Clinical Trial Results

Research Sponsor: Eisai Ltd.

Drug Studied: Eribulin, also called E7389

Short Trial Title: A trial to learn how eribulin and irinotecan work together and their safety in children with cancer that has come back or has not responded to previous treatment

Thank you!

You, your parents, or your caregiver took part or were involved in this clinical trial for the trial drugs eribulin and irinotecan. All of the participants helped researchers learn more about eribulin to help children with certain types of cancer.

Eisai, a Japanese pharmaceutical company and the sponsor of this trial, thanks you for your help. Eisai is committed to improving health through continuing research in areas of unmet need and sharing with you the results of the trial you participated in.

Eisai prepared this summary with a medical and regulatory writing organization called Certara Synchrogenix.

If you, your parents, or your caregiver have questions about the results, please speak with the doctor or staff at your trial site.

What has happened since the trial started?

The trial included 40 participants from 22 sites in France, Germany, Greece, Italy, Poland, Spain, and the United Kingdom. It started in March 2018 and ended in May 2021.

The sponsor of the trial reviewed the data collected and created a report of the results. This is a summary of that report.

Why was the research needed?

Researchers wanted to learn about the safety of eribulin and irinotecan when given together to children with cancer. They were also looking for a different way to treat children with 3 types of cancer that has come back or has not responded to treatment, and with no known cure. The 3 cancer types were rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and Ewing sarcoma (EWS).

The standard way to treat these cancers is with treatments that help shrink tumors.

Eribulin and irinotecan are treatments that help shrink tumors. Irinotecan is sometimes given alone to children with cancer.

The researchers also wanted to find out if children had any adverse events during the trial. An adverse event is a medical problem that may or may not be caused by the trial drug.

The main questions the researchers wanted to answer in this trial were:

- What are the safest doses of eribulin and irinotecan when given together to children with cancer?
- How effective are the selected doses of eribulin and irinotecan in children with RMS, NRSTS, and EWS that has come back or has not responded to treatment?
- What adverse events did participants receiving eribulin and irinotecan have?

It is important to know that this trial was designed to get the most accurate answers to the questions listed above. There were other questions the researchers wanted to learn more about, but these were not the main questions the trial was designed to answer.

What kind of trial was this?

To answer these questions, researchers asked for the help of participants like you. The participants in the trial were between 4 and 17-years-old. Of all participants, over half (21 participants) were male, and under half (19 participants) were female.

This trial was "open-label". This means that the participants, their parents or caregivers, the trial doctors and staff, and the sponsor knew which drugs the participants received.

This trial had 2 parts:

- **In Part 1**, the researchers wanted to learn about the safety of different doses of eribulin and irinotecan are when taken together. The participants in this part of the trial had a total of 7 different types of cancer.
- **In Part 2**, using the selected doses of eribulin and irinotecan from Part 1, the researchers wanted to learn how eribulin and irinotecan shrinks the tumors of participants with RMS, NRSTS, and EWS.

Participants were not allowed to take part in Part 1 if they had been given eribulin within 6 months of the start of the trial. Participants were not allowed to take part in Part 2 if they had been given eribulin at any time, or if they had been given irinotecan at any time, unless they had responded positively to irinotecan.

Participants were not allowed to take part in the trial if they had any 1 of a group of diseases resulting from damaged nerves or nerves that did not work properly, which is also called neuropathy.

Participants with certain heart problems were also not allowed to take part in the trial.

You received eribulin and irinotecan through a needle into your vein, also called intravenously or IV. The figure below shows how treatment was given in your trial.

- The amount of eribulin and irinotecan you received was measured in milligrams (mg) and based on your body surface area measured in meters squared (m^2).
- The researchers used different doses of irinotecan in Part 1 to find out which were safe when it was given with eribulin.
- The trial treatment was given in repeating 21-day time periods called treatment cycles.
- The different doses of trial treatment were called Schedule A and Schedule B.

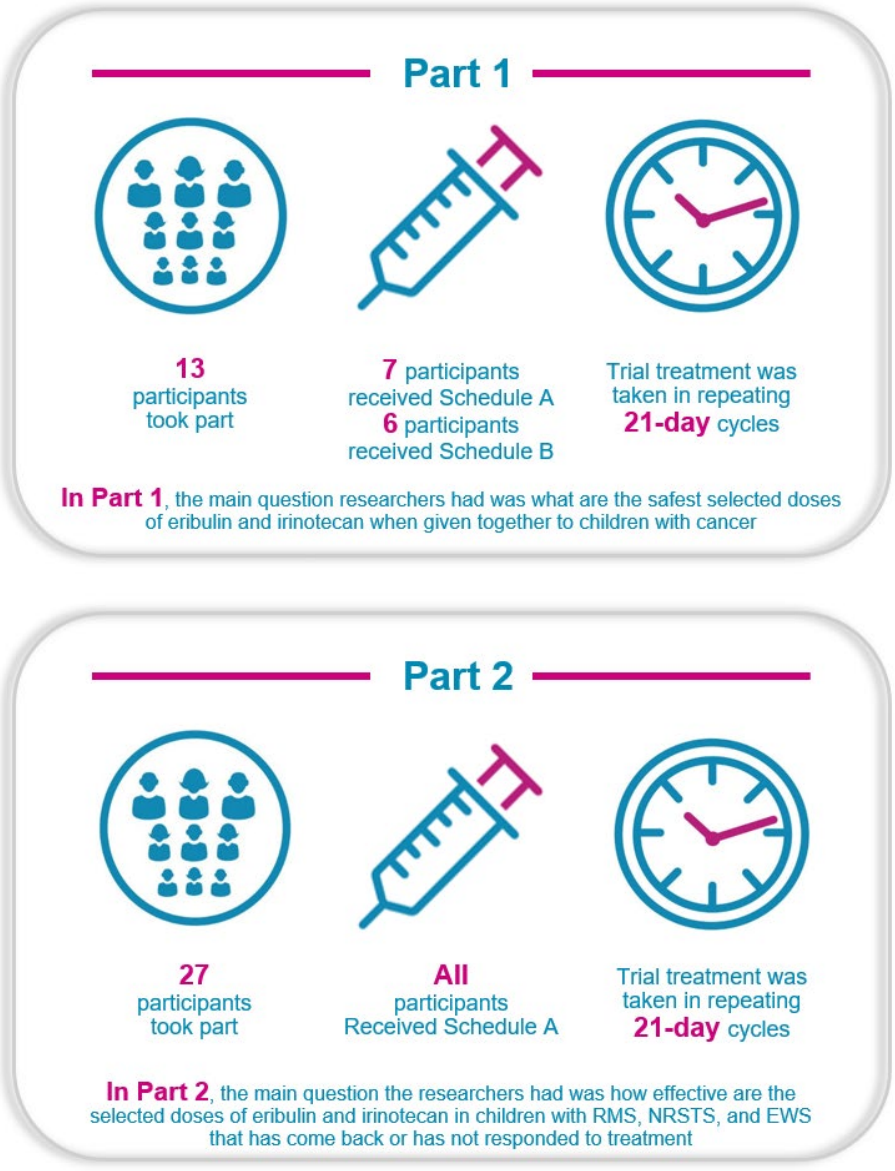
The table on the next page shows the doses in both schedules.

During Part 1, participants received either Schedule A or Schedule B

	Schedule A 21-day cycles	Schedule B 21-day cycles
Eribulin	1.4 mg/m^2 on days 1 and 8	1.4 mg/m^2 on days 1 and 8
Irinotecan	20 or 40 mg/m^2 on days 1, 2, 3, 4, and 5	100 or 125 mg/m^2 on days 1 and 8

The Figure below shows how trial treatment was given in your trial.

How did participants receive the treatment?



What happened during the trial?

Before the trial started, the participants, had tests, procedures, and scans. These were done so that the doctors could do a full check-up and make sure that each participant could join the trial.

During Part 1 and Part 2 of the trial, participants along with their parents or caregivers visited the trial site around 13 times. During these visits, the trial doctors gave the participants the trial treatments, continued to check their health, and performed tests and procedures, including:

- Physical examination
- Scans to assess how the tumor was responding
- Blood and urine tests
- Check the participant's heart health
- Check for adverse events

Up to 28 days after the last dose, all participants visited the trial site. The trial doctors did further check-ups on the participants including checks for adverse events. The participants then entered a follow-up period and information was collected on each participant for at least 4-weeks and up to 1-year. Each participant could continue receiving treatment until:

- Their cancer got worse
- They had adverse events that made it difficult to continue
- The study doctors thought that they were not benefiting from the treatment
- They chose to leave the trial

What were the results of the trial?

This is a summary of the main results of this trial. The results each participant had might be different and are not in this summary. But the results each participant had are part of the summary of results.

A full list of the questions researchers wanted to answer can be found on the websites listed at the end of this summary. If a full report of the trial results is available, it can also be found on these websites.

Researchers look at the results of many trials to decide which treatment options may work best and are well tolerated. Other trials may provide added information or different results. Always talk to a doctor before making any treatment decisions.

What are the safest doses of eribulin and irinotecan when given together to children with cancer?

To answer this question, researchers looked at the results from Part 1. The participants received different doses of eribulin and irinotecan during Part 1.

Trial doctors checked if the participants had adverse events that would prevent a dose increase of trial treatment. These adverse events are called dose-limiting toxicities or DLTs.

Researchers then looked at the highest dose that each participant received before they had a DLT. During the trial, none of the participants had a DLT.

Based on the safety results from Part 1 the doctors and experts decided that they would use Schedule A during Part 2.

During Part 2, participants received Schedule A

	Schedule A 21-day cycles
Eribulin	1.4 mg/m^2 on days 1 and 8
Irinotecan	40 mg/m^2 on days 1, 2, 3, 4, and 5

How effective are the selected doses of eribulin and irinotecan in children with RMS, NRSTS, and EWS that has come back or has not responded to treatment?

To answer this question, the researchers looked at the results from Part 2. Trial doctors looked at the scan results and compared the size of each participant's tumor before they started the trial treatment, and after they had received the trial treatment.

- Overall, 3 out of 27 participants had a decrease in tumor size. These responses to treatment were in 1 participant out of 9 in each of the 3 groups (RMS, NRSTS, and EWS). The 3 participants with a tumor that decreased in size, responded to treatment for different lengths of time. The participant with RMS responded to treatment for 2.9 months, the participant with NRSTS responded to treatment for 1.4 months, and the participant with EWS responded to treatment for 15.4 months.
- Overall, 11 out of 27 participants had tumors that did not grow while they were receiving treatment. This is 41% of the participants in Part 2.
- Out of 27 participants, 13 benefited from the trial treatment during Part 2. This is 48% of the participants in Part 2. These 13 participants had tumors that decreased in size or did not grow for 11-weeks or longer.

What medical problems did participants have?

Medical problems that happen in clinical trials are called “adverse events”. Adverse events are common and are often reported during clinical trials of cancer drugs. An adverse event is called “serious” when it is life-threatening, causes lasting problems, or the participant needs to be admitted to a hospital.

This section is a summary of the adverse events that happened during Part 1. These medical problems may or may not be caused by the trial drug. The websites listed at the end of this summary may have more information about the medical problems that happened in this trial. A lot of research is needed to know whether a drug causes a medical problem.

How many participants had adverse events?

During Part 1, all of the participants had at least 1 adverse event. The table below shows the type of adverse events the participants had:

Type of Adverse Events in Part 1

	Out of 7 participants who received Schedule A	Out of 6 participants who received Schedule B
How many participants had adverse events?	7 (100%)	6 (100%)
How many participants had serious adverse events?	4 (57%)	1 (17%)
How many participants stopped receiving the trial drug because of adverse events?	0 (0%)	0 (0%)

During Part 2, all of the participants had at least 1 adverse event. The table below shows the type of adverse event that the participants had.

Type of Adverse Events in Part 2

	Out of 9 participants with RMS	Out of 9 participants with NRSTS	Out of 9 participants with EWS
How many participants had adverse events?	9 (100%)	9 (100%)	9 (100%)
How many participants had serious adverse events?	5 (56%)	4 (44%)	3 (33%)
How many participants stopped receiving the trial drug because of adverse events?	2 (22%)	0 (0%)	2 (22%)

What were the most common serious adverse events?

During Part 1, 5 out of 13 participants had at least 1 serious adverse event. This is 39% of participants in Part 1. Out 13 participants, 2 died from a serious adverse event. This is 15% of the participants in Part 1. These deaths were not related to the trial treatments.

The table below shows the most common serious adverse events that happened during Part 1. There were other serious adverse events, but these happened in fewer participants.

Most Common Serious Adverse Events in Part 1

	Out of 7 participants who received Schedule A	Out of 6 participants who received Schedule B
Fever	3 (43%)	0 (0%)
Growth of tumor cells	1 (14%)	1 (17%)
Bacterial infection in the blood	1 (14%)	0 (0%)

During Part 2, 12 out of 27 participants had at least 1 serious adverse event. This is 44% of participants in Part 2. Out of 27 participants, 5 died from a serious adverse event. This is 19% of participants in Part 2. These deaths were not related to the trial treatments.

The table below shows the most common serious adverse events that happened in 2 or more participants. There were other serious adverse events, but these happened in fewer participants.

Most Common Serious Adverse Events in Part 2

	Out of 9 participants with RMS	Out of 9 participants with NRSTS	Out of 9 participants with EWS
Growth of tumor cells	1 (11%)	2 (22%)	0 (0%)
Fever with low levels of white blood cells called neutrophils in the blood	0 (0%)	1 (11%)	1 (11%)
Build-up of fluid containing cancer cells around the lungs	1 (11%)	1 (11%)	0 (0%)

What were the most common adverse events?

During Part 1, the most common adverse events were low levels of white blood cells, low levels of red blood cells, and vomiting.

The table below shows the most common adverse events that happened in 6 or more of the participants. There were other adverse events, but these happened in fewer participants.

Most Common Adverse Events in Part 1

	Out of 7 participants who received Schedule A	Out of 6 participants who received? Schedule B
Low levels of white blood cells called neutrophils in the blood	5 (71%)	4 (67%)
Low levels of red blood cells in the blood	4 (57%)	2 (33%)
Vomiting	2 (29%)	4 (67%)

During Part 2, the most common adverse events were diarrhea, low levels of white blood cells called neutrophils in the blood, and reduced levels of red blood cells in the blood.

The table below shows the most common adverse events that happened in 12 or more of the participants in Part 2. There were other adverse events, but these happened in fewer participants.

Most Common Adverse Events in Part 2

	Out of 9 participants with RMS	Out of 9 participants with NRSTS	Out of 9 participants with EWS
Diarrhea	4 (44%)	5 (56%)	5 (56%)
Low levels of white blood cells called neutrophils in the blood	6 (67%)	3 (33%)	5 (56%)
Reduced levels of red blood cells in the blood	3 (33%)	4 (44%)	5 (56%)

How many participants had adverse reactions?

Adverse reactions are medical problems that the trial doctors thought were caused by the trial drug. This section is a summary of the adverse reactions that happened during this trial.

What were the most common adverse reactions?

During Part 1, all of the participants had at least 1 adverse reaction. Many of the adverse reactions were mild, some were more severe but were not serious adverse reactions.

The table on the next page shows the most common adverse reactions that were more severe than mild but were not serious and happened in 5 or more participants.

The most common were low levels of different types of white blood cells in the blood. There were other adverse reactions, but these happened in fewer participants.

Most Common Adverse Reactions in Part 1

	Out of 7 participants who received Schedule A	Out of 6 participants who received Schedule B
Low levels of white blood cells called neutrophils in the blood	5 (71%)	3 (50%)
A decrease in the number of white blood cells called leukocytes in the blood	2 (29%)	3 (50%)
A decrease in the number of white blood cells called neutrophils in the blood	3 (43%)	2 (33%)

During Part 2, 26 out of 27 participants had at least 1 adverse reaction. This is 96% of participants in Part 2. Many of the adverse reactions were mild, some were more severe but were not serious adverse reactions.

The table below shows the most common adverse reactions that were more severe than mild but were not serious and happened in 4 or more participants.

There were other adverse reactions, but these happened in fewer participants. The most common were decreased levels of different types of white and red blood cells in the blood.

Most common adverse reactions in Part 2

	Out of 9 participants with RMS	Out of 9 participants with NRSTS	Out of 9 participants with EWS
A decrease in the levels of white blood cells called neutrophils in the blood	5 (56%)	3 (33%)	5 (56%)
Low levels of white blood cells called neutrophils in the blood	3 (33%)	2 (22%)	4 (44%)
Low levels of red blood cells in the blood	1 (11%)	1 (11%)	2 (22%)

What were the most common serious adverse reactions?

In Part 1, 2 out of 13 participants had a serious adverse reaction. This is 15% of participants in Part 1. Both of these participants had a serious adverse reaction of fever. One of these participants also had a serious adverse reaction of bacterial infection in the blood. None of the participants in Part 1 died from a serious adverse reaction.

In Part 2, 2 out of 27 participants had a serious adverse reaction. This is 7% of participants in Part 2. Both of these participants had a serious adverse reaction of fever with low levels of white blood cells in the blood. None of the participants in Part 2 died from a serious adverse reaction.

How has this trial helped patients and researchers?

In this trial, researchers learned about the safety of eribulin and irinotecan when given to children with cancer. They also learned how eribulin and irinotecan may have helped children with RMS, NRSTS, and EWS that is coming back or not responding to treatment.

Researchers look at the results of many trials to decide which treatment options may work best and are well tolerated. This summary shows only the main results from this one trial. Other trials may provide new information or different results.

Further clinical trials with eribulin are planned.

Where can I learn more about the trial?

You can find more information about this trial on the websites listed below. If a full report of the trial results is available, it can also be found here:

- http://www.clinicaltrialsregister.eu - Once you are on the website, click "**Home and Search**", then type 2016-003352-67 in the search box and click "**Search**".
- http://www.clinicaltrials.gov - Once you are on the website, type NCT03245450 into the search box and click "**Search**".

Full trial title: A Phase 1/2 Single-Arm Study Evaluating the Safety and Efficacy of Eribulin Mesilate in Combination with Irinotecan in Children with Refractory or Recurrent Solid Tumors.

Protocol number: E7389-G000-213

Eisai, the sponsor of this trial, has headquarters in Tokyo, Japan, and regional headquarters in Nutley, New Jersey, USA and Hatfield, Hertfordshire, UK. The phone number for general information is +44-845-676-1400.

Thank you

Eisai would like to thank you for your time and interest in participating in this clinical trial. Your participation has provided a valuable contribution to research and improvement in health care.

Eisai Co., Ltd. is a global research and development-based pharmaceutical company headquartered in Japan. We define our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our human health care (hhc) philosophy. With over 10,000 employees working across our global network of R&D facilities, manufacturing sites, and marketing subsidiaries, we strive to realize our hhc philosophy by delivering innovative products in multiple therapeutic areas with high unmet medical needs, including Oncology and Neurology. For more information, please visit http://www.eisai.com.

synchrogenix
A CERTARA COMPANY

Synchrogenix is a worldwide medical and regulatory writing organization and is not involved in recruiting participants or in conducting clinical trials.
Synchrogenix Headquarters 2 Righter Parkway, Suite 205 Wilmington, DE 19803
http://www.synchrogenix.com • 1-302-892-4800