Clinical Study Results

Research Sponsor: Eisai Inc.
Drug Studied: H3B-6527
Short Study Title: A study to learn about the safety of H3B-6527 in participants with advanced hepatocellular carcinoma

Thank you!

You took part in this clinical study for the study drug, H3B-6527. You and all of the participants helped researchers learn more about whether H3B-6527 can help patients with a type of liver cancer called hepatocellular carcinoma, also known as HCC. HCC is one of the common types of liver cancer. Patients with HCC are often diagnosed when the disease is already advanced. Some participants in this study had a rare type of cancer that forms in the bile duct called cholangiocarcinoma. Bile ducts are the tubes that connect the liver and gall bladder to the small intestine. A cholangiocarcinoma that forms inside the liver is called intrahepatic cholangiocarcinoma, or ICC. Symptoms of ICC and advanced HCC include pain in the upper right part of the abdomen, bloating or swelling in the belly, and yellow skin and eyes.

Eisai, a Japanese pharmaceutical company and the sponsor of this study, 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 study you participated in.

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

If you participated in the study and have questions about the results, please speak with the doctor or staff at your study site.

What has happened since the study started?

The study started in December 2016.

The study included 304 participants from 54 study sites in the following countries:

Belgium	Canada	France
Italy	Russia	Singapore
South Korea	Spain	Taiwan
United Kingdom	United States	

Of the 304 participants, 128 took study drug at least once.

The sponsor of the study reviewed the main results collected up to January 2021 and some safety results of the study until February 2022 and created a report of the results. This is a summary of that report.

Why was the research needed?

Researchers were looking for a different way to treat people who have advanced HCC. The standard treatments for HCC are surgery and other medicines that help shrink tumors. A tumor is a lump in the body made of cancer cells that have joined together. But the standard treatments may not help all patients in the later stages of advanced HCC.

The researchers in this study wanted to learn more about the drug named H3B-6527. This drug may target and block specific proteins that help cancer cells survive and grow. The researchers wanted to study the safety of H3B-6527 in patients with advanced HCC. They also wanted to find out if the participants had any medical problems during the study.

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

- What is the highest dose of H3B-6527 that can be taken by participants with advanced HCC in the study?
- What adverse events did participants taking H3B-6527 have? An adverse event is a medical problem that may or may not be caused by the study drug.

It is important to know that this study was designed to get accurate answers to the questions listed above. There were other questions the researchers wanted to answer to learn more about how H3B-6527 works. But, these were not the main questions the study was designed to answer.

What kind of study was this?

To answer these questions, researchers asked for the help of men and women like you. The participants in the study were 30 to 84 years old. Of these participants, 71% were male, and 29% were female. Participants in the study either had ICC or advanced HCC that was coming back and could not be removed by surgery.

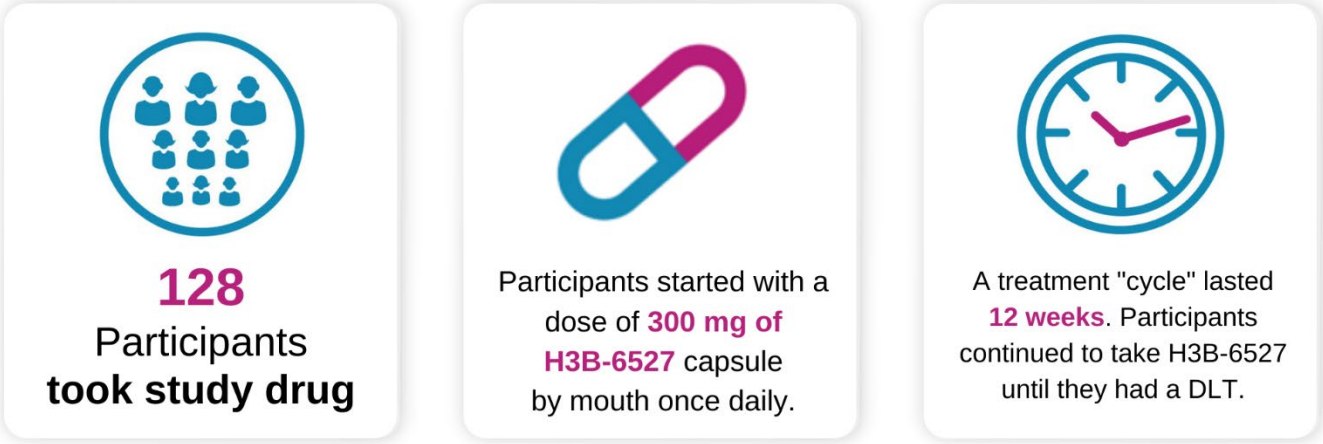
This study was "open-label". This means that the participants, the study doctors and staff, and the sponsor knew which treatment the participants received.

The study was divided into 2 parts:

In Part 1, the researchers wanted to find the highest dose and recommended dose of H3B-6527 that participants could take before they would have dose-limiting toxicities, or DLTs. DLTs are medical problems that would prevent the participants from taking a higher dose of H3B-6527. At the start of the study, the participants took H3B-6527 at a dose of 300 milligrams, also known as mg, by mouth once daily. The participants were then allowed to take H3B-6527 at doses up to 2000 mg once daily until they experienced a DLT.

In Part 2, the researchers further optimized the recommended dose identified in Part 1. They did this by looking at the overall results, including safety, effectiveness, and how H3B-6527 affects the body and the blood.

The figure below shows how study drug was given in your study.



What happened during the study?

Before the study started, the study doctors or staff did a full check-up to make sure each participant could join the study.

The study doctors or staff also:

- confirmed the participants had ICC or advanced HCC that was coming back and could not be removed by surgery
- asked what medicines each participant was taking
- took blood and urine samples
- checked each participant's heart health using an electrocardiogram, also called an ECG

During the Treatment period, the participants took their assigned dose of H3B-6527 capsules once or twice daily by mouth with or without food.

Throughout the Treatment period, the study doctors or staff:

- asked participants if they had any medical problems and the medicines they were taking
- took blood and urine samples
- continued to check each participant's heart health using an ECG

Each participant continued taking H3B-6527 in the study until:

- their HCC symptoms got worse;
- they had intolerable medical problems;
- they decided not to participate in the study; or
- the sponsor ended the study.

Thirty days after their last dose, all participants who stopped taking H3B-6527 returned to the study site.

The participants:

- were asked if they had any medical problems and the medicines they were taking
- had their blood and urine samples taken

Some participants were contacted to check their health every 12 weeks for up to 12 months.

The figure below shows how the study was done.

How did this study work?

Before the study started

The study doctors or staff:

- checked participant's health to make sure they could join the study
- confirmed that the participant had HCC or ICC
- took blood and urine samples
- checked each participant's heart health using ECG

During Treatment period

All participants who could join the study took an assigned dose of **H3B-6527**.

The study doctors or staff:

- asked if participants had medical problems and medicines they were taking
- took blood and urine samples

After their last dose

All participants returned to study site **30 days** after taking their last dose of **H3B-6527**.

The study doctors or staff asked participants if they had medical problems.

Some participants were contacted to check their health every 12 weeks for up to 12 months.

What were the results of the study?

This is a summary of the main results of this study up to January 2021 and some safety results of the study until February 2022. The results each person had might be different and are not in this summary. But the results each person 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 study results is available, it can also be found on these websites.

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

What is the highest dose of H3B-6527 that can be taken by participants with advanced HCC in the study?

To answer this question, researchers looked at the DLTs experienced by the participants who got different doses of H3B-6527 in Part 1 of the study.

After Part 1 of the study, researchers learned that H3B-6527 was generally well tolerated at a dose of 1000 mg once daily. Researchers decided to use this dose in Part 2 of the study to further optimize its overall results.

Researchers also learned that participants who took H3B-6527 with doses up to 2000 mg once daily did not experience DLTs.

What medical problems did participants have?

Medical problems that happen in clinical studies are called “adverse events”. 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 and adverse reactions that happened during this study. These medical problems may or may not be caused by the study drug. The websites listed at the end of this summary may have more information about the medical problems that happened in this study. A lot of research is needed to know whether a drug causes a medical problem.

In this section, information about medical problems is shown for participants who:

- were in Parts 1 and 2 of the study,
- took 1000 mg H3B-6527 once daily either with or without food, and
- took 500 mg H3B-6527 twice daily with food.

How many participants had adverse events?

In this study, 126 out of 128 participants (98%) had at least 1 adverse event.

The table below shows how many participants had adverse events in this study.

Adverse Events in This Study

	Out of 29 participants who took H3B-6527 1000 mg once daily with or without food during Part 2 of the study	Out of 40 participants who took H3B-6527 500 mg twice daily with food during Part 2 of the study	Out of 42 participants who took H3B-6527 1000 mg once daily with or without food	Out of 50 participants who took H3B-6527 500 mg twice daily with food	Out of 128 participants overall
How many participants had adverse events?	28 (97%)	40 (100%)	41 (98%)	49 (98%)	126 (98%)
How many participants had serious adverse events?	11 (38%)	17 (43%)	13 (31%)	20 (40%)	44 (34%)
How many participants stopped taking the study drug because of adverse events?	5 (17%)	3 (8%)	7 (17%)	6 (12%)	18 (14%)

What were the most common serious adverse events?

Out of 128 participants, 44 participants (34%) had serious adverse events.

There were 10 participants (8%) who died due to an adverse event.

The most common serious adverse events were:

- weakness (5 participants)
- bleeding of the tumor (4 participants)
- cancer that is getting worse (4 participants)

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

Most Common Serious Adverse Events in This Study

	Out of 29 participants who took H3B-6527 1000 mg once daily with or without food during Part 2 of the study	Out of 40 participants who took H3B-6527 500 mg twice daily with food during Part 2 of the study	Out of 42 participants who took H3B-6527 1000 mg once daily with or without food	Out of 50 participants who took H3B-6527 500 mg twice daily with food	Out of 128 participants overall
Weakness	1 (3%)	1 (3%)	2 (5%)	1 (2%)	5 (4%)
Bleeding of the tumor	0	3 (8%)	0	4 (8%)	4 (3%)
Cancer that is getting worse	1 (3%)	2 (5%)	1 (2%)	2 (4%)	4 (3%)
Diarrhea	0	3 (8%)	0	3 (6%)	3 (2%)
Broken bone due to a disease	1 (3%)	2 (5%)	1 (2%)	2 (4%)	3 (2%)

What were the most common adverse events?

Of the 126 participants who had adverse events, the most common adverse events were:

- diarrhea (73 participants)
- increase in level of aspartate aminotransferase or AST (32 participants)
- feeling sick (32 participants)

The table below shows the adverse events that happened in 10% or more of participants overall. There were other adverse events, but these happened in fewer participants.

Most Common Adverse Events in This Study

	Out of 29 participants who took H3B-6527 1000 mg once daily with or without food during Part 2 of the study	Out of 40 participants who took H3B-6527 500 mg twice daily with food during Part 2 of the study	Out of 42 participants who took H3B-6527 1000 mg once daily with or without food	Out of 50 participants who took H3B-6527 500 mg twice daily with food	Out of 128 participants overall
Diarrhea	10 (35%)	28 (70%)	19 (45%)	34 (68%)	73 (57%)
Increase in level of AST[a]	2 (7)	14 (35%)	4 (10%)	15 (30%)	32 (25%)
Feeling sick	6 (21%)	8 (20%)	11 (26%)	10 (20%)	32 (25%)
Pain in abdomen	5 (17%)	9 (23%)	7 (17%)	9 (18%)	27 (21%)
Tiredness	3 (10%)	9 (23%)	4 (10%)	9 (18%)	26 (20%)
Increase in level of ALT[a]	0	10 (25%)	2 (5%)	12 (24%)	24 (19%)
Decreased appetite	4 (14%)	11 (28%)	5 (12%)	13 (26%)	24 (19%)
Vomiting	5 (17%)	5 (13%)	8 (19%)	5 (10%)	23 (18%)
Weakness	6 (21%)	7 (18%)	7 (17%)	9 (18%)	22 (17%)
Increase in level of bilirubin[b]	3 (10%)	9 (23%)	4 (10%)	9 (18%)	19 (15%)
Constipation	4 (14%)	3 (8%)	5 (12%)	4 (8%)	14 (11%)
Low red blood cell count	0	4 (10%)	0	4 (8%)	13 (10%)
Pain in joint	0	4 (10%)	4 (10%)	5 (10%)	13 (10%)
Swelling of ankles and feet	3 (10%)	5 (13%)	4 (10%)	5 (10%)	13 (10%)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

[a] ALT and AST are enzymes in the liver that doctors use to check the health of the liver. Increase in levels of ALT and AST could mean there is a problem in the liver.

[b] Bilirubin is a substance found in the liver. A build-up of bilirubin causes the yellowish appearance of skin and the whites of the eyes.

How many participants had adverse reactions?

Adverse reactions are medical problems that the study doctors thought were caused by the study drug. An adverse reaction 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 reactions that happened during this study.

Medical problems that the participants had in the study were classified into Grades 1 to 5 depending on how severe they were. Higher grade means more severe medical problem: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (fatal).

In this study, 89 out of 128 participants (70%) had adverse reactions. Out of these, 42 participants (33%) had adverse reactions that were Grade 2 or more.

The table below shows how many participants had adverse reactions in this study.

Adverse Reactions in This Study

	Out of 29 participants who took H3B-6527 1000 mg once daily with or without food during Part 2 of the study	Out of 40 participants who took H3B-6527 500 mg twice daily with food during Part 2 of the study	Out of 42 participants who took H3B-6527 1000 mg once daily with or without food	Out of 50 participants who took H3B-6527 500 mg twice daily with food	Out of 128 participants overall
How many participants had adverse reactions?	17 (59%)	32 (80%)	25 (60%)	40 (80%)	89 (70%)
How many participants had serious adverse reactions?	3 (10%)	4 (10%)	3 (7%)	4 (8%)	10 (8%)
How many participants stopped taking the study drug because of adverse reactions?	1 (3%)	1 (3%)	2 (5%)	1 (2%)	5 (4%)

How many participants had serious adverse reactions?

Out of 128 participants, 10 participants (8%) had a serious adverse reaction.

No participants in this study died due to serious adverse events that the study doctors thought to be caused by study drug.

What were the most common adverse reactions?

The most common adverse reactions that were Grade 2 or more were:

- diarrhea (16 participants)
- tiredness (10 participants)
- increase in level of AST (8 participants)

The table below shows the adverse reactions that were Grade 2 or more and happened in 2% or more of participants overall. There were other adverse reactions, but these happened in fewer participants.

Most Common Adverse Reactions That Were Grade 2 or More in This Study

	Out of 29 participants who took H3B-6527 1000 mg once daily with or without food during Part 2 of the study	Out of 40 participants who took H3B-6527 500 mg twice daily with food during Part 2 of the study	Out of 42 participants who took H3B-6527 1000 mg once daily with or without food	Out of 50 participants who took H3B-6527 500 mg twice daily with food	Out of 128 participants overall
Diarrhea	1 (3%)	5 (13%)	5 (12%)	5 (10%)	16 (13%)
Tiredness	1 (3%)	3 (8%)	1 (2%)	3 (6%)	10 (8%)
Increase in level of AST[a]	1 (3%)	6 (15%)	1 (2%)	6 (12%)	8 (6%)
Feeling sick	1 (3%)	1 (3%)	2 (5%)	1 (2%)	6 (5%)
Increase in level of ALT[a]	0	3 (8%)	0	3 (6%)	4 (3%)
Increase in level of bilirubin[b]	1 (3%)	2 (5%)	1 (2%)	2 (4%)	4 (3%)
Low red blood cell count	0	1 (3%)	0	1 (2%)	3 (2%)
Damage in the cells of the liver	0	3 (8%)	0	3 (6%)	3 (2%)
Increase in level of liver enzymes	0	1 (3%)	1 (2%)	1 (2%)	3 (2%)
Low level of albumin[c]	1 (3%)	1 (3%)	1 (2%)	1 (2%)	3 (2%)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

[a] ALT and AST are enzymes in the liver that doctors use to check the health of the liver. Increase in levels of ALT and AST could mean there is a problem in the liver.

[b] Bilirubin is a substance found in the liver. A build-up of bilirubin causes the yellowish appearance of skin and the whites of the eyes.

[c] Albumin is a protein found in the blood that is made by the liver. Levels of albumin in blood can drop if the liver is damaged.

How has this study helped patients and researchers?

In this study, researchers learned more about how H3B-6527 may have helped people with advanced HCC. Researchers look at the results of many studies to decide which treatment options may work best and are well tolerated. This summary shows only the main results from this one study. Other studies may provide new information or different results.

Further clinical studies with H3B-6527 are not planned.

Where can I learn more about the study?

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

- http://www.clinicaltrials.gov - Once you are on the website, type **NCT02834780** into the search box and click "**Search**".

Full study title: An Open-Label Multicenter Phase 1 Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of H3B-6527 in Subjects With Advanced Hepatocellular Carcinoma

Protocol number: H3B-6527-G000-101

Eisai, the sponsor of this study, 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 study. 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.

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