PRINCIPAL INVESTIGATOR: Steven Pavletic, MD

STUDY TITLE: A Phase 1/2 Study of Baricitinib, a JAK1/2 Inhibitor, in Chronic Graft-Versus-Host Disease (cGVHD) after Allogeneic Hematopoietic Stem Cell Transplantation (SCT)

STUDY SITE: NIH Clinical Center

Cohort: *Affected Patient*

Consent Version: *02/15/2022*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Steven Pavletic, MD
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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

Chronic graft versus host disease (cGVHD) is reported to occur in about 36% of patients that have had a hematopoietic stem cell transplant using donor cells. It is the leading cause of death in patients who survive 2 – 5 years after transplant. There are no FDA approved agents in the treatment of cGVHD, but patients are generally treated with high doses of steroids. Unfortunately, only half of the patients receiving steroids have any long-term benefit and there is no generally accepted treatment once steroids have not worked.

Baricitinib is an investigational drug that specifically inhibits the proteins (JAK 1 and JAK 2) which are involved in communication in the immune system and which are thought to play a role in cGVHD and other inflammatory diseases. JAK has been tested in other JAK related inflammatory diseases such as rheumatoid arthritis with promising results. In this trial, we plan to test the safety and effectiveness of baricitinib in patients with cGVHD that has not responded to therapy.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to participate in this study because you have been diagnosed with moderate to severe chronic graft versus host disease that has not responded to therapy.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 31 patients will be enrolled in this study.

DESCRIPTION OF RESEARCH STUDY

We plan to study two doses of baricitinib on this study. The drug will be tested at a lower dose level initially, but if there is not sufficient response, we will test at a higher dose level. If at any given dose level, more than one third of patients develop intolerable side effects, no further patients will be enrolled at that dose level. Individual patients that experience intolerable side effects will be given a lower dose.

The study therapy period will be divided into cycles, each lasting 28 days. On this study, you will take the drug every day, by mouth, at the approximately the same time each day for 12 weeks (3 cycles). Depending on your response to the drug, you may take it an additional 12 weeks (6 cycles total).

Baricitinib tablets should be swallowed whole and not broken or chewed. If you miss a dose, it should be taken as soon as possible the same day, unless it is within 1 hour of the next dose, at which time the dose should not be made up.

Patients whose disease does not worsen will have the option of taking baricitinib for an additional 6 months, making the maximum length of treatment ~ 1 year.

Before you begin the study

You will need certain tests before you begin the study to determine if you are eligible. Most of these tests would be performed as part of your usual medical care for your disease and may include: medical history and physical exam, routine blood and urine tests, pregnancy test (if you are a woman that can become pregnant), tests to measure your lung function, tests for certain viruses

and other infections, EKG and echocardiogram to test heart function and a chest CT scan. These tests were performed on a separate protocol.

During the Study

If it is determined that you are eligible for the study and you chose to sign the consent, you will begin study therapy as described above and undergo the tests listed below. You may not have to repeat some of the tests performed at baseline (before you begin taking baricitinib) if you have already done them as a part of screening.

Performed at baseline only:

- Tests for certain viruses
- Pregnancy test in women that can have children
- Evaluations by the following groups:
    - Dermatology (skin)
    - Ophthalmology (eyes)
    - Dental
    - Gynecology (female patients only)
    - Occupational therapy (questionnaires are only required if you are able to read English)

Performed at baseline and every 2 weeks for the first 3 cycles and on the first day of subsequent cycles:

- History and physical exam including weight and vital signs
- Routine blood tests

Performed at every visit

- Pregnancy test in women that can have children

Performed every 3 cycles

- Tests to measure your lung function
- cGVHD assessment and questionnaires. The questionnaires will take about 15 minutes and will only be required if you are able to read English.
- Routine urine tests

Performed at baseline and after 6 cycles

- Photographs to document any lesions you may have
- Occupational therapy evaluation, with questionnaires you will be asked to complete during your visit about how you feel

Performed before every cycle for first 4 cycles and before cycle 7

- Electrocardiogram to monitor your heart function

Additional Research tests

Research testing will be performed on your blood, saliva and on tissue samples (biopsies) from your skin and your mouth. They will be used to study how your immune system responds to the study drug and to measure the levels of drug in your body.

- Research blood will be collected on day 1 of each cycle for the first 4 cycles, then every 3 cycles until the end of treatment. A research blood sample to measure the level of baricitinib in your blood will be performed on the first day you receive medication, at the following times—before your dose, and then 1, 2 and 4 hours after the dose. We will also measure the level of baricitinib in your blood after you have taken the drug for 7 continuous days (on day 15 of the cycle). These research bloods make be repeated if we change the dose of baricitinib.
- Saliva, oral swabs, and optional skin and oral biopsies will be collected at baseline and after you have completed 6 cycles of study therapy. You will be asked to sign a separate consent for the biopsies at the time of the procedures.

When you are finished taking the drugs

When you complete your study therapy you will have the following tests performed at your last study visit:

- History and physical exam
- Tests to measure your lung function
- Disease assessments including: CT scans or MRIs (if your physician thinks necessary); body photography; cGVHD questionnaires
- Routine blood (about 5 tablespoons) and urine tests
- Research blood tests (about 8 tablespoons)
- We may ask you to complete the occupational therapy forms again at this time

If you discontinue the study therapy at any other time, you will be asked to return to the clinic within 30 days after your last dose to complete the above assessments.

Regardless of the reason for stopping study therapy, all patients will be contacted by phone ~ 30 days after your last dose of study therapy. We will ask you about any side effects that you might experience. We may follow you for side effects for longer if they are still present at the 30-day phone call.

You will also be invited for an optional follow up visit at 3 months after your last dose. If you are able to come to clinic, we will perform the following tests; otherwise, you will be assessed by phone at this time:

- History and physical exam
- Routine blood tests (about 5 tablespoons)
- cGVHD symptom assessment
- Research blood tests (about 8 tablespoons)

We will continue to follow you with phone calls to you or to your primary physician and 12, 18 and 24 months after your last dose to determine your survival status, to ask about medications you

are taking for your cGVHD, to ask about your cancer status and to determine whether or not you have returned to work.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. Women who are pregnant or breastfeeding should not take baricitinib. Studies of baricitinib in animals have shown harmful effects in both the mother and unborn babies, including abnormal formation of the bones. It is not known whether baricitinib passes into the breast milk of humans, or if it is harmful to a child who is breastfeeding. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice abstinence or two effective forms of birth control before starting study treatment, during study treatment, and for at least one week after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

In addition, if you are a male, you should not donate sperm during the study, and for at least one week after you finish study treatment.

Effective forms of birth control include:

- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

The baricitinib used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

Risks of baricitinib

Baricitinib is a molecule that blocks the effects of proteins in the body called Janus kinases. Blocking these proteins can affect the immune system. One effect may be an improvement in inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematous (lupus), atopic dermatitis, or diabetic kidney disease. Drugs that affect the immune system can increase the risk of infection and cancer. Baricitinib may also increase these risks.

This section describes possible risks seen with baricitinib. It also describes other notable events associated with baricitinib. Event rates for bad effects are based on safety data from 1,142 people with RA who took baricitinib. Not enough safety data are available from people with other diseases to calculate reliable event rates. However, the type and severity of their events were similar to those seen in the people with rheumatoid arthritis.

Baricitinib is removed from the body by the kidneys. People with reduced kidney function do not remove baricitinib as quickly as those with normal kidney function. People with reduced kidney function may require a lower dose of baricitinib.

The bad effects we know about so far are listed below. You could have some, all, or none.

Very Common (10% or greater)	**Common** (1 to less than 10%)	**Uncommon** (0.1 to less than 1%)
• Cough, stuffy or runny nose, scratchy or sore throat, sneezing • Higher amounts of cholesterol in the blood • Upper respiratory tract infections	• Small changes in blood tests related to the liver • Higher number of blood platelets (parts of the blood that aid in clotting) • Cold sores and shingles • Nausea, abdominal pain • Headache • Acne • Urinary tract infection • Viral infection	• Cancers of the skin, blood cells, lung, prostate, breast, uterus, ovary, kidney, and colon • Changes in blood test related to muscle • Clots in the blood vessels of the legs, which may dislodge and travel to the lungs • Lower number of white blood cells, including special types of white blood cells (blood cells that fight infections) • Higher amounts of fat in the blood • Weight gain • Heart attack • Stroke • Death

Additional study drug risks:

A large, randomized trial of tofacitinib (a drug similar to baricitinib) in patients with rheumatoid arthritis detected a higher risk of heart attack, stroke, cancer and blood clots and death when compared to standard therapy with anti-inflammation drugs. Based on these studies, in September 2021 the FDA extended this warning to baricitinib and another protein inhibitor drug used in arthritis. This warning has not been extended to similar drugs used for cancer (or GVHD).

Risks of blood collection

Taking blood may cause some discomfort, bleeding or bruising where the needle enters the body, and in rare cases, it may result in fainting. There is a small risk of infection. Some people have not felt well when having their blood taken. Some people have felt dizzy while having their blood drawn or after. Let the nurse know if you would prefer to lie down while you have your blood drawn.

Risks of skin and oral biopsies

Skin and oral punch biopsies may be associated with temporary bleeding, bruising and/or infection at the collection site and discomfort. Local anesthesia will be used to decrease the risk of discomfort.

Risks of Pulmonary Function Tests (PFTs)

PFTs are safe for most participants; however, some may experience dizziness, shortness of breath and fainting. In rare PFTs may lead to a collapsed lung. In participants with asthma, PFTs may precipitate an asthma attack.

Risks of ECG and echocardiogram

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram.

Risks of Questionnaires

The potential risk of questionnaires include questions that may be sensitive in nature.

Potential Benefits of Participation

The aim of this study is to see if this experimental treatment will cause your cGVHD symptoms to improve. We do not know if you will receive personal medical benefits from taking part in this study. Ptential benefits could include the lessening of your symptoms that are caused by the cGVHD. Because there is not much information about the drug's effect on your cGVHD, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

REMOTE ASSESSMENTS

In the first quarter of 2020, a pandemic was announced for COVID-19 (Coronavirus Disease 2019) which is caused by the virus SARS-CoV-2. In light of the pandemic, tele-medicine has been used as an alternative way to perform assessments without having participants in clinical trials come to the clinic. Your study doctor may determine that the risks associated with you visiting the clinic

during the COVID-19 pandemic may outweigh the benefit from seeing you in person at the clinic. Remote assessments may be performed at the discretion of your study doctor via phone, email, or video chat to speak with you directly about the following: patient history, verbal exam, symptom reporting, education, and questionnaires.

ALTERNATIVE APPROACHES OR TREATMENTS

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- Getting treatment or care for your cGVHD without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cGVHD. It does not treat the cGVHD directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy for the following reasons:

- You complete study therapy as outlined above (6 months or 12 months total)
- if he/she believes that it is in your best interest
- if your cGVHD gets worse during treatment even at the highest study dose that you can tolerate
- if you have side effects from the treatment that your doctor thinks are too severe
- if your treatment is interrupted for more than 28 days
- if you become pregnant
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Eli Lily and Company or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team

for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug developed by Eli Lily and Company through a joint study with your researchers and the company. The company also provides financial support for this study.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used.

Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will reimburse the cost for some of your expenses such as those for hotel, travel, meals. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

If your travel to the NIH Clinical Center (e.g. flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor (Center for Cancer Research) or their agent(s)
- Qualified representatives from Eli Lilly and Compant, the pharmaceutical company who produces Baricitinib.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Steven Pavletic, MD, 240-760-6174, pavletis@mail.nih.gov. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.