Official Title	Acalabrutinib for Chronic Graft-Versus-Host Disease
NCT Number	NCT04198922
Document Type	Informed Consent Form
Document Date	4/19/2023

Fred Hutchinson Cancer Center
University of Washington

Consent to take part in a research study:

Acalabrutinib for Chronic Graft vs. Host Disease

Contact Information:
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Ask to page Dr. Stephanie Lee or the LTFU Attending

Important things to know about this study.

You are invited to participate in a research study. The purpose of this research is see if acalabrutinib is helpful in the treatment of chronic graft-versus-host disease (GVHD).

People who agree to join the study will be asked to attend up to 16 visits over about 26 months. The study involves taking an oral medication (acalabrutinib) and attending regular study visits for physical exams, blood draws, lung function testing, and other assessments.

We do not know if acalabrutinib would help treat chronic GVHD, and it could even make your condition/disease worse. Acalabrutinib could cause side effects such as headache, diarrhea, fatigue, and anemia, as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat chronic GVHD instead of participating in this study. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

We invite you to join this research study.

Since you have active chronic GVHD after hematopoietic cell transplantation that is not responding to treatment, we would like to ask you to join this research study. We will enroll up to 50 people at many transplant centers across the United States.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in this study. You are free to say yes or no, or to drop out after joining. There is no penalty or loss of benefits if you say no. Whatever you decide, your regular medical care will not change.

Why are we doing this study?

We are doing this study to see if acalabrutinib is helpful in the treatment of chronic GVHD. The study will enroll people who have active chronic GVHD despite at least one prior chronic GVHD treatment. The study will also examine how chronic GVHD affects quality of life and symptoms.

This study is funded and supported by AstraZeneca. AstraZeneca will be providing acalabrutinib for this study.

About chronic GVHD

Chronic GVHD is an important complication of transplant that can cause unwanted symptoms and disability in many different parts of your body. Many people with chronic GVHD do not respond well to initial treatments, and therefore will need to go on to additional types of chronic GVHD treatment. This research study will investigate whether a drug called acalabrutinib can effectively treat chronic GVHD.

About the Study Drug

Acalabrutinib is used to treat a type of cancer called mantle cell lymphoma. It is an oral therapy (tablet) that you will take twice daily for up to six cycles. Each cycle is 28 days. If your GVHD improves or remains stable, you can choose to continue taking the study medication for up to eighteen more cycles (total of 24 cycles). However, you cannot take it for longer than 24 cycles from the date you started. Acalabrutinib is a type of medication called a Bruton's tyrosine kinase (BTK) inhibitors. A different BTK inhibitor, ibrutinib, has been approved by the FDA for the treatment of adult patients with cGVHD after failure of one or more lines of systemic immunosuppressive therapy. This trial will study whether acalabrutinib can help patients with chronic GVHD.

What research tests, procedures, and treatments are part of this study?

If you decide to join this study, we will do the following study visits:

Screening visit. Your doctor will discuss the study with you and ensure that you are eligible to take part. If you choose to take part in this study, you will be asked to sign this form. You will be assigned a study number which will be used to identify you throughout the study. Your medical history will be reviewed. As part of your screening visit:

1. You will have a physical exam.
2. Laboratory tests (blood counts, chemistry, liver function tests) will be performed. Additional tests will be performed to confirm that you do not have serious infectious problems including hepatitis and HIV.
3. If you are a woman of child-bearing potential, a pregnancy test will be performed.
4. An electrocardiogram (ECG) will be performed.
5. You will complete a questionnaire about your chronic GVHD.
6. Your doctor will complete a questionnaire about your chronic GVHD.

Study visits and study treatments. If your doctor determines you are eligible for the study, you will return for monthly study visits on the first day of each cycle for the first 6 cycles. At these monthly visits (Cycle 1 through Cycle 6):

1. You will have a physical exam.
2. You will complete a questionnaire about your chronic GVHD. (Cycle 1; Cycle 4)
3. Your doctor will complete a questionnaire about how your chronic GVHD is responding to treatment.
4. Laboratory tests (blood counts, chemistry, liver function tests) will be performed.
5. Before your first dose of the study drug, we will collect a research blood sample from you. We will collect research blood again at Cycle 2 and Cycle 4.
6. Lung function testing may be performed (Pulmonary Function Test at Cycle 1, then spirometry only at Cycle 4).
7. You will pick up your next month's supply of study drug and a diary to help you keep track of your doses. You will need to return any unused study drug bottles and/or pills and your completed drug diary at each visit.

If you choose to continue taking acalabrutinib after you complete the first 6 months of treatment, you will have visits every 3 months (starting with a visit at Cycle 7). At these visits:

1. You will have a physical exam.
2. You will complete a questionnaire about your chronic GVHD.
3. Your doctor will complete a questionnaire about how your chronic GVHD is responding to treatment.
4. Laboratory tests (blood counts, chemistry, liver function tests) will be performed.
5. Lung function testing (spirometry) will be performed.
6. You will pick up your next supply of study drug and a diary to help you keep track of your doses. You will need to return any unused study drug bottles and/or pills and your completed drug diary.

If you or your doctor suspects your GVHD is getting worse, or if you are experiencing negative side effects between regularly scheduled study visits, you will come in for a visit. At this visit:

1. You will have a physical exam.
2. You will complete a questionnaire about your chronic GVHD.
3. Your doctor will complete a questionnaire about how your chronic GVHD is responding to treatment.
4. Laboratory tests (blood counts, chemistry, liver function tests) will be performed.
5. You will return your study drug diary and any unused study drug bottles and/or pills.

If you permanently stop taking the study drug for any reason, you will be required to complete a “treatment termination” visit within 7 days of your last dose. At this visit:

1. You will have a physical exam.
2. Laboratory tests (blood counts, chemistry, liver function tests) will be performed.
3. You will return your study drug diary and any unused study drug bottles and/or pills.

Follow-up. After you have finished taking acalabrutinib, you will enter the follow-up part of the study. You will have a safety follow-up visit or phone call about 30 days after your last dose of acalabrutinib. After the safety follow-up, we will continue to follow you through your medical records (long term follow-up).

Study assessments and procedures:

- *Physical Exam*. A physical exam will include vital signs and weight measurements. The provider will also review any symptoms you may be having related to your transplant.

- *Laboratory Tests*. Tests such as blood counts and liver function tests will be done to help check that it is safe for you to take acalabrutinib, and to monitor how your GVHD is responding to treatment.

- *Questionnaires*. You will be asked to complete a questionnaire up to 8 times for this study: on Day 1 of Cycles 1, 4, 7, and every 3 months thereafter. The questionnaire will take you about 20-30 minutes to fill out. The questionnaire will ask you about:

  → Your GVHD symptoms

  → Your physical and mental health

  → Your quality of life

  → Your overall well-being

  → Your ability to do physical activities

- *Blood Draw.* You will have some extra blood drawn for this research study. In most cases, this blood can be collected from you when you are already having blood drawn for your clinic visit. These samples will be used to study how acalabrutinib affects the body. Research blood samples will be collected at enrollment, Cycle 2 Day 1, and Cycle 4 Day 1. You will not have more than 20 mL (about 1 tablespoon) of blood drawn for this research test at a single visit.

- *Study treatment (acalabrutinib).* The study treatment is taken orally twice a day for 6 cycles (28 day cycles). You will have an option to continue taking the drug if your GVHD is improving and you are not having any severe side effects. The doses can be adjusted if necessary, and your doctor will explain that to you.

How long will I be in this study?

We think you will be in this study for up to 26 months after study enrollment.

Your doctor may stop this study treatment if it is in your best interest to do so. If you stop study treatment, we will ask you to continue the planned study follow up. The major possible reasons for stopping study treatment are the following:

- Your doctor feels that you have responded to treatment and do not need further treatment.
- You have unacceptable toxicity from the treatment.
- You are not able to comply with the study treatment schedule.
- The study therapy is stopped, and you are changed to another chronic GVHD treatment because your doctor feels your chronic GVHD is not responding well to this treatment.
- You have a recurrence of the cancer or blood disorder for which you received the transplant.

You may decide not to take part or to withdraw from the study at any time. If you decide to withdraw from the study, there is no penalty or loss of benefits in your routine medical care or any other benefit(s) that you would otherwise be entitled to receive. If you decide to stop receiving treatment, the study nurse or doctor will request that you complete the remaining study follow-up visits and procedures. If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information could not be removed from the study records.

In addition, you should consult your study doctor to discuss future treatment and procedures for your continued care.

What are the side effects (risks)?

In this part of the consent form, we tell you the side effects we expect from the tests and treatments in this study. There may be side effects we do not know about yet. If we learn about other side effects, we will tell you.

The treatment and procedures involved in this study may involve risks that are not possible to predict. We carefully watch everyone in the study for side effects. If you want more information about side effects and risks, ask the study doctor or nurse.

Questionnaires. Some questions about the impact of chronic GVHD may upset you. You may skip any question for any reason.

Blood Draw. The risks of blood draws are pain, bruising, infection, redness, and swelling at the site of the needle entry. There is a chance you may feel dizzy while your blood is being drawn. If you have severe anemia, blood collection for research may be delayed or canceled.

Electrocardiogram (ECG). An electrocardiogram is a test that records the electrical activity of the heart. You will be asked to lie down, and electrodes (small wires) will be placed on your arms, legs and chest. In general, there are no risks. There is no risk of shock because this procedure only records electrical impulses and does not give off electricity. Sometimes there is a mild skin reaction or rash to the sticky material on the soft pads that are used to place the wires (leads) on the skin.

Lung Function Testing. PFTs are usually safe for most people. However, because the test may require you to breathe in and out quickly, you may feel dizzy and there is a risk that you might faint. If you feel lightheaded, tell your study doctor. The test may cause you to have an asthma attack if you have asthma.

Acalabrutinib. The following side effects have been observed in patients who have been treated with acalabrutinib. We are not sure if these side effects will be the same in this study.

As of 30 December 2018, over 2600 patients have received acalabrutinib through their participation in clinical trials with either single agent acalabrutinib or acalabrutinib in combination with other anti-cancer agents (other drugs) for the treatment of blood cell cancers, non-blood cell cancers, or rheumatoid arthritis.

Acalabrutinib is an approved drug for the treatment of adult patients with mantle cell lymphoma.

As with any drug, there may be unknown and potentially serious or life-threatening side effects that could occur with acalabrutinib. The full side-effect profile of acalabrutinib is not yet known. Side effects can vary from mild to very serious and may vary from person to person. You may have some or no side effects. Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

Serious side effects that may occur with acalabrutinib include:

Hemorrhage (Bleeding)
Events of bleeding have occurred in patients treated with acalabrutinib. These include minor events such as nose bleed, bruising, or ecchymosis (bleeding in skin) and major events which could be fatal such as internal bleeding in the bowel or bleeding in the brain. If you are using any blood thinners (drugs that prevent your blood from clotting e.g. aspirin or warfarin) your risk for bleeding may be increased.

Infections
Infections have been reported to occur in patients receiving acalabrutinib. The most commonly reported infections were upper respiratory infection, sinus infection, pneumonia (lung infection), and urinary tract infection. Infections that are uncommon or rare, but which can result in severe disability or death, have also occurred in patients receiving acalabrutinib. These infections include hepatitis B virus (HBV) reactivation and

progressive multifocal leukoencephalopathy (PML). HBV reactivation is where a type of liver virus infection becomes active again if you had a previous infection with that virus. PML is a rare, serious brain infection caused by a virus, usually in patients with weakened immune systems, and can result in severe disability or death.

Tell your study doctor right away if you experience any symptoms of an infection such as fever, runny nose, sore throat, cough, and feeling tired. If you have previously had HBV or any other viral liver infection, your study doctor may need to monitor you closely.

Cytopenias (Low Blood Cell Counts)
Patients receiving acalabrutinib can experience low blood cell counts. Your study doctor will do blood tests while you receive acalabrutinib to check your blood cell counts, which include:

- White blood cells - cells that fight against infections
- Red blood cells – cells that carry oxygen throughout your body
- Platelets – cells that help your blood to clot

Second Primary Malignancies
The development of a second cancer has been reported to occur in some patients who receive acalabrutinib. The majority of these cancers were skin cancers. If you develop a second cancer, you may need to stop the study drug, and your doctor may need to do further tests to diagnose what the cancer is.

Atrial Fibrillation/Atrial Flutter
Atrial fibrillation and atrial flutter are abnormal heart rhythms, which have been reported to occur in some patients who receive acalabrutinib. Atrial fibrillation or flutter may occur more commonly in patients with other risk factors for cardiac (heart) disease, such as hypertension (high blood pressure), diabetes mellitus, acute infections, or a previous history of atrial fibrillation. While atrial fibrillation or flutter often may not cause symptoms, some patients may experience palpitations (feeling like your heart is beating too hard or too fast), fainting, chest pain, or shortness of breath. If you have any of the symptoms described above, tell your doctor.

Acalabrutinib side effects considered caused by the drug are provided in the table below. These side effects are based on analyses of safety data as of December 2018, from over 1000 patients who received single-agent acalabrutinib, mostly at 100 mg twice a day, for the treatment of blood cell cancers.

Hepatotoxicity (Liver Injury)
Some patients experienced hepatotoxicity while taking acalabrutinib. However, there is no clear association between treatment with acalabrutinib and an increased risk of liver dysfunction.

Very Common (in at least 10% of patients)

- Decreased white blood cell count
- Decreased neutrophil count
- Anemia
- Diarrhea
- Nausea
- Sinus infection
- Joint pain
- Musculoskeletal pain
- Second primary malignancy
- Headache
- Constipation
- Abdominal pain
- Vomiting
- Fatigue
- Upper respiratory tract infection
- Dizziness
- Bruising
- Rash
- Hemorrhage (bleeding)

Common (at least 1% but less than 10% of patients)

- Decreased platelet count
- Atrial fibrillation/flutter
- Muscle weakness
- Pneumonia
- Sinusitis
- Urinary tract infection
- Respiratory infections
- Shingles
- Cold sores
- Stomach virus
- Oral thrush
- Ear infections
- Sepsis
- Skin infections
- Tooth infection
- Sore throat
- Pink eye
- Flu
- Bronchitis
- Common cold
- Second primary malignancy, excluding non-melanoma skin
- Non-melanoma skin malignancy
- Nose bleeds

Tumor Lysis Syndrome (TLS)

A case of TLS was reported in a patient with chronic lymphocytic leukemia. TLS occurs when a drug kills a large amount of cancer cells at the same time causing the contents of the cancer cells to spill into the blood stream. This can lead to severe organ malfunctions that can be life-threatening if not monitored and treated promptly. If your study doctor deemed you're at risk for tumor lysis syndrome, you will be closely monitored during the study.

Unknown/Unexpected Side Effects

In addition to the side effects listed above, there are side effects that are not known or do not happen often when patients take these study drugs, including severe or life-threatening allergic reactions, or interactions with another medication, including those that are fatal.

There may also be side effects that we cannot predict. Other drugs may be given to make side effects that occur less serious and less uncomfortable. Many side effects go away shortly after the study drug or procedure is stopped, but in some cases side effects can be serious, long lasting or permanent.

For more information about side effects, ask the study doctor and/or the research staff.

Reproductive risks

There is a potential risk of harmful effects to an unborn baby or nursing child when a woman is taking acalabrutinib during pregnancy or while nursing. Pregnancy or fathering a child should be avoided during this study. If you are female and can have children, a pregnancy test (urine or blood) will be performed prior to administration of the study drug.

You cannot participate in this study if any of the following occur:

1. You are currently pregnant or become pregnant during the course of the study
2. You are currently breastfeeding

All women who can have children MUST agree to one of the following:

- The use of a highly effective method of birth control from the time of enrollment until 2 days after you stop acalabrutinib. OR
- Practicing true abstinence or exclusively non-heterosexual activity, if this is in line with your usual lifestyle.

All men should refrain from sperm donations during treatment with acalabrutinib until 28 days after their final dose.

The following are highly effective methods of birth control that your study doctor will discuss with you if you are a woman of child-bearing potential:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

There are no contraception requirements for men who participate in this study, but you must contact the study doctor immediately if your partner becomes pregnant while you are participating in this study.

Female subjects who become pregnant while taking acalabrutinib must stop taking the study drug immediately. If you or your partner should become pregnant while you are participating in this study, or if you suspect that you have become pregnant, you must

contact your study doctor immediately.

What are the benefits?

We do not know if this study will help patients directly. If you take part in this study there may not be direct medical benefits to you. The major potential benefit is that this study treatment could improve your chronic GVHD. The information learned from this study may someday be of benefit to future patients. You may benefit by being closely followed for your health status.

You have other choices besides this study.

You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.

If you do not join this study, you have other choices for treatment. Before you decide to take part in this study, your study doctor will talk with you about other options available to you, which may include other medications, treatments, or dose changes in your current medications. Each of these choices has risks and benefits. You should talk to your doctor about them.

Protecting your Privacy as an Individual and the Confidentiality of Your Personal Information

Your medical and research records will be confidential to the extent permitted by law. Information from this study will be collected into an electronic database. Data will be entered into the database through a secure website. Only staff with a password will be allowed to see or enter data. Your information in the database will be identified with your study ID only. Only the study staff at your center will have the link between your study ID and your name.

Some people or organizations may need to look at your research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- The study supporter, AstraZeneca, and its agents.
- Institutional Review Boards (IRBs), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect your rights as a research participant.
- Staff at Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Cancer Care Alliance.
- Office for Human Research Protections, Food and Drug Administration, and other agencies as required.

We will do our best to keep your personal information confidential. But we cannot guarantee total confidentiality. Personal information from your records will not be

released without your written permission. Your personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Such cases are rare.

We will not use your personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

A description of this clinical trial will be available on *http://www.clinicaltrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Information about your participation in this study (including a copy of this consent form) will be made part of your permanent medical record. If you authorize others to see your medical record, they will see a copy of this consent form.

Will you pay me to be in this study?

There is no payment for being in this study.

How much will this study cost me?

You or your insurance company will not be billed for tests and procedures done specifically for this study (i.e., extra blood drawn for research, pregnancy tests, or questionnaires). Acalabrutinib will be provided free of charge from AstraZeneca for up to 24 months.

There are some extra costs for being in this study. You or your insurer will have to pay these costs. Some insurers will not pay for research. Check with your insurer before you join this study.

The extra costs are:

- Cost of tests that are given more often than usual.
- Cost of standard doctor visits and lab tests.
- Cost of any other medical care you may need because of this study.

Whether you are in the study or not, you or your insurance company will be responsible for medications, tests, clinic, and hospital visits as part of your routine care as a transplant recipient. AstraZeneca will not pay any money to you or pay any of your medical bills.

What if I get sick or hurt in this study?

For a life-threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.

If you get sick or hurt in this study, tell the study doctor in person or call (206) 667-5160.

Emergency medical treatment is available at the usual charge. AstraZeneca, the company providing the Acalabrutinib for this study will pay for the reasonable costs of medical care for an injury or illness caused by a defect in the manufacture or design of Acalabrutinib. You or your insurance company will have to pay for medical care or hospitalization for injuries or illnesses that are not caused by a defect in the manufacture or design of Acalabrutinib. There are no funds to pay you for a loss of a job, or other costs to you or your family.

You will not lose your legal right to seek payment for treatment if you sign this form.

What will my information and/or tissue samples be used for?

In addition, be aware that by agreeing to participate in this study, your information or tissue samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by an oversight group known as an institutional review board if required by law. The information that identifies you will first be removed from your information or tissue samples. If you do not want your information or tissue samples to be used for future research studies without your consent, you should not participate in this study.

Your rights

You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.

If you join this study, you do not have to stay in it. You may stop at any time (even before you start). There is no penalty for stopping. Your regular medical care will not change.

If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.

During the study, we may learn new information you need to know. For example, some information may affect your health or well-being. Other information may make you change your mind about being in this study. If we learn this kind of information, we will tell you.

Your responsibilities

If you join this study, you will have some responsibilities.

- Follow the schedule of study visits and procedures.
- Take study medications as directed.
- Prevent pregnancy.
- Tell us about side effects.

For more information

If you have questions or concerns about this study, you may talk to your doctor anytime. Other people you can talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	(206) 667-6190 (Dr. Stephanie Lee) (206) 667-6830 (Research Coordinator)
If you get sick or hurt in this study	(206) 667-6190 (Dr. Lee)
Your rights as a research participant	(206) 667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center) (206) 543-0098 or email hsdinfo@uw.edu (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	(206) 606-1113 or toll free at (800) 804-8824

Emergency number (24 hours): (206) 598-6190

Signature

If you have read this form (or had it read to you), asked any questions, and agree to participate, please sign:

Participant / Printed Name, Signature, and Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature / Printed Name, Signature, and Date

Protocol: FH 8801, Fred Hutch RG1006135
Current version date: February 1, 2023
Previous version date: March 5, 2020
Copies to: Data management, patient, protocol coordinator