Zorevunersen, an investigational medicine for Dravet syndrome: Clinical study results

The original article summarized here was titled 'Zorevunersen in children and adolescents with Dravet syndrome' and published in the *New England Journal of Medicine* at: https://www.nejm.org/doi/full/10.1056/NEJMoa2506295

Study names and protocol numbers: This summary reports the results of four studies.

MONARCH: An Open-Label Study to Investigate the Safety of Single and Multiple Ascending Doses in Children and Adolescents With Dravet Syndrome (protocol STK-001-DS-101)

ADMIRAL: A Study of the Safety of Multiple Increasing Doses of STK-001 in Children and Adolescents With Dravet Syndrome (protocol STK-001-DS-102)

SWALLOWTAIL: An Open-Label Extension Study of STK-001 for Patients With Dravet Syndrome (protocol STK-001-DS-501)

LONGWING: An Extension Study for Patients With Dravet Syndrome, a Severe Form of Epilepsy, Who Previously Participated in Studies of STK-001 in the United Kingdom (protocol STK-001-DS-502)

Medicine studied: **Zorevunersen** (formerly STK-001)

Sponsor: **Stoke Therapeutics**

Study dates: **MONARCH:** June 29, 2020 to November 16, 2023

ADMIRAL: July 29, 2021 to November 7, 2023

SWALLOWTAIL: January 20, 2021 to present

LONGWING: May 9, 2022 to present

Note: The SWALLOWTAIL and LONGWING studies are ongoing, but the data presented in this summary are current as of May 30, 2025.

Clinical trial identifiers: NCT04442295 (MONARCH), ISRCTN99651026 (ADMIRAL), NCT04740476 (SWALLOWTAIL), and ISRCTN12811235 (LONGWING)

Date of summary: **June 1, 2026**

Note of thanks

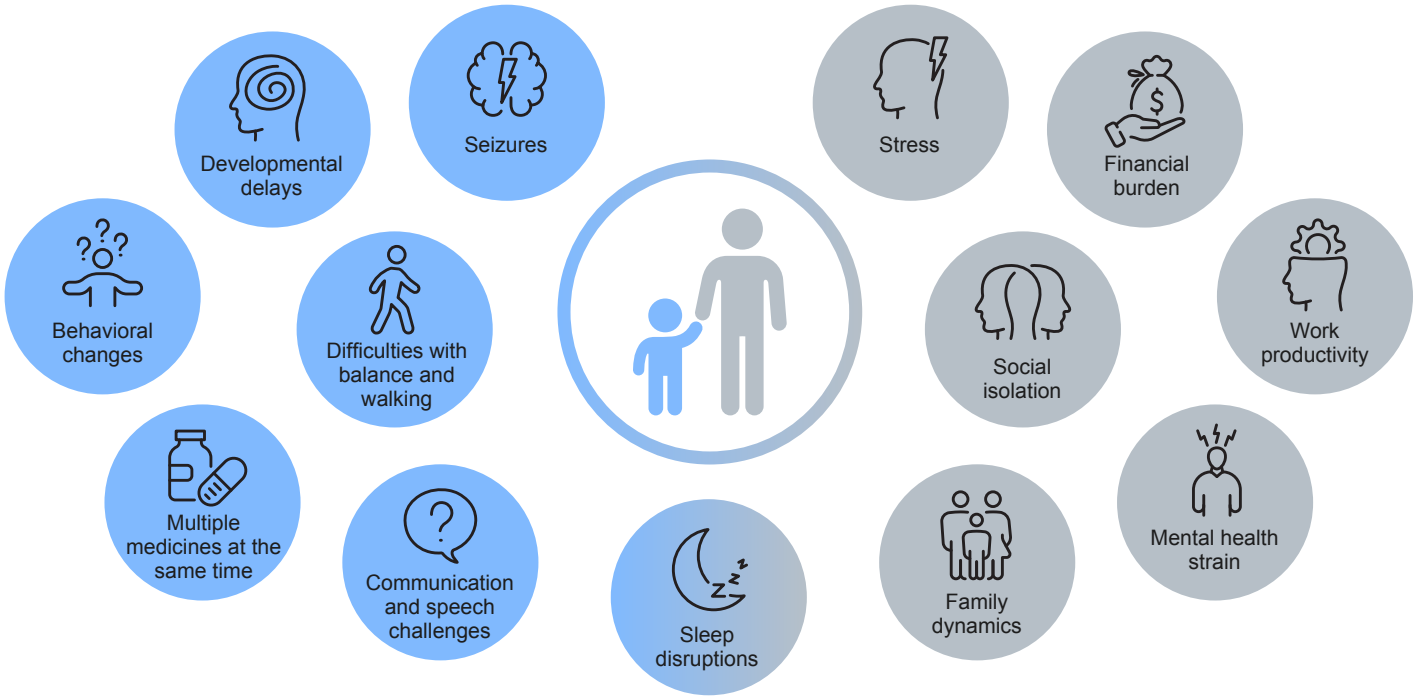
Stoke Therapeutics would like to thank the patients, caregivers, investigators, healthcare providers, and research staff who participated in this study.

WHY WERE THESE STUDIES DONE?

What is Dravet syndrome?

Dravet syndrome is a genetic neurodevelopmental disorder that produces frequent seizures and many nonseizure symptoms, including difficulties with communication, learning, movement, and everyday skills. Patients with Dravet syndrome begin experiencing seizures during early childhood, typically within the first year of life. As children with Dravet syndrome grow, their development often slows down or stops progressing. This means they may not learn new skills as quickly as they once did. Over time, there is a noticeable difference between children with Dravet syndrome and typically developing children. The difference is especially noticeable in areas such as communication, learning, and everyday skills. Researchers have found that Dravet syndrome also impacts caregivers **(Figure 1)**.

Figure 1. Effects of Dravet syndrome on patients and caregivers



Dravet syndrome can have many effects on patients and caregivers. Patients can experience seizures, developmental delays, behavioral changes, and more, while caregivers often experience stress, financial burden, social isolation, and other effects.

In more than 90% of cases, the underlying cause of Dravet syndrome is a change in a gene called *SCN1A*. These changes cause patients with Dravet syndrome to produce lower than normal amounts of a protein called $Na_V1.1$. The $Na_V1.1$ protein is important for the brain to function properly. An insufficient amount of $Na_V1.1$ protein is a key contributor to the seizure and nonseizure symptoms of Dravet syndrome.

What is zorevunersen?

Zorevunersen is an investigational medicine being studied for Dravet syndrome that works by making more $Na_V1.1$ protein. Zorevunersen aims to treat the genetic cause of Dravet syndrome rather than targeting individual symptoms. Zorevunersen does not permanently change a person's genes. It is currently being tested in clinical trials and is not approved for patients to use outside of clinical trials.

What was the purpose of the studies?

These four studies were done to assess the safety of zorevunersen among participants receiving it, along with their usual anti-seizure medicine(s), and to understand how one or multiple doses of zorevunersen would affect the symptoms of Dravet syndrome.

Researchers wanted to know:

- Will there be any medical problems (also called adverse events) during the studies and will any of those medical problems be serious?
- Will zorevunersen reduce the number of seizures experienced by participants with Dravet syndrome?
- Will zorevunersen improve the participants' overall medical condition?
- Will zorevunersen improve nonseizure symptoms in participants with Dravet syndrome, including the participants' communication skills and everyday skills?
- Which doses of zorevunersen might be most effective to treat the symptoms of Dravet syndrome?

WHAT HAPPENED DURING THE STUDIES?

How were the studies designed?

Before starting the studies, participants were observed for 4 weeks. During this time, they continued to receive their usual medicines (clobazam, fenfluramine, cannabidiol, valproate, etc.), and their caregivers recorded the number of seizures that happened. Doctors also confirmed that the participants were eligible for the studies during this time.

The MONARCH study (conducted in the United States) and the ADMIRAL study (conducted in the United Kingdom) were open-label Phase 1/2a studies **(Figure 2)**. Open-label means that all participants received zorevunersen, and all participants, caregivers, and researchers knew that zorevunersen was given. All participants kept taking their usual medicines along with zorevunersen throughout the studies. Zorevunersen was given by intrathecal injection in the back, meaning it was injected into the fluid surrounding the spinal cord. An anesthetic medicine is sometimes offered to prepare for the intrathecal injection.

Phase 1/2a study: A clinical trial in a small number of people that helps researchers decide the right dose and understand how safe a medicine is. The results are used to plan future studies in larger groups of people.

The MONARCH and ADMIRAL studies tested different amounts of zorevunersen and how often it was given to collect information about its effects on symptoms of Dravet syndrome and possible medical problems.

In the MONARCH study:

- Some participants were given one dose of zorevunersen (10, 20, 30, 45, or 70 mg) on the first day.
- Other participants were given three doses of zorevunersen (20, 30, or 45 mg). These doses were given on Day 1, Day 29, and Day 57.

In the ADMIRAL study:

- Some participants were given three doses of zorevunersen (30, 45, or 70 mg) on Day 1, Day 57, and Day 85.
- Other participants were given two doses of 70 mg each on Day 1 and Day 57.

After participants received their last dose, they were observed for about 6 months so doctors could track their seizures and record any medical problems that the participants had during the study. Researchers recorded all medical problems that occurred or got worse at any time from the time that zorevunersen was first given to participants to when the studies ended. The medical problems could be caused by zorevunersen, by something unrelated to zorevunersen (for example, Dravet syndrome itself, how zorevunersen was given, or other medicines that the participant was taking), or even by chance. Sometimes, the cause of the medical problem is unknown. By collecting this information, researchers can understand what effects zorevunersen might have on a participant.

Participants who finished MONARCH or ADMIRAL and qualified were able to join longer studies called open-label extension studies **(Figure 2)**. The extension studies were called SWALLOWTAIL in the United States and LONGWING in the United Kingdom. They were designed to see if participants had any medical problems when zorevunersen was used over a longer period of time and the effects of zorevunersen on seizures and nonseizure outcomes.

Extension study: A study that continues after an earlier trial, where participants can keep taking the study medicine. These studies help researchers learn more about long-term safety and effects of the medicine.

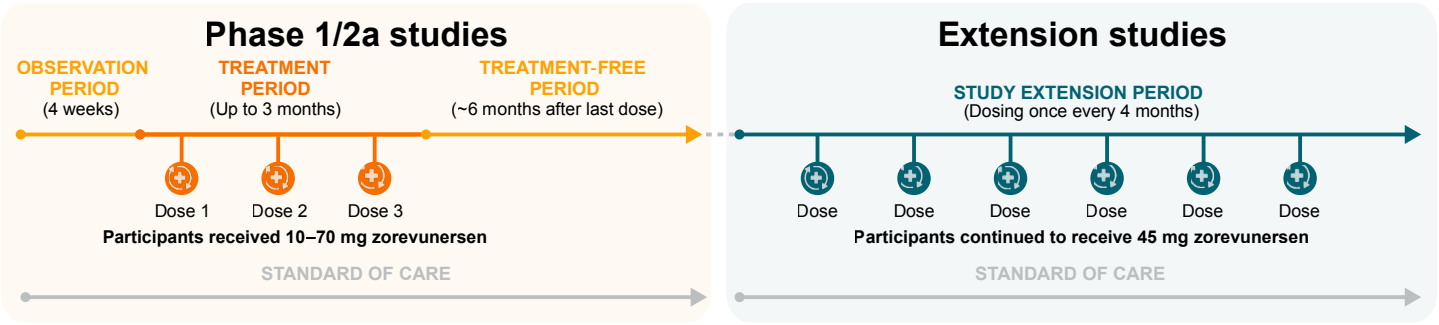
In the extension studies:

- Participants received three initial doses, each up to 45 mg, once every 4 months.
- Participants could continue to receive ongoing treatment with 45 mg every 4 months.

Participants returned for follow-up visits after treatment, so doctors could check their health and record if they had any medical problems.

This overall study design helped researchers understand how much and how often zorevunersen may be given and how it affects people with Dravet syndrome over time.

Figure 2. Design of Phase 1/2a and extension studies



In the **Phase 1/2a studies**, participants received different amounts of zorevunersen and at different times.

In the **extension studies**, participants continued to receive zorevunersen (up to 45 mg per dose) over a longer period of time.

Who participated in the studies?

The studies included children and adolescents with Dravet syndrome.

In the MONARCH study, participants were 2 to 18 years of age. In the ADMIRAL study, participants were 2 to younger than 18 years of age.

To take part, participants had to:

- Have a **confirmed diagnosis of Dravet syndrome** with a variant in the *SCN1A* gene
- Have **at least 4 convulsive seizures during a 28-day observation period** (convulsive seizures are seizures that cause visible body movements)
- Be taking **at least one medicine** to treat their seizures and have previously tried at least two anti-seizure medicines

In other words, participants in these studies were experiencing frequent seizures despite taking medicines to treat seizures.

Participants who completed MONARCH or ADMIRAL could continue into the long-term extension studies based on certain criteria, including how well they tolerated zorevunersen.

Where did the studies take place?

The MONARCH and SWALLOWTAIL studies took place in the United States, and the ADMIRAL and LONGWING studies took place in the United Kingdom.

When did the studies take place?

The MONARCH study was conducted from June 29, 2020, to November 16, 2023; the ADMIRAL study was conducted from July 29, 2021, to November 7, 2023.

The SWALLOWTAIL study began on January 20, 2021; the LONGWING study began on May 9, 2022. These two studies are still ongoing, and participants continue to receive zorevunersen.

WHAT WERE THE RESULTS OF THE STUDIES?

How many people participated in the studies?

In the Phase 1/2a studies (MONARCH and ADMIRAL), 81 participants received at least one dose of zorevunersen. The overall age of participants was 10 years (range 2–18 years) and 43% were 13 years of age or older. Out of these participants, 80 finished the studies, and most of them (75 participants) went on to join the longer-term extension studies (SWALLOWTAIL and LONGWING). As of May 30, 2025, 58 participants were still taking zorevunersen in the extension studies.

What medical problems did participants have during the studies?

Researchers recorded all medical problems that occurred or got worse from the time that zorevunersen was first given to when the studies ended. The medical problems could be caused by zorevunersen, by something unrelated to zorevunersen (for example, Dravet syndrome itself, how zorevunersen was given, or other medicines that the participant was taking), or even by chance. Sometimes, the cause of the medical problem is unknown. By collecting this information, researchers can understand what effects zorevunersen might have on a participant.

Of the 81 participants who were in the Phase 1/2a studies, 78 of them, or 96%, had at least one medical problem. The most common medical problems, which were reported by at least 10% of participants, are described in **Table 1** below:

Table 1. Medical problems frequently reported by participants across the Phase 1/2a studies

Common medical problems (regardless of cause)

Medical problem	Phase 1/2a (81 participants)
Headache after spinal injection	20 out of 81 participants (25%)
Fever	19 out of 81 participants (23%)
Seizure	17 out of 81 participants (21%)
Infection involving the nose, sinus, throat, voice box, or windpipe	16 out of 81 participants (20%)
Vomiting	16 out of 81 participants (20%)
Vomiting from spinal injection	15 out of 81 participants (19%)
Irritability	12 out of 81 participants (15%)
COVID-19	11 out of 81 participants (14%)
Cerebrospinal fluid protein elevation	11 out of 81 participants (14%)
Diarrhea	11 out of 81 participants (14%)
Bruising	10 out of 81 participants (12%)
Common cold	9 out of 81 participants (11%)
Pain from spinal injection	9 out of 81 participants (11%)
Runny nose	9 out of 81 participants (11%)

Common medical problems thought to be related to zorevunersen

Medical problem	Phase 1/2a (81 participants)
Cerebrospinal fluid protein elevation	11 out of 81 participants (14%)

Of the 75 participants who were in the extension studies, 75 of them, or 100% of participants, had at least one medical problem. The most common medical problems, which were reported by at least 10% of participants, are described in **Table 2** below:

Table 2. Medical problems frequently reported by participants across the extension studies

Common medical problems (regardless of cause)

Medical problem	Extension studies (75 participants)
Cerebrospinal fluid protein elevation	34 out of 75 participants (45%)
Fever	30 out of 75 participants (40%)
COVID-19	22 out of 75 participants (29%)
Infection involving the nose, sinus, throat, voice box, or windpipe	19 out of 75 participants (25%)
Fall	17 out of 75 participants (23%)
Pain from spinal injection	17 out of 75 participants (23%)
Seizure	17 out of 75 participants (23%)
Headache	13 out of 75 participants (17%)
Vomiting	13 out of 75 participants (17%)
Flu	12 out of 75 participants (16%)
Common cold	12 out of 75 participants (16%)
Strep throat	12 out of 75 participants (16%)
Headache after spinal injection	12 out of 75 participants (16%)
Diarrhea	10 out of 75 participants (13%)
Abnormal walking	10 out of 75 participants (13%)
Cough	9 out of 75 participants (12%)
Ear infection	9 out of 75 participants (12%)
Insomnia	8 out of 75 participants (11%)
Viral infection	8 out of 75 participants (11%)
Viral infection involving the nose, sinus, throat, voice box, or windpipe	8 out of 75 participants (11%)

Common medical problems thought to be related to zorevunersen

Medical problem	Extension studies (75 participants)
Cerebrospinal fluid protein elevation	33 out of 75 participants (44%)

Across studies, the only medical problem that occurred in more than 10% of participants and was thought to be related to zorevunersen was cerebrospinal fluid protein elevation.

Did participants have any serious medical problems during the studies?

A medical problem is serious if it causes death, disabilities, or birth defects. A medical problem can also be serious if it is life-threatening or causes a participant to stay at a hospital, or, if they are already staying in one, to stay longer.

In the Phase 1/2a studies, 18 out of 81 participants, or 22%, had a serious medical problem, but only one participant had serious medical problems that researchers thought were related to zorevunersen. The most common serious medical problem in the Phase 1/2a studies was a seizure. This happened in 5% of participants. None of the seizures were thought to be related to zorevunersen by the researchers.

One participant in the Phase 1/2a ADMIRAL study had unexpected serious medical problems. These medical problems included behavioral changes, abnormal eye movements, difficulty moving, and potential vision problems. Similar medical problems to those that the patient experienced have not been reported in any other patient treated with zorevunersen or in animals given higher doses of zorevunersen.

In the extension studies, 22 out of 75 participants, or 29%, had a serious medical problem. The most common serious medical problem in the extension studies was a seizure. This happened in 5% of participants. None of the seizures or other reported serious medical problems were thought to be related to zorevunersen by the researchers.

Two participants (one in the Phase 1/2a studies and one in the extension studies) died from sudden unexpected death in epilepsy. A third participant in the extension studies died from poor nutrition. Researchers did not believe that these three deaths were related to zorevunersen.

Did anyone stop taking the medicine because of medical problems?

Yes, one participant in the extension studies stopped taking zorevunersen because of a medical problem. This participant had cerebrospinal fluid protein elevation. The participant did not have any symptoms from this medical problem, but it was thought to be related to zorevunersen or the spinal injection procedure.

How did the seizures experienced by participants change during the studies?

Before receiving zorevunersen, participants had frequent convulsive seizures. Researchers measured how many seizures each participant had over 28-day periods.

After receiving zorevunersen, many participants had fewer seizures. In the Phase 1/2a studies, participants who took one 70 mg dose of zorevunersen had a median of 57% fewer seizures 6 months after their last dose. Participants who took more than one 70 mg dose had a median of 74% fewer seizures 6 months after their last dose **(Figure 3)**.

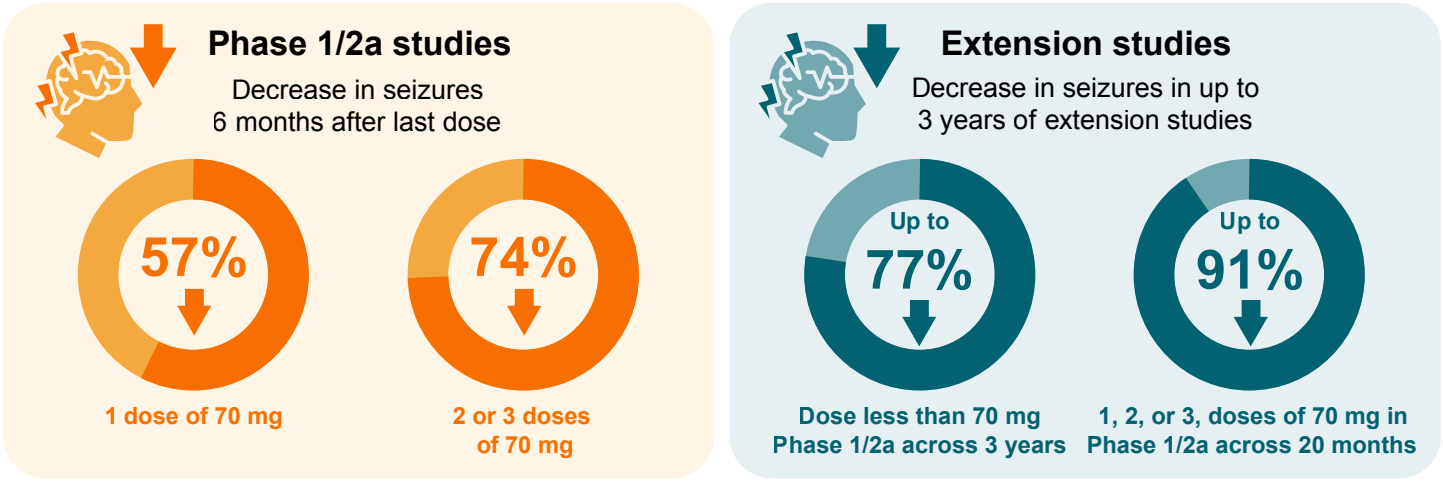
In the extension studies, researchers kept track of how often participants had seizures while they continued to receive zorevunersen. They collected information about seizures over a period of 3 years to see how well the medicine worked during extended treatment.

For participants who had received less than a 70 mg dose in the earlier Phase 1/2a studies, the number of seizures was reduced by a median of 7% to 77% through 3 years in the extension studies. In general, the effects were greater with more time on treatment.

For participants who had received one or more 70 mg doses, the number of seizures was reduced by a median of 59% to 91% through 20 months of the extension studies **(Figure 3)**. Participants who had received multiple 70 mg doses in the Phase 1/2a studies generally had the largest decreases in the number of seizures over time.

Overall, many participants continued to have fewer seizures during long-term treatment.

Figure 3. Effect of zorevunersen on seizures of participants



Participants experienced a reduction in seizures after treatment with zorevunersen in the Phase 1/2a and extension studies.

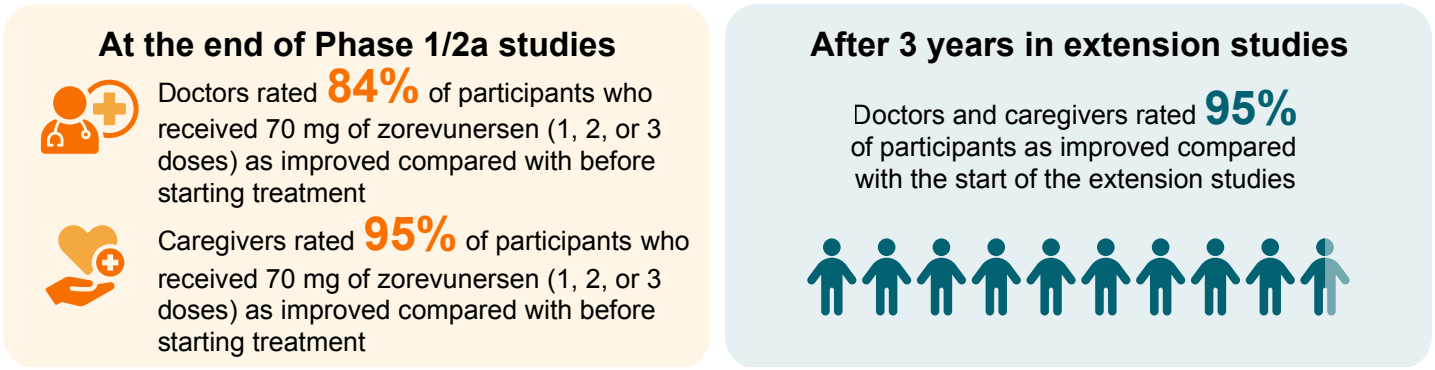
How did the overall medical condition and quality of life of participants change after treatment?

Researchers also asked doctors and caregivers to rate each participant's overall medical condition during the studies. They used a scale to describe whether participants were improved, the same, or worse.

At the end of the Phase 1/2a studies, doctors rated 84% of participants who received 1, 2, or 3 doses of 70 mg of zorevunersen as improved compared with before starting treatment. Caregivers rated 95% of these participants as improved **(Figure 4)**.

After 3 years of treatment in the extension studies, both doctors and caregivers rated 95% of all participants as improved compared with the start of the extension studies **(Figure 4)**.

Figure 4. Effect of zorevunersen on overall medical condition of participants



The overall medical condition of most participants improved through the Phase 1/2a and extension studies.

The improvements in the overall medical condition of participants who received zorevunersen appeared greater than those typically seen in people with Dravet syndrome who take their usual medicines.

Participants who received zorevunersen were also reported to have a better quality of life after treatment.

Quality of life: How well a person is doing in everyday life at a given time, including both positive and negative aspects such as health, comfort, mood, and daily activities.

How did communication and everyday skills of participants change after treatment?

Dravet syndrome can affect communication and everyday skills. Researchers measured adaptive behavior, which refers to the everyday neurodevelopmental skills people use to communicate, interact with others, manage daily activities, and perform motor skills. These skills were measured in 17 to 18 patients from the ADMIRAL study who continued into the LONGWING study and in 74 patients from the extension studies using a tool called the Vineland™-3 assessment, a standardized caregiver-reported tool used to measure adaptive behavior. Participants in the Phase 1/2a ADMIRAL study showed improvements from baseline in everyday skills, such as expressing themselves and understanding others, with scores getting higher over time.

Participants' everyday skills and communication abilities continued to improve further in the extension studies measured over 3 years **(Figure 5)**. Compared with the baseline of the extension studies, participants' scores generally improved on the Vineland-3 assessment. These improvements were greater than what is typically seen in people with Dravet syndrome who take their usual anti-seizure medicines.

Figure 5. Effect of zorevunersen on communication and everyday skills of participants through the extension studies

Communication and everyday skills of participants improved through longer-term treatment in extension studies.

What do these results mean?

The results of these studies suggest that treatment with zorevunersen may reduce seizures and improve overall health, quality of life, communication, and everyday life skills in people with Dravet syndrome. Many participants had fewer seizures and were rated as improved by doctors and caregivers, and these improvements continued through the Phase 1/2a studies and longer-term treatment in extension studies for up to 3 years.

What were the limitations of the studies?

All studies have limitations, which do not mean that the studies were done poorly but rather that we need to be careful when making conclusions from the results. Some limitations of these studies are described below.

Both the Phase 1/2a and extension studies were open-label and did not include a control group. These factors make it hard to know whether zorevunersen is responsible for the changes seen.

Open-label: This means that participants, caregivers, and researchers knew that participants were given zorevunersen and the dose they received, which might introduce bias into the results.

Control group: A group that receives a treatment with no medicine in it, used for comparison to help determine whether a medicine has an effect.

One final limitation is generalizability, which means taking the results from the Phase 1/2a and extension studies and applying the conclusions to all patients with Dravet syndrome. For participants to be eligible to take part in the Phase 1/2a and extension studies, they had to meet certain criteria. Therefore, the results reported here may only apply to patients similar to those in the studies and not to all patients with Dravet syndrome.

Are there any plans for more studies?

To help address these limitations and gather more information about this medicine, researchers are further studying zorevunersen in a larger, randomized, controlled study called a Phase 3 study. Phase 3 studies include a larger number of participants than Phase 1/2a studies. Randomized means that patients will be randomly assigned to a group in the study.

In the Phase 3 study, one group will receive zorevunersen, while the control group will not. This will help researchers better understand how well the medicine works and the medical problems that may occur with its use.

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

More information about the summarized studies is available at:

MONARCH: https://clinicaltrials.gov/study/NCT04442295

ADMIRAL: https://www.isrctn.com/ISRCTN99651026

SWALLOWTAIL: https://clinicaltrials.gov/study/NCT04740476

LONGWING: https://www.isrctn.com/ISRCTN12811235

WHERE CAN I FIND MORE INFORMATION ABOUT DRAVET SYNDROME?

Contact the Dravet Syndrome Foundation and Dravet Syndrome UK for more information about Dravet syndrome.

Dravet Syndrome Foundation: https://dravetfoundation.org

Dravet Syndrome UK: https://www.dravet.org.uk