NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the safety of VAY736 with ibrutinib in people with chronic lymphocytic leukemia

Thank you!

Thank you to the participants who took part in the clinical trial for **chronic lymphocytic leukemia (CLL)**. Every participant helped the researchers learn more about the trial drug **VAY736**, also called **ianalumab**, when given with **ibrutinib**.

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public. We hope this helps the participants understand their important role in medical research.

Trial information

Trial number: CVAY736Y2102

Novartis drug studied: **VAY736**, also known as **ianalumab**

Sponsor: Novartis

If you were a participant and have any questions about the results, please talk to the doctor or staff at the trial site.

This summary only shows the results of a single clinical trial. Other clinical trials may have different results.

What was the main purpose of this trial?

The purpose of this trial was to learn the highest dose of **VAY736** with **ibrutinib** that was safe for people with **chronic lymphocytic leukemia (CLL)**. **Ibrutinib** is a standard treatment for CLL. However, **ibrutinib** may or may not work or may stop working to treat CLL over time. Giving **VAY736** together with **ibrutinib** may prevent **ibrutinib** from not working, or prevent it from stopping to work over time.

Chronic lymphocytic leukemia (CLL) is a type of blood cancer. In CLL, cancer starts in the young forms of certain white blood cells (called **lymphocytes**) in the bone marrow. Bone marrow is the tissue inside of bones that helps make blood cells. The cancer cells grow out of control and then go into the blood.

VAY736, also called ianalumab, is a trial drug that is a type of immunotherapy. **Immunotherapy** is a treatment that helps the immune system to kill cancer cells. **VAY736** blocks a protein called B-cell activating factor receptor (BAFF-R) that is found on certain cancer cells. BAFF-R helps a type of lymphocyte, called a B cell, to survive. By blocking BAFF-R, **VAY736** may kill cancer cells.

Ibrutinib, pronounced as eye-broo-ti-nib, is a drug approved in the United States to treat different types of blood cancers, including CLL. **Ibrutinib** blocks a protein called Bruton's tyrosine kinase (BTK) that is found in certain cancer cells. BTK sends signals that helps cancer cells grow and survive. By blocking BTK, **ibrutinib** can slow the growth of and kill cancer cells.

Trial drug
VAY736 also called ianalumab

Pronounced as
ee-an-ah-luh-mab

This trial was the first time that **VAY736** and **ibrutinib** were given together to people. Therefore, the researchers have to test increasing doses in different groups of participants to find the highest safe dose of **VAY736** with **ibrutinib**. The researchers also needed to carefully check all the medical problems that happened during the trial and identify any that could cause changes in dosing. This is what researchers call a dose escalation trial, which is the first step in testing a trial drug.

The trial's purpose was to answer these main questions:

- What was the highest dose of VAY736 that was safe for participants to receive with ibrutinib and what was the recommended dose to use in more participants?
- What medical problems, also called adverse events, happened during this trial?

  ↳ An **adverse event** is any sign or symptom that participants have during a trial. Adverse events **may** or **may not** be caused by treatments in the trial.

How long was this trial?

The trial began in April 2018 and ended early in September 2023. The participants received treatment in the trial for up to 9 months.

In September 2023, the sponsor decided to end this trial early due to business reasons and not due to safety concerns.

This trial was designed to have 2 parts:

- **Part 1** looked at the safety of increasing doses of **VAY736** with **ibrutinib** in small groups of participants to find the highest dose that is safe and choose a recommended dose to give in Part 2.
- **Part 2** was designed to look at the effects of the recommended dose of **VAY736** with **ibrutinib** at the same dose or a lower dose than in Part 1 in larger groups of participants. Because the trial ended early, Part 2 was not completed.

Who was in this trial?

39 participants with CLL received treatment in this trial – 28 men and 11 women. Participants' ages ranged from 39 to 82 years. Their average age was 64 years.

This trial took place in the United States.

The number of participants by race is shown below.

Race

2	Black or African American
36	White
1	Not reported

The participants could take part in Part 1 if they:

- Were receiving **ibrutinib** at a dose of **420 mg**
- Had received **ibrutinib** alone for either:
  - At least a year and did not have their CLL go away, or
  - Any amount of time and had their CLL change (mutate) in ways that could stop **ibrutinib** from treating it

The participants could take part in Part 2 if they:

- Were receiving ibrutinib at a dose of **420 mg or lower**
- Had received ibrutinib **alone or with** another treatment for either:
  - At least a year and did not have their CLL go away, or
  - Any amount of time and had their CLL change (mutate) in ways that could stop **ibrutinib** from treating it

What treatments did the participants receive?

The treatments in this trial were:

VAY736, which was received through a needle in a vein called an intravenous (IV) infusion. Participants received it on Days 1 and 15 of each **cycle**.

The first group of participants received the planned dose of 0.3 milligrams of **VAY736** per kilogram of body weight (mg/kg). After this dose was found to be safe, another group received a higher dose. This continued until the highest dose of **VAY736** that was safe was found.

What is a cycle?

A **cycle** is a treatment period that is repeated. In this trial, the cycle was a 4-week treatment period during which participants received **VAY736** every 2 weeks and took **ibrutinib** every day.

Ibrutinib, which was taken by mouth as tablets or capsules every day of each cycle. In Part 1, participants took 420 mg. In Part 2, participants took 280 mg or 420 mg.

In this trial, the participants, researchers, and trial staff knew what treatment each participant received. All participants received **VAY736** with **ibrutinib**.

What happened during this trial?

Before treatment — About 1 month

The trial staff checked to make sure the participants could be in this trial.

During treatment — Up to about 9 months

During **Part 1**, the first group of participants started treatment with the lowest dose of **VAY736** with 420 mg **ibrutinib** for about a month. If there were no safety concerns after a month, the next group was opened to new participants to start treatment with a higher dose of **VAY736**. This continued with each next group receiving a higher dose of **VAY736** until researchers found the highest dose that was safe to give with 420 mg **ibrutinib**.

In Part 1, the number of participants in each dose group was:

- **0.3 mg/kg VAY736** with 420 mg **ibrutinib** – 4 participants
- **1 mg/kg VAY736** with 420 mg **ibrutinib** – 3 participants
- **3 mg/kg VAY736** with 420 mg **ibrutinib** – 4 participants
- **9 mg/kg VAY736** with 420 mg **ibrutinib** – 4 participants

In Part 2, researchers planned to give more participants the recommended dose of **VAY736** from Part 1 with **ibrutinib** at a dose of 420 mg or lower. The number of participants in each dose group was:

- **3 mg/kg VAY736** with 420 mg **ibrutinib** – 23 participants
- **3 mg/kg VAY736** with 280 mg **ibrutinib** – 1 participant

Because the trial ended early, **Part 2** was not completed as planned and only 1 participant received a lower dose of **ibrutinib**.

Trial doctors could lower a participant's dose of any of the trial treatments, if needed.

Participants received **VAY736** for 6 cycles and stopped treatment if their CLL went away. If a participant's cancer did not go away, they received treatment for 2 more cycles and trial doctors did a final check of their CLL.

After treatment — Up to 2 years

Trial staff checked participants' general health and medical problems for up to 30 days after participants' last dose of trial treatment.

If a participant's cancer did not get worse after completing 8 cycles, they returned to their trial site for follow-up visits to check their CLL for up to 2 years or until their cancer got worse.

Trial doctors checked the participants' general health throughout the trial.

What were the main results of this trial?

What was the highest dose of VAY736 that was safe for participants to receive with ibrutinib and what was the recommended dose to use in more participants?

The researchers concluded that:

- **The highest dose of VAY736** that was safe for participants in this trial was 9 mg **VAY736** with 420 mg **ibrutinib**
- **3 mg/kg VAY736** with 420 mg **ibrutinib** was the recommended dose to use with more participants in Part 2. This decision was based on all the information researchers collected during this trial.

To learn this, researchers kept track of how many participants had:

- **Dose limiting toxicities (DLTs)** in Part 1, up to 1 month after their first dose of **VAY736** with 420 mg **ibrutinib** (during the first treatment cycle). DLTs are medical problems that:
  - Were severe or life threatening
  - Caused the trial doctor to lower the participant's dose
- **To pause a trial treatment**, which means stopping a treatment for a period of time before receiving it again. This is called a dose interruption. Trial doctors kept track of this number in Part 1 and 2.
- **To lower the dose of a trial treatment**, which means receiving a smaller amount or receiving it less often. This is called a dose reduction. Trial doctors kept track of this number in Part 1 and 2.

What are dose limiting toxicities (DLTs)?

DLTs are medical problems that:

- The trial doctors think could be related to the trial treatment
- Lead to a pause or lowering of the dose of treatment

No participants in Part 1 had DLTs.

The table on the next page shows the number of participants who had to pause treatment or receive a lower dose from Part 1 and Part 2.

From these results and results of drug levels in the blood and possible signs of effects on cancer, the researchers chose **3 mg/kg VAY736** with **420 mg ibrutinib** to use with more participants in Part 2.

How many participants had to pause treatment or receive a lower dose?

	0.3 mg/kg VAY736 420 mg ibrutinib 4 participants	1 mg/kg VAY736 420 mg ibrutinib 3 participants	3 mg/kg VAY736 280 mg ibrutinib 1 participant	3mg/kg VAY736 420 mg ibrutinib 27 participants	9 mg/kg VAY736 420 mg ibrutinib 4 participants
Had to pause VAY736	0 of 4 0%	1 of 3 33%	0 of 1 0%	5 of 27 19%	0 of 4 0%
Had to lower the dose of VAY736	0 of 4 0%	0 of 3 0%	0 of 1 0%	1 of 27 4%	0 of 4 0%
Had to pause ibrutinib	0 of 4 0%	1 of 3 33%	0 of 1 0%	10 of 27 37%	0 of 4 0%
How to lower the dose of ibrutinib	0 of 4 0%	0 of 3 0%	0 of 1 0%	0 of 27 0%	0 of 4 0%

What medical problems, also called adverse events, happened during this trial?

Trial doctors keep track of all medical problems called **adverse events** that happen in trials, even if they think the adverse events are not related to the trial treatments.

Many trials are needed to know if a drug or treatment causes an adverse event.

This section is a summary of the adverse events that happened from the start of trial treatment up to 30 days after their last dose of trial treatment.

An **adverse event** is:

- Any **sign or symptom** that the participants have during a trial
- Considered **serious** when it is life-threatening, causes lasting problems, the participant needs hospital care, or results in death

Adverse events **may** or **may not** be caused by treatments in the trial.

All 39 participants had adverse events. 4 participants had adverse events that were considered serious. No participants died. 1 participant left the trial due to an adverse event. The researchers concluded that the participants could tolerate the adverse events, and they would not prevent future trials of **VAY736** with **ibrutinib** in people with CLL.

How many participants had adverse events?

Participants who:	0.3 mg/kg VAY736 420 mg ibrutinib 4 participants	1 mg/kg VAY736 420 mg ibrutinib 3 participants	3 mg/kg VAY736 280 mg ibrutinib 1 participant	3 mg/kg VAY736 420 mg ibrutinib 27 participants	9 mg/kg VAY736 420 mg ibrutinib 4 participants
Had at least 1 **serious adverse event**	0 of 4	2 of 3	0 of 1	2 of 27	0 of 4
Had at least 1 **other adverse event**	4 of 4	3 of 3	1 of 1	27 of 27	4 of 4
Left the trial due to an adverse event	0 of 4	0 of 3	0 of 1	1 of 27	0 of 4

What serious adverse events did the participants have?

4 participants had 1 or more serious adverse events:

- **Lower number of a type of white blood cell called neutrophils** (neutrophil count decreased) – 1 participant who received **1 mg/kg VAY736** with 420 mg **ibrutinib** and 1 participant who received **3 mg/kg VAY736** with 420 mg **ibrutinib**
- **Chest pain that is not heart related** (non-cardiac chest pain) – 1 participant who received **3 mg/kg VAY736** with 420 mg **ibrutinib**
- **Blockage in the small intestine** (small intestinal obstruction) – 1 participant who received **3 mg/kg VAY736** with 420 mg **ibrutinib**
- **Infection that is life threatening** (Escherichia sepsis) – 1 participant who received **1 mg/kg VAY736** with 420 mg **ibrutinib**

What other adverse events did the participants have?

39 participants had other adverse events.

The table below shows the other adverse events that happened in **8 or more participants.** Additional adverse events happened in fewer participants.

	0.3 mg/kg VAY736 420 mg ibrutinib 4 participants	1 mg/kg VAY736 420 mg ibrutinib 3 participants	3 mg/kg VAY736 280 mg ibrutinib 1 participant	3 mg/kg VAY736 420 mg ibrutinib 27 participants	9 mg/kg VAY736 420 mg ibrutinib 4 participants
High blood sugar Hyperglycemia	2 of 4 50%	3 of 3 100%	0 of 1 0%	10 of 27 37%	1 of 4 25%
Low levels of red blood cells Anemia	2 of 4 50%	3 of 3 100%	0 of 1 0%	8 of 27 30%	1 of 4 25%
High levels of a type of fat in the blood Hypertriglyceridemia	2 of 4 50%	2 of 3 67%	0 of 1 0%	7 of 27 26%	1 of 4 25%
High blood pressure Hypertension	1 of 4 25%	2 of 3 67%	0 of 1 0%	6 of 27 22%	0 of 4 0%
High levels of uric acid in the blood Hyperuricemia	1 of 4 25%	1 of 3 33%	0 of 1 0%	7 of 27 26%	0 of 4 0%
Lower number of neutrophils, a type of white blood cell Neutrophil count decreased	1 of 4 25%	3 of 3 100%	0 of 1 0%	4 of 27 15%	1 of 4 25%
Feeling weak and tired Fatigue	0 of 4 0%	1 of 3 33%	0 of 1 0%	7 of 27 26%	0 of 4 0%
Lower number of lymphocytes, a type of white blood cell Lymphocyte count decreased	2 of 4 50%	0 of 3 0%	0 of 1 0%	6 of 27 22%	0 of 4 0%

What was learned from this trial?

Researchers learned about the safety of **VAY736** with **ibrutinib** in people with CLL. The trial ended early due to business reasons and not due to safety concerns.

The researchers concluded that:

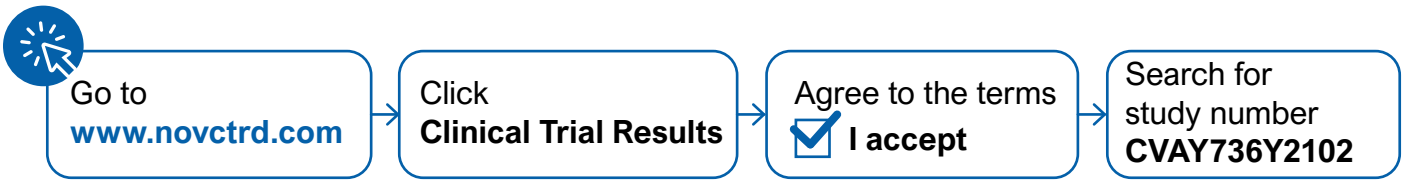
- The highest dose that was safe for participants in this trial was 9 mg/kg **VAY736** with 420 mg **ibrutinib**
- **3 mg/kg VAY736** with 420 mg **ibrutinib** was the recommended dose to use in more participants in Part 2. This decision was based on all the information researchers collected during this trial.
- The participants could tolerate the adverse events, and they would not prevent future trials of **VAY736** with **ibrutinib** in people with CLL

When this summary was written, the sponsor had no plans for future trials of **VAY736** with **ibrutinib** in people with CLL.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website **www.novctrd.com**

Follow these steps to find the scientific summary:



For more information about this trial, go to this website:

- clinicaltrials.gov – search using the number **NCT03400176**

Other trials of **VAY736** and **ibrutinib** may appear on the public websites above. When there, search for **VAY736**, **ianalumab**, or **ibrutinib**.

Full clinical trial title: Phase Ib open-label study of VAY736 and ibrutinib in patients with chronic lymphocytic leukemia (CLL) on ibrutinib therapy

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