The placebo looked like fenfluramine, but did not have any fenfluramine in it. The researchers used the placebo to help make sure the effects they found in the studies were actually caused by fenfluramine.

Doses of fenfluramine were measured in milligrams per kilogram (mg/kg). This means that the amount of fenfluramine that the participants took each day was based on their body weight.

Fenfluramine can be made in 2 forms: fenfluramine hydrochloride, and fenfluramine base. The type of fenfluramine that participants took in these studies was **fenfluramine hydrochloride**.

Participants in all the studies could continue receiving the standard treatments for Dravet syndrome. Participants in Study 2 Part 2 must have been taking a drug called stiripentol as part of their standard treatment. For this reason, the participants in Study 2 Part 2 received a lower dose of fenfluramine.

In Study 1 and Study 3, none of the participants took more than 30 mg of fenfluramine in a single day. In Study 2 Part 2, none of the participants took more than 20 mg of fenfluramine in a single day.

None of the participants, caregivers, study doctors, or study staff knew what treatment each participant was taking. UCB staff also did not know. Some studies are done this way because knowing what treatment the participants are taking can affect the results of the study. After each study was completed, UCB learned what treatment each participant took so they could create a report of the results.

The researchers used a computer program to randomly choose if the participants took fenfluramine or the placebo. This helped make sure the treatments were chosen fairly and comparing the results for the treatments was as accurate as possible.

The chart below shows the treatments the researchers planned to study in **Study 1** and **Study 3**:

	Group 1	Group 2	Group 3
	**Study 1:** 40 participants **Study 3:** 48 participants	**Study 1:** 39 participants **Study 3:** 46 participants	**Study 1:** 40 participants **Study 3:** 48 participants
	The **placebo** taken as a liquid by mouth	**Fenfluramine** taken as a liquid by mouth: **0.2 mg/kg** per day	**Fenfluramine** taken as a liquid by mouth: **0.2 mg/kg** per day for the first day, then slowly increased over 8 days to **0.8 mg/kg** per day
	2 doses each day for up to 16 weeks		

The chart below shows the treatments the researchers planned to study in **Study 2 Part 2**:

	Group 1	Group 2
	44 participants	43 participants
	The **placebo** taken as a liquid by mouth	**Fenfluramine** taken as a liquid by mouth: **0.2 mg/kg** per day for the first day, then slowly increased over 14 days to **0.5 mg/kg** per day
	2 doses each day for up to 17 weeks	

After finishing treatment in these 3 studies, all participants had the option of taking fenfluramine in a separate **extension study**. During the last 2 weeks of treatment, the participants who were taking 0.8 mg/kg or 0.5 mg/kg per day of fenfluramine had their dose decreased slowly. This was so that they could either prepare to join the extension study or stop taking fenfluramine if they did not want to join the extension study.

What happened during the 3 studies?

This section shows how the studies were planned to be done.

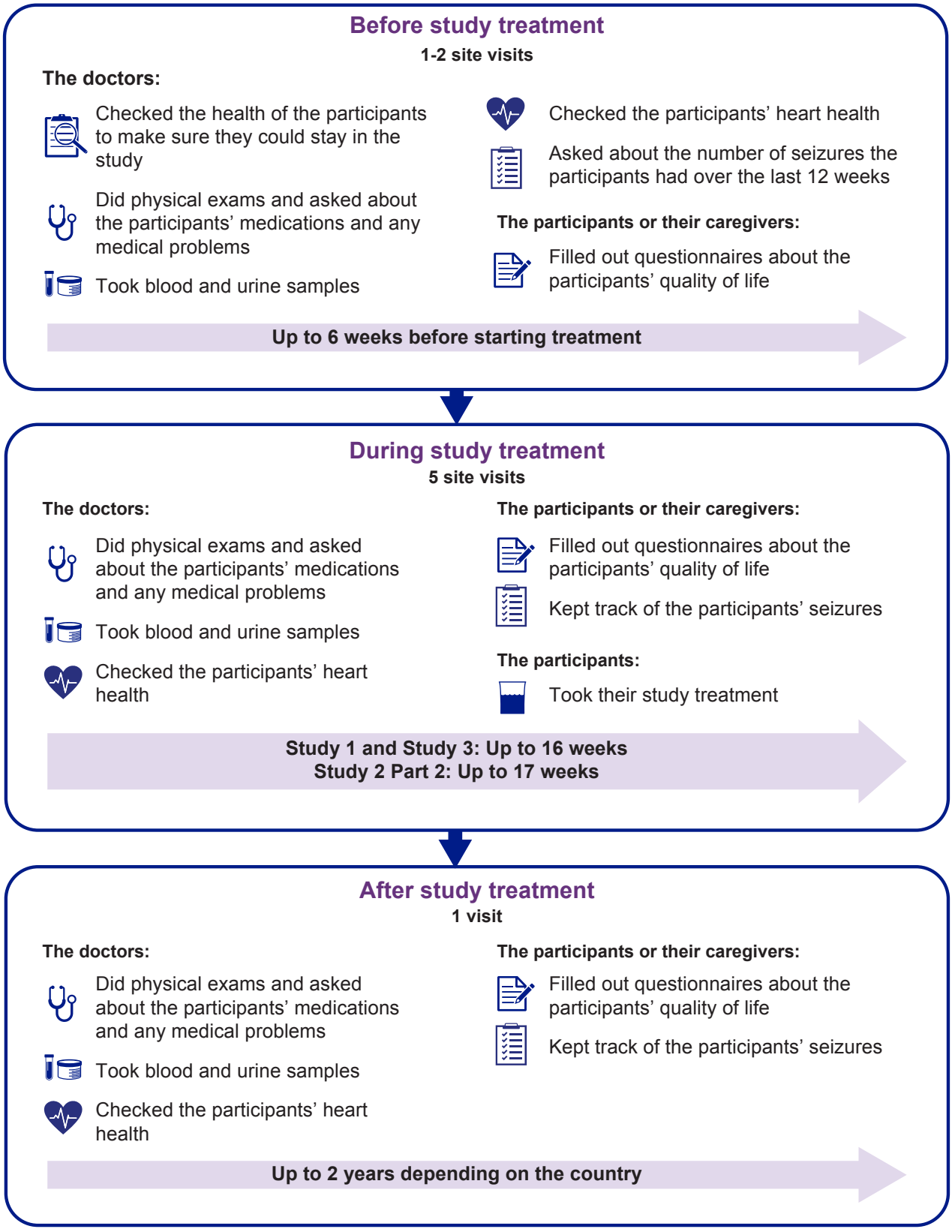
Before joining their study, the participants visited their clinic 1 or 2 times. Each participant or their parent or caregiver learned about the study and decided to join the study or to let the participant join the study. This is called “informed consent”.

Then, the study doctors and study staff asked about the participants’ medical history and checked their health to make sure they could join the study. The study doctors also asked about how many seizures the participants had in the 12 weeks before they started taking fenfluramine or the placebo. This part lasted up to 6 weeks.

During their study, the participants visited the clinic 5 times. During these visits, the study doctors did physical exams, collected blood and urine samples, and checked the participants’ heart health.

Throughout the study, the participants or their caregivers kept track of the participants’ seizures in an electronic diary. The study doctors kept track of any medical problems reported by the participants or observed by the doctors or study staff.

The chart below shows how the 3 studies were planned to be done:



What were the results of the 3 studies?

This is a summary of the main results from the 3 studies. These are the results from all the participants combined. The individual results of each participant might be different and are not in this summary.

Deciding which treatments work best usually takes results from several studies. Other studies may provide new information or different results. Always talk to a doctor before making any treatment decisions.

Did fenfluramine help the participants have fewer seizures?

Yes. In each of the 3 studies, the participants who took fenfluramine had fewer seizures compared to the participants who took the placebo.

To answer this question, the researchers asked the participants or their caregivers to keep track of the participants' seizures in an electronic diary. The researchers were specifically interested in types of seizures called **convulsive** seizures, which are common in Dravet syndrome. Using the results in the electronic diaries, the researchers calculated the average number of convulsive seizures that each participant had over 4-week periods. The researchers called this the **convulsive seizure frequency** (**CSF**).

Researchers wanted to learn whether the number of seizures the participants had changed over time. To keep track of this, the researchers calculated the difference in the participants' CSF from before taking fenfluramine or the placebo to after taking fenfluramine or the placebo. This difference is also called the **change from baseline**.

The **change from baseline in the CSF** helps researchers keep track of changes in the number of seizures that the participants have over time:

- If the change from baseline is a **positive number**, it means that the number of seizures **increased** during the study.
- If the change from baseline is a **negative number**, it means that the number of seizures **decreased** during the study.

In Study 1 and Study 3, researchers calculated the change from baseline after 14 weeks of treatment. In Study 2 Part 2, researchers calculated the change from baseline after 15 weeks of treatment.

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In each study, researchers compared the change from baseline in the CSF between the participants who took fenfluramine and the participants who took the placebo.

The average change from baseline in the CSF for each study is shown below.

Study	Group	CSF change from baseline
Study 1 (ZX008-1501 and ZX008-1502)	**0.8 mg/kg per day of fenfluramine**	**-13.1** (13.1 **fewer** seizures every 4 weeks)
	Placebo	**-6.7** (6.7 **fewer** seizures every 4 weeks)
Study 3 (ZX008-1501 and ZX008-1502)	**0.8 mg/kg per day of fenfluramine**	**-3.5** (3.5 **fewer** seizures every 4 weeks)
	Placebo	**1.5** (1.5 **more** seizures every 4 weeks)
Study 2 Part 2 (ZX008-1504)	**0.5 mg/kg per day of fenfluramine**	**-3.2** (3.2 **fewer** seizures every 4 weeks)
	Placebo	**0.7** (0.7 **more** seizures every 4 weeks)

The researchers also kept track of seizures in the participants who took **0.2 mg/kg per day of fenfluramine** in **Study 1** and **Study 3**. But, this was not part of the main question that the researchers were interested in answering, so these results are not in this summary.

What medical problems did the study doctors report as possibly related to the study treatment?

This section is a summary of the medical problems that the participants had during these 3 studies that the doctors reported as possibly related to the study treatment. These medical problems are called “adverse reactions”.

In these studies, the doctors did not know whether the participants were taking fenfluramine or the placebo when the medical problems happened.

Some participants had more than 1 adverse reaction.

This summary also includes information about serious adverse reactions. An adverse reaction is considered “serious” when it is life-threatening, causes lasting problems, or requires hospital care.

Other studies may or may not show that these medical problems were related to the study treatment. The results from several studies are often needed to decide if a treatment causes an adverse reaction. Always talk to a doctor before making any treatment decisions.

Did any adverse reactions happen during these 3 studies?

Information about the adverse reactions in each study is shown below.

Adverse reactions in **Study 1**

	Placebo (out of 40 participants)	**0.2 mg/kg per day of fenfluramine** (out of 39 participants)	**0.8 mg/kg per day of fenfluramine** (out of 40 participants)
How many participants had serious adverse reactions?	none	none	5.0% (2 participants)
How many participants had adverse reactions?	17.5% (7 participants)	43.6% (17 participants)	67.5% (27 participants)
How many participants stopped taking their study treatment due to adverse reactions?	none	none	10.0% (4 participants)

Adverse reactions in **Study 3**

	Placebo (out of 48 participants)	**0.2 mg/kg per day of fenfluramine** (out of 46 participants)	**0.8 mg/kg per day of fenfluramine** (out of 48 participants)
How many participants had serious adverse reactions?	none	none	2.1% (1 participant)
How many participants had adverse reactions?	35.4% (17 participants)	47.8% (22 participants)	66.7% (32 participants)
How many participants stopped taking their study treatment due to adverse reactions?	2.1% (1 participant)	none	2.1% (1 participant)

Adverse reactions in **Study 2 Part 2**		
	Placebo (out of 44 participants)	**0.5 mg/kg per day of fenfluramine** (out of 43 participants)
How many participants had serious adverse reactions?	2.3% (1 participant)	2.3% (1 participant)
How many participants had adverse reactions?	34.1% (15 participants)	72.1% (31 participants)
How many participants stopped taking their study treatment due to adverse reactions?	none	4.7% (2 participants)

What serious adverse reactions did the participants have?

The serious adverse reactions in **Study 1** are shown below.

Serious adverse reaction	**Placebo** (out of 40 participants)	**0.2 mg/kg per day of fenfluramine** (out of 39 participants)	**0.8 mg/kg per day of fenfluramine** (out of 40 participants)
Low energy or tiredness (Lethargy)	none	none	2.5% (1)
Diarrhea	none	none	2.5% (1)
A serious seizure	none	none	2.5% (1)
Weight loss	none	none	2.5% (1)
Decreased appetite	none	none	2.5% (1)
Feeling sleepy (Somnolence)	none	none	2.5% (1)

The serious adverse reaction in **Study 3** is shown below.

Serious adverse reaction	**Placebo** (out of 48 participants)	**0.2 mg/kg per day of fenfluramine** (out of 46 participants)	**0.8 mg/kg per day of fenfluramine** (out of 48 participants)
Increased levels of liver proteins in the blood, which may be a sign of liver injury	none	none	2.1% (1)

The serious adverse reactions in **Study 2 Part 2** are shown below:

Serious adverse reaction	**Placebo** (out of 44 participants)	**0.5 mg/kg per day of fenfluramine** (out of 43 participants)
Low energy or tiredness (Lethargy)	none	2.3% (1)
Several seizures in a short amount of time (Seizure cluster)	2.3% (1)	none
A serious seizure	2.3% (1)	none

None of the participants in the 3 studies died due to serious adverse reactions.

What adverse reactions did the participants have?

The most common adverse reaction in all 3 studies was decreased appetite.

The tables below show the adverse reactions that happened in 10.0% or more of participants in any treatment group for each study. There were other adverse reactions, but those happened in fewer participants.

Adverse reactions in 10.0% or more of participants in any group in Study 1

Adverse reaction	**Placebo** (out of 40 participants)	**0.2 mg/kg per day of fenfluramine** (out of 39 participants)	**0.8 mg/kg per day of fenfluramine** (out of 40 participants)
Decreased appetite	5.0% (2)	20.5% (8)	35.0% (14)
Feeling sleepy (Somnolence)	5.0% (2)	12.8% (5)	10.0% (4)
Low energy or tiredness (Lethargy)	2.5% (1)	7.7% (3)	15.0% (6)
Abnormal result from an echocardiogram, which is a possible sign of heart problems	2.5% (1)	2.6% (1)	17.5% (7)
Diarrhea	none	12.8% (5)	2.5% (1)

Adverse reactions in 10.0% or more of participants in any group in Study 3

Adverse reaction	**Placebo** (out of 48 participants)	**0.2 mg/kg per day of fenfluramine** (out of 46 participants)	**0.8 mg/kg per day of fenfluramine** (out of 48 participants)
Decreased appetite	6.3% (3)	21.7% (10)	35.4% (17)
Feeling sleepy (Somnolence)	10.4% (5)	8.7% (4)	20.8% (10)
Abnormal result from an echocardiogram, which is a possible sign of heart problems	4.2% (2)	13.0% (6)	10.4% (5)
Diarrhea	4.2% (2)	10.9% (5)	6.3% (3)
Feeling tired (Fatigue)	2.1% (1)	6.5% (3)	10.4% (5)

Adverse reactions in 10.0% or more of participants in any group in Study 2 Part 2

Adverse reaction	**Placebo** (out of 44 participants)	**0.5 mg/kg per day of fenfluramine** (out of 43 participants)
Decreased appetite	11.4% (5)	39.5% (17)
Feeling tired (Fatigue)	4.5% (2)	16.3% (7)
Low energy or tiredness (Lethargy)	4.5% (2)	14.0% (6)

What did the researchers learn from these 3 studies?

The results of these 3 studies have helped researchers learn more about using fenfluramine in people living with Dravet syndrome.

Deciding which treatments work best for patients almost always takes results from several studies. This summary shows only the main results from 3 studies. Other studies may provide new information or different results.

The purpose of this summary is only to share information. If you need medical advice about your or your child's health or situation, please contact your doctor.

When this document was approved, further clinical studies with fenfluramine were ongoing.

Where can I learn more about these 3 studies?

You can find more information about these 3 studies at the websites listed below:

- ZX008-1501 and ZX008-1502 (**Study 1** and **Study 3**)
  www.clinicaltrials.gov/ct2/show/study/NCT02682927
  www.clinicaltrialsregister.eu/ctr-search/trial/2015-004167-37/results

- ZX008-1504 (**Study 2**)
  www.clinicaltrials.gov/ct2/show/study/NCT02926898
  www.clinicaltrialsregister.eu/ctr-search/trial/2016-000474-38/results

If you have questions about this study, UCB contact information is available at www.ucb.com/UCBcares.

Study Information

Protocol Numbers: ZX008-1501 (Study 1 and Study 3), ZX008-1502 (Study 1 and Study 3), and ZX008-1504 (Study 2 Part 2)

Study Sponsor: UCB Biopharma SRL sponsored this study. It is referred to as UCB in this summary.

Full Title of ZX008-1501 and ZX008-1502: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Full Title of ZX008-1504: 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)

National Clinical Trial Numbers: NCT02682927 (ZX008-1501 and ZX008-1502) and NCT02926898 (ZX008-1504)

EudraCT Numbers: 2015-004167-37 (ZX008-1501 and ZX008-1502) and 2016-000474-38 (ZX008-1504)

Thank you

Participants in clinical studies belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.

This summary was last updated on 16 December 2024.
The final clinical study reports are dated 27 April 2018 (Study 1), 12 November 2021 (Study 3), and 21 December 2018 (Study 2 Part 2).