AstraZeneca

Clinical Trial Results

Research Sponsor: Acerta Pharma B.V., a member of the AstraZeneca group of companies

Drugs Studied: Acalabrutinib, obinutuzumab, rituximab, and venetoclax

Trial Purpose: This trial was done to learn how acalabrutinib works and about its safety when given with obinutuzumab or rituximab, and with venetoclax in participants with chronic lymphocytic leukemia

Protocol Number: ACE-CL-003

Thank you

Thank you to the participants who took part in the clinical trial for the drug acalabrutinib, given with obinutuzumab or rituximab, and with venetoclax in participants with chronic lymphocytic leukemia. Acalabrutinib is also called ACP-196 or Calquence.

Acerta Pharma BV sponsored this trial and believes it is important to share the results of this trial with the participants and the public. Acerta Pharma BV reviewed the results of this trial so far and created a report of those results. This is a summary of that report.

An independent non-profit organization called CISCRP helped prepare this summary of the trial results. We hope it helps the participants understand and feel proud of their important role in medical research.

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

Who took part in this trial?

The researchers asked for the help of men and women with chronic lymphocytic leukemia, also called "CLL". The participants in this trial were 42 to 76 years old when they joined.

All of the participants had cancer that was getting worse

Roughly half of the participants had already had at least 1 treatment for their cancer, but it was getting worse.

The other half of the participants had never had any treatment for their cancer, or were unable to have any other treatment.

This trial included 69 men and women in the United States.

Why was the research needed?

Researchers are looking for a better way to treat CLL in adults. Before a treatment can be approved for people to receive, researchers do clinical trials to find out how it works and how safe it is.

In people with cancer, the body is not able to control the growth of some cells. CLL is a type of blood cancer that affects white blood cells and bone marrow, which is the spongy material found inside some bones. In CLL, the bone marrow produces too many white blood cells, which are not fully developed and do not work properly. Over time, this can cause problems such as a higher risk of infections, fatigue, unusual bleeding or bruising, and swollen glands in the neck, armpits, or groin.

Researchers think that the trial drug, acalabrutinib, may be helpful in treating certain types of cancer when it is given with obinutuzumab, rituximab, or venetoclax. These drugs are designed to work by stopping the cancer cells from growing out of control.

What was the purpose of this trial?

This was a "Phase 1" trial. In this trial, the researchers wanted to learn how acalabrutinib works when given with obinutuzumab, rituximab, or venetoclax. They also wanted to know if the participants had any medical problems during the trial.

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

- How many participants who received acalabrutinib with obinutuzumab responded to treatment?
- Did the participants feel that treatment with acalabrutinib, when given with obinutuzumab, rituximab, or venetoclax, affected their symptoms and quality of life?
- How did the participants' overall health change during the trial?
- What medical problems did the doctors report as possibly related to the trial treatments?

The answers to these questions are important to know before other trials can be done to find out if acalabrutinib helps improve the health of people with CLL when given with obinutuzumab, rituximab, or venetoclax.

What treatments did the participants receive?

In this trial, the participants were assigned to 1 of 4 treatment groups. The participants who had already had treatment for their cancer were in different groups to the participants who had not had treatment for their cancer. This helps the researchers to understand if this had any effect on the participants' response to the trial treatments.

- **Group 1** received acalabrutinib with obinutuzumab and **had** already had treatment for their cancer
- **Group 2** received acalabrutinib with obinutuzumab and **had not** already had treatment for their cancer
- **Group 3** received acalabrutinib with rituximab and venetoclax and **had** already had treatment for their cancer
- **Group 4** received acalabrutinib with obinutuzumab and venetoclax and **had not** already had treatment for their cancer

In this summary, "trial treatment" means anything the participants received as a part of the trial. This includes acalabrutinib, when given with obinutuzumab, rituximab, or venetoclax. Acalabrutinib is the treatment that the researchers wanted to learn more about.

This was an "open-label" trial. This means the participants, researchers, trial doctors, and other trial staff knew what each participant was receiving.

The researchers first started the treatments in Group 1 and Group 2 to learn about the safety of the trial treatments. Then, they started treatments for Group 3 and Group 4.

Treatment was given in "cycles" lasting 4 weeks. In the first cycle, participants took only acalabrutinib. Then, the participants also had their other trial drugs in combination. So, participants in all 4 groups were having 2 drugs in combination beginning in the second cycle. Then, beginning in the third cycle, Group 3 and Group 4 were having 3 drugs in combination.

The chart below shows the treatment plan for the participants. The doses of treatment were measured in milligrams, also known as "mg".

	Group 1	Group 2	Group 3	Group 4
	26 participants	19 participants	12 participants	12 participants
	Already had treatment	Had **not** already had treatment	Already had treatment	Had **not** already had treatment
	• **acalabrutinib:** as a capsule by mouth • **obinutuzumab:** through a needle into a vein		• **acalabrutinib:** as a capsule by mouth • **rituximab:** through a needle into a vein • **venetoclax:** as a tablet by mouth	• **acalabrutinib:** as a capsule by mouth • **obinutuzumab:** through a needle into a vein • **venetoclax:** as a tablet by mouth
	• **acalabrutinib:** twice daily • **obinutuzumab:** four times in the second cycle, then 1 time at the start of each cycle for 5 cycles		• **acalabrutinib:** twice daily • **rituximab:** once a week for 4 weeks in the second cycle, then once at the start of each cycle until the 7th cycle • **venetoclax:** once a day in the third cycle starting at a very low dose. This slowly got higher to 400 mg a day. This was then taken once a day until the end of cycle 15	• **acalabrutinib:** twice daily • **obinutuzumab:** four times in the second cycle, then 1 time at the start of each cycle for 5 cycles • **venetoclax:** once a day in the third cycle starting at a very low dose. This slowly got higher to 400 mg a day. This was then taken once a day until the end of cycle 15
	Participants stayed in the trial until their cancer got worse, or they decided to leave the trial. The participants were able to stay in the trial for as long as the doctors felt the trial treatment was helping them.			

What happened during this trial?

The participants have been in the trial for up to nearly 7 years. But, the entire trial may take over 11 years to finish.

The trial started in January 2015 and the part of the trial that this summary is based on ended in August 2021.

Before the participants received treatment, they visited their trial site once. This part of the trial lasted for up to 1 month. At this visit, the trial doctors asked the participants if they wanted to join the trial and made sure the participants could join. They also:

- did physical exams and asked about the participants' medications and any medical problems they were having
- took blood and urine samples
- checked the participants' heart health using an electrocardiogram, also called an "ECG"
- took images of the participants' cancer using a CT scan
- did a type of surgery called a "biopsy" to take small samples of the participants' bone marrow and lymph nodes
- asked participants questionnaires to learn how their cancer was affecting their daily life and wellbeing

The trial doctors also did some of these tests and measurements throughout the trial.

While the participants received treatment, they visited their trial site many times. The number of visits was different for each treatment group, but was at least once a month for the first year. Then visits changed to every 3 months until the end of the second year. For participants on the trial longer than 2 years, they visited the trial site every 6 months. Participants stayed in the trial until their cancer got worse, or they decided to leave the trial. The participants were able to stay in the trial for as long as the doctors felt the trial treatment was helping them. For some participants, this was longer than 3 years. The information presented here is from the start of the trial until its closure in August 2021.

After the participants received treatment, they visited their trial site at least once. This visit was done about 1 month after the last dose of treatment was given. At these visits, the trial doctors checked the health of the participants.

What were the results of this trial?

This is a summary of the main results from this trial overall. The individual results of each participant might be different and are not in this summary.

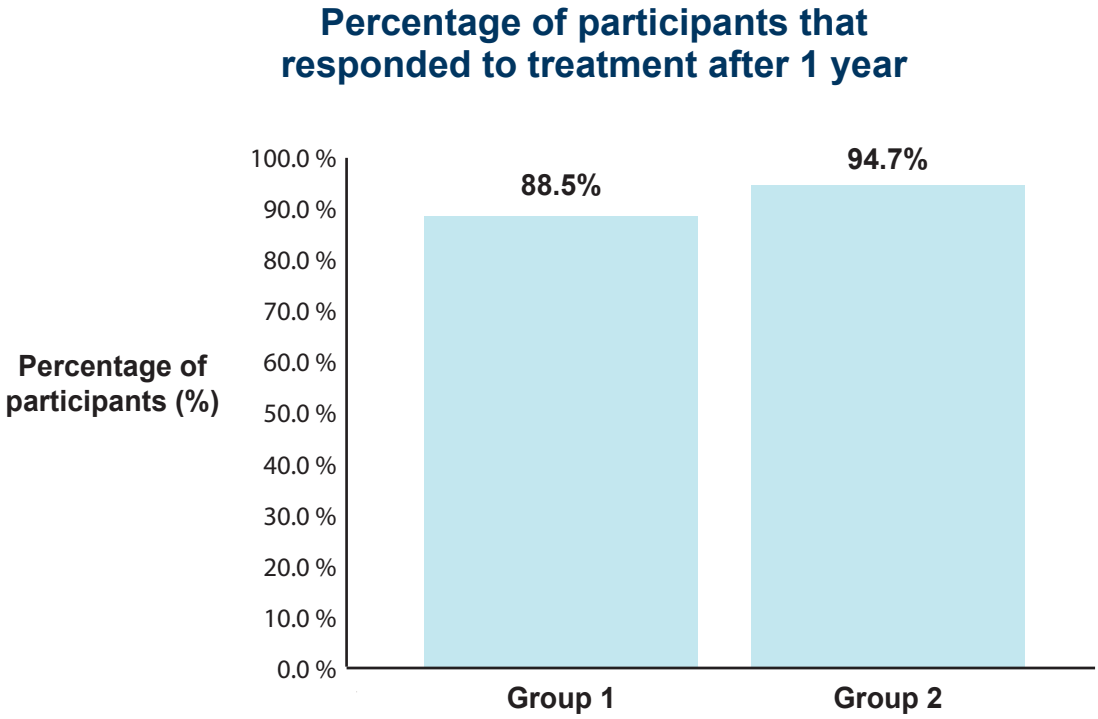
Researchers look at the results of many trials to decide which treatments work best and are safest. Other trials may provide new information or different results. Always talk to a doctor before making any treatment changes.

How many participants who received acalabrutinib with obinutuzumab responded to treatment?

In this trial, researchers wanted to find out how many participants in Group 1 and Group 2 responded to treatment after 1 year. "Responding" meant that their cancer was improving. The trial doctors measured the participants' response to treatment by monitoring their health during the trial.

Group 1 had already tried treatment for their cancer. Group 2 had not had any treatment before joining this trial. All of the participants in these 2 groups received acalabrutinib with obinutuzumab.

Below is a chart that shows the percentage of participants that responded to treatment after 1 year.



In Group 1, **88.5%** of participants responded to treatment. This was 23 out of 26 participants.

In Group 2, **94.7%** of participants responded to treatment. This was 18 out of 19 participants.

Did the participants feel that treatment with acalabrutinib, when given with obinutuzumab, rituximab, or venetoclax, affected their symptoms and quality of life?

During the trial, participants were asked to complete questionnaires about how they felt their treatment was affecting their symptoms and quality of life. Through these questionnaires, the researchers wanted to learn whether the participants thought their symptoms were getting better or worse. They also wanted to learn about the effect that the treatment was having on participants' daily lives, as well as the social and emotional effects. Questionnaire answers helped the researchers get a score of the participants' quality of life. The higher the score, the better the participant felt their symptoms were. With a higher score, there may have been a smaller effect of treatment on the participants' daily life.

The participants in Group 1 and Group 2 felt that treatment with acalabrutinib with obinutuzumab **did not** lower their quality of life and make their symptoms worse after 2 years of treatment.

The participants in Group 3 felt that treatment with acalabrutinib with rituximab and venetoclax **did not** lower their quality of life and make their symptoms worse after 2 years of treatment.

The participants in Group 4 felt that treatment with acalabrutinib with obinutuzumab and venetoclax **did not** lower their quality of life and make their symptoms worse after 2 years of treatment.

How did the participants' overall health change during the trial?

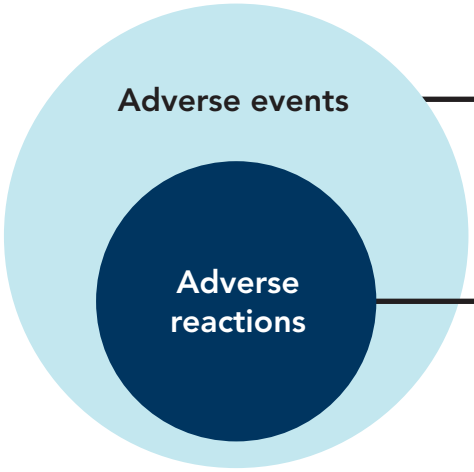
To answer this question, the doctors did tests and measurements of the participants' health throughout the trial. The doctors did physical exams and tested the participants' blood and urine samples to check their overall health. They also did ECGs to check the participants' heart health. The researchers compared the participants' results during the trial to their results from the start of the trial.

Overall, the researchers found that these tests and measurements showed small changes to the participants' health during this trial. But, the researchers did not consider these changes to be meaningful.

The trial doctors also kept track of the "adverse events" that the participants had.

In this summary, there is information about 2 different types of medical problems that the participants had during this trial after receiving trial treatment. An **adverse event** is **any** medical problem that a participant has during a trial. Doctors keep track of all adverse events that happen in trials, whether or not these may be related to the trial treatments. An **adverse reaction** is different from an adverse event because it is reported by the doctor as **possibly related** to the trial treatments. An adverse event or adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or requires hospital care.

Adverse reactions are adverse events that the trial doctors think may be related to the treatments



Adverse events are all of the medical problems the participants had during this trial.

Adverse reactions are medical problems the participants had during this trial that the doctor reported as possibly related to the trial treatment.

The information below is a summary of the **adverse events** that happened in this trial. More details about **adverse reactions** in this trial are included later in the summary.

	Group 1 (out of 26 participants)	**Group 2** (out of 19 participants)	**Group 3** (out of 12 participants)	**Group 4** (out of 12 participants)
How many participants had adverse events?	100% (26)	100% (19)	100% (12)	100% (12)
How many participants had serious adverse events?	46.2% (12)	21.1% (4)	16.7% (2)	33.3% (4)
How many participants stopped receiving trial treatment due to adverse events?	15.4% (4)	5.3% (1)	16.7% (2)	16.7% (2)

Across all treatment groups

The most common serious adverse events were:

- Lung infection
- Inflammation of the deep skin tissue
- Diarrhea
- Difficulty breathing
- Fainting
- Fever
- Fever with very low numbers of a type of white blood cell called neutrophils
- Inflammation of the gallbladder
- Pus-filled swelling on a limb

The most common adverse events were:

- Infection of the upper airways
- Diarrhea
- Rash
- Cough
- Headache
- Nausea
- Weight gain
- Joint pain
- Fall
- Fatigue
- Constipation
- Tingling or prickling sensation
- Muscle aches

What medical problems did the doctors report as possibly related to the trial treatments?

This section is a summary of the medical problems that the participants had during this trial that the doctors reported as **possibly related** to the trial treatments. These medical problems are called "**adverse reactions**". An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or requires hospital care. The results from several trials are needed to decide if a treatment causes an adverse reaction.

The websites listed at the end of this summary may have other information about adverse reactions or other medical problems that happened during this trial.

Did any adverse reactions happen during this trial?

In this trial, the researchers wanted to learn if the medical problems the participants had were related to specific drugs in the treatment they were receiving, because the participants were receiving a combination of the drugs.

The participants in Group 1 and Group 2 all received acalabrutinib and obinutuzumab, so their results are combined.

The participants in Group 3 and Group 4 took acalabrutinib with venetoclax, and also received either obinutuzumab or rituximab. Obinutuzumab and rituximab are similar drugs because they work in a similar way in the body. The results of Group 3 and Group 4 are also combined.

The table below shows the number of adverse reactions and serious adverse reactions, and how many participants stopped receiving trial treatment due to adverse reactions. This includes information for adverse reactions the doctors thought were related to one of the trial drugs, or the drugs together.

	Group 1 and Group 2 (out of 45 participants)	**Group 3 and Group 4** (out of 24 participants)
How many participants had adverse reactions?		
Acalabrutinib	80.0% (36)	83.3% (20)
Obinutuzumab	60.0% (27)	16.7% (4)
Venetoclax	These groups did not receive this treatment	41.7% (10)
Rituximab		29.2% (7)
Acalabrutinib and obinutuzumab together	42.2% (19)	There is no information for these groups
Acalabrutinib, obinutuzumab and venetoclax together	These groups did not receive this treatment	none
How many participants had serious adverse reactions?		
Acalabrutinib	none	none
Obinutuzumab	none	none
Venetoclax	These groups did not receive this treatment	4.2% (1)
Rituximab		none
Acalabrutinib and obinutuzumab together	2.2% (1)	There is no information for these groups
Acalabrutinib, obinutuzumab and venetoclax together	These groups did not receive this treatment	4.2% (1)
How many participants stopped receiving trial treatment due to adverse reactions?		
Acalabrutinib	4.4% (2)	4.2% (1)
Obinutuzumab	none	none
Venetoclax	These groups did not receive this treatment	none
Rituximab		none
Acalabrutinib and obinutuzumab together	none	There is no information for these groups
Acalabrutinib, obinutuzumab and venetoclax together	These groups did not receive this treatment	4.2% (1)

What serious adverse reactions happened during this trial?

Serious adverse reaction	Group 1 and Group 2 (out of 45 participants)	Group 3 and Group 4 (out of 24 participants)
Fever and very low numbers of a type of white blood cell called neutrophils	2.2% (1)	4.2% (1)
High levels of bacteria in the blood, leading to organ damage	none	4.2% (1)

None of the participants died during this trial because of adverse reactions.

What adverse reactions happened during this trial?

The most common adverse reactions were diarrhea, mild allergic reaction to the drug given by IV infusion, and nausea.

The table below shows the adverse reactions that happened in 25.0% or more of participants during the trial. There were other adverse reactions, but those happened in fewer participants.

Most common adverse reactions		
Adverse reaction	**Group 1 and Group 2** (out of 45 participants)	**Group 3 and Group 4** (out of 24 participants)
Diarrhea	35.6% (16)	62.5% (15)
Mild allergic reaction to the drug given by IV infusion	42.2% (19)	29.2% (7)
Nausea	33.3% (15)	41.7% (10)
Headache	31.1% (14)	41.7% (10)
Weight gain	35.6% (16)	16.7% (4)

What did researchers learn from this trial?

This trial helped researchers learn more about how acalabrutinib affects people with CLL when given with obinutuzumab, rituximab, or venetoclax.

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

At the time this summary was made and approved by the sponsor, further clinical trials with acalabrutinib were not planned.

Where can I learn more about this trial?

You can find more information about this trial on the websites listed below.

- www.clinicaltrials.gov. Once you are on the website, type **"NCT02296918"** into the **"Other terms"** search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"ACE-CL-003"** into the search box, and click **"Find a Study"**.

Full Trial Title: A Phase 1b Study of ACP-196 in Combination with Obinutuzumab for Patients with Relapsed/Refractory or Untreated CLL/SLL/PLL

Acerta Pharma BV (a member of the AstraZeneca Group of Companies)
Protocol Number: ACE-CL-003

National Clinical Trials Number: NCT02296918

Acerta Pharma BV (a member of the AstraZeneca Group of Companies) sponsored this study and has its headquarters in Oss, The Netherlands.

The phone number for the AstraZeneca Information Center is +1-877-240-9479.

Thank you

Clinical trial participants 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.

CISCRP

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting participants for clinical trials, nor is it involved in conducting clinical trial.

CISCRP | One Liberty Square, Suite 1100 • Boston, MA 02109 | 1-877-MED-HERO | www.ciscrp.org

Version 1.0 2022_08_17