Title: Impact of Once-Weekly Rifapentine and Isoniazid on the Steady State Pharmacokinetics of Dolutegravir and Darunavir Boosted with Cobicistat in Healthy Volunteers

NCT: 02771249

Document Date: May 11, 2021

PRINCIPAL INVESTIGATOR: **Clare Sun, MD**

STUDY TITLE: **Duvelisib for Ibrutinib-Resistant Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)**

STUDY SITE: **National Heart, Lung, and Blood Institute**

Cohort: Affected patient

Consent Version: *Consents should be versioned using the date of the last revision. Each time the consent is revised, you must update the version date. Use this space to specify the version date.*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator:
Clare Sun
clare.sun@nih.gov
301-402-1806

Research Nurse:
Pia Nierman
pia.nierman@nih.gov
301-827-1094

KEY INFORMATION ABOUT THIS RESEARCH

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.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to be in this research study because you have a form of cancer called chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). You have been receiving ibrutinib to treat CLL/SLL, but your CLL/SLL is no longer responding to ibrutinib or has developed mutations in certain genes that would eventually stop ibrutinib from working. We want to find out if adding another drug called duvelisib to your treatment will help your cancer.

Duvelisib is a type of drug that blocks proteins inside CLL/SLL cells. The specific protein blocked by duvelisib helps CLL/SLL cells live and grow. Laboratory studies have shown that duvelisib can kill CLL/SLL cells obtained from patients who no longer respond to ibrutinib. Drugs similar to duvelisib can control CLL/SLL in some patients who no longer respond to ibrutinib and we want to know if duvelisib has the same effect.

You will take duvelisib by mouth twice daily. Your CLL/SLL might get worse if ibrutinib is suddenly stopped. To prevent this from happening, you will continue ibrutinib at your current dose with duvelisib for the first 6 months. You will then continue duvelisib alone until your

CLL/SLL no longer responds to duvelisib or you experience intolerable side effects from duvelisib.

You must return to the NIH monthly during the first 6 months of this study then every 3 months thereafter. Blood tests, bone marrow biopsies and CT scans will be performed periodically to see how your CLL/SLL is responding. Blood tests will also be used to monitor the safety of duvelisib. Visits will take place at the NIH Clinical Center. Most visits, including tests, will take less than a day. The study staff will provide specific dates and times for your study visits and tests.

You may continue taking most medications that were prescribed before you started the study. Because these other medicines might interact with the study drugs, we ask that you tell us about all of your medications or changes in the medications you take, including prescription drugs, over-the-counter products, vitamins, and herbal supplements.

Patients treated with duvelisb may be at an increased risk of developing certain infections. You will take an antibiotic and an antiviral medication to prevent such infections. You may also require steroids if you experience side effects related to a heightened immune system or granulocyte-colony stimulating factor if your white blood cell count decreases below normal.

Side effects occurring in more than 25 out of 100 patients treated with duvelisib for blood cancer were:

- Infections that could be caused by a bacteria, virus, or fungus.
- Frequent loose watery stools (diarrhea) and/or inflammation of the intestines (colitis).
- Decrease in number of white blood cells that helps fight infection with or without fever.
- Rash which may be itchy or may cause blisters.
- Feeling tired or weak.
- Fever.
- Cough.
- Feeling sick to your stomach

Side effects occurring in more than 10 but less than 25 out of 100 subjects treated with duvelisib for blood cancer were:

- Abnormally high level of enzymes produced by the liver meaning that it could affect how your liver functions.
- Pain in your muscles and/or joints.
- Decrease in red blood cells and decrease in cells in the blood that help the blood to clot.
- Swelling which may be in a specific location or may be more generalized.
- Decreased appetite

In addition, a small number of subjects experienced severe inflammation of the lungs which can be serious and can lead to death in rare cases (<1%).

If you have any new and concerning systemic symptoms (e.g. fevers, rigors, severe fatigue), respiratory symptoms (e.g. shortness of breath, persistent cough, chest pain), or gastrointestinal

symptoms (e.g. diarrhea or blood in your stool), you should immediately notify your doctor for further evaluation.

Your participation will continue as long as you continue to respond to and tolerate duvelisib, as long as the duvelisib remains available, until you decide that you no longer want to be in this study, or the Sponsor decides to stop or interrupt the study.

The possible benefit from this study is that duvelisib will help treat your CLL/SLL. If you decide to participate in this study, your health will be monitored very closely which may provide a benefit to you. By being in this study, you will give doctors more information about how well duvelisib works. It may help doctors understand your condition better and may help future patients with CLL/SLL.

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose to be treated by your home health care provider. Venetoclax (Venclexta®) is a Bcl-2 inhibitor approved for previously treated CLL/SLL. Idelalisib (Zydelig®), a PI3Kδ inhibitor, combined with rituximab (Rituxan®), a monoclonal antibody, is approved for CLL/SLL after 2 prior therapies. If you received ibrutinib as the first treatment for your CLL/SLL, chemotherapy combined with monoclonal antibody is also an option. Other experimental treatments may be available at other research centers.

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

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?

This is a research study. The purpose of this research study is to evaluate the safety and efficacy of duvelisib for CLL/SLL no longer responding to ibrutinib or CLL/SLL with mutations in certain genes that would eventually prevent ibrutinib from working. Duvelisib is approved by the U.S. Food and Drug Administration (FDA) to treat CLL/SLL after 2 prior therapies, but has not been specifically tested after treatment with ibrutinib.

WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this study, you will be asked to:

- Complete physical exam, laboratory tests, CT scan, bone marrow biopsy, and possibly lymph node biopsy and/or lymphapheresis before starting duvelisib.
- Take duvelisib twice daily and continue ibrutinib at your current dose for the first 6 months to prevent your CLL/SLL from worsening if ibrutinib is suddenly stopped. Ibrutinib will be supplied from the NIH Clinical Center Pharmacy. Continue to take duvelisib until your CLL/SLL stops responding or you develop intolerable side effects.
- Obtain laboratory tests every 2 weeks during the first 2 months to monitor the safety of duvelisib. These tests can be performed at an outside laboratory provided you share the results with us.
- Return to the NIH Clinical Center every month for follow-up during the first 6 months and every 3 months thereafter. We will perform a physical exam and laboratory tests at these visits and CT scans and procedures described below. You may be asked to come more frequently if your CLL/SLL does not respond to treatment or you develop side effects.
- Undergo a CT scan to see how your CLL/SLL is responding to treatment after 3 months, 6 months, 12 months on duvelisib, and annually thereafter.
- Undergo a bone marrow biopsy after 3 months and 6 months on duvelisib and when you achieve complete remission.

Some of your blood samples obtained during this study may be stored for the duration of the study. Your identity will be protected by using a code, such as a number, to label these samples. These blood samples may be used for the following:

- Research associated with this study.
- Future research or be given to another investigator for future research without consent. Any such research would either protect or remove any personally identifiable information about you.
- Development of medical products or processes. You will not gain financially from any products or processes that may result from this research even if your blood is used.
- DNA sequencing, including whole exome sequencing.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last as long as your CLL/SLL is responding to treatment and you do not experience intolerable side effects. Most visits will range from 4-8 hours in length and will occur every month during the first 6 months and every 3 months thereafter. If you discontinue duvelisib, then for your safety you will be asked to return approximately 30 days after your last dose of duvelisib. If you discontinue duvelisib for reasons other than disease progression or to start new anti-CLL therapy, you will also be asked to return every 6 months to monitor your CLL/SLL. After your CLL/SLL progresses or you start new anti-CLL therapy, you will be asked to return or be contacted by telephone yearly to see how you are doing.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 36 people participate in this study at the NIH Clinical Center.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

Duvelisib

All the side effects of duvelisib are not known. The effects of duvelisib when combined with other medications or substances such as alcohol are not known and might result in serious or even life-threatening reactions. Therefore, you should always discuss the use of any drugs (over-the-counter, prescription, herbal, recreational) or substances such as alcohol, with your study doctor prior to taking duvelisib, and while you are participating in this study.

Side effects can go away while continuing to take the drug, or shortly after you stop taking the drug, but some side effects could be long-lasting, permanent, serious, life threatening, or even cause death. Everyone taking part in the study will be watched carefully for any side effects, and the drug may be stopped if intolerable or concerning side effects develop. You should talk to your study doctor about any side effects that you have while taking part in the study.

Approximately 700 subjects with blood cancers have received study treatment (either duvelisib and/or another treatment for their cancer) on studies of duvelisib. Based on available information from subjects who received duvelisib on these studies, a list of potential side effects has been identified. These potential side effects may or may not be caused by duvelisib (for example, they may be due to underlying blood cancer or other medical conditions the subjects had before the study).

Should information become available that might change your decision to participate in this study, you will be informed immediately. You can always decide whether or not to continue participating in this study. As new risks are identified, you will also be informed of these risks. You will be asked to sign a new consent form that confirms you have been made aware of the new risks and agree to continue participating in this study.

As of 19 July 2018, the side effects seen in subjects with blood cancer who have taken duvelisib alone as a single anti-cancer treatment (total daily doses range from 16 mg to 200 mg), with most subjects with blood cancer having received a total daily dose of 50 mg (25 mg 2 times a day) are listed below. Most side effects seen were mild and subjects recovered with or without holding treatment with duvelisib. However, some side effects were severe, led to hospitalization, were life-threatening, or caused death.

The most common side effects are described in the table below.

Side effects occurring in more than 25 out of 100 subjects treated with duvelisib for blood cancer were
• Infections that could be caused by a bacteria, virus, or fungus. This includes infections that affect the throat, lungs and sinuses such as the common cold or pneumonia. The most frequent infections occurred in the lungs. Infection can spread to vital organs causing the organs to not function properly (sepsis). In some cases, infections can be life-threatening and may cause death (4% fatal), such as lung infections or sepsis. In rare instances (<1%), more specific infections that would typically not occur in people with normal immunity can occur in people with decreased immune systems (such as people with cancer). Such infections may include infections with viruses such as Herpes simplex virus,

Cytomegalovirus or Epstein-Barr virus (a virus that can cause mononucleosis otherwise known as "mono"); and infections with fungus such as Aspergillus, Candida, or Pneumocystis. Report any new or worsening signs and symptoms of infections such as fever and chills or any other sign of infection. You may require medical attention and should immediately notify your doctor for further evaluation. Your doctor may prescribe medications such as antibiotics or antivirals to help prevent some of these infections.

- Frequent loose watery stools (diarrhea) and/or inflammation of the intestines (colitis). This can be life-threatening and may cause death in rare cases (<1%). Tell your doctor right away if you have any new or worsening diarrhea, stool with mucus or blood, or if you have severe stomach-area (abdominal) pain. You may require medical attention and should immediately notify your doctor for further evaluation.
- Decrease in number of white blood cells that helps fight infection with or without fever.
- Rash which may be itchy or may cause blisters. In rare cases (<1%), you could have peeling of the skin which could be serious, life-threatening or may cause death. Tell your doctor right away if you get a new or worsening skin rash or other skin reaction including painful sores or ulcers on your skin, lips, or in your mouth, severe rash with blisters or peeling skin, rash with itching or rash with fever.
- Feeling tired or weak.
- Fever.
- Cough.
- Feeling sick to your stomach

Side effects occurring in more than 10 but less than 25 out of 100 subjects treated with duvelisib for blood cancer were:

- Abnormally high level of enzymes produced by the liver meaning that it could affect how your liver functions. Tell your doctor right away if you get any symptoms of liver problems, including yellowing of your skin or the white part of your eyes (jaundice), pain in the stomach-area (abdominal) region, bruising or bleeding more easily than normal.
- Pain in your muscles and/or joints.
- Decrease in red blood cells which can cause tiredness and shortness of breath and decrease in cells in the blood that help the blood to clot.
- Swelling which may be in a specific location or may be more generalized.
- Decreased appetite
- Sores in your digestive tract (nose, mouth, stomach, etc.) which can lead to not wanting to eat.
- Throwing up or vomiting
- Shortness of breath.
- Headache.
- Difficulty having a bowel movement or constipation.
- Abdominal pain
- Decrease in potassium in your blood which can cause muscle weakness or cramps, or changes in heart rhythms.

In addition, a small number of subjects experienced severe inflammation of the lungs which can be serious and can lead to death in rare cases (<1%). Tell your doctor right away if you get new or worsening cough or difficulty breathing. Your doctor may do tests to check your lungs if you have breathing problems during treatment. Your doctor may treat you with a steroid medicine if you develop inflammation of the lungs that is not due to an infection.

If you have any new and concerning systemic symptoms (e.g. fevers, rigors, severe fatigue), respiratory symptoms (e.g. shortness of breath, persistent cough, chest pain), or gastrointestinal symptoms (e.g. diarrhea or blood in your stool), you should immediately notify your doctor for further evaluation.

Additional Potential Effects While on Treatment with duvelisib

Exposure to Sun: The effect of duvelisib on the skin, especially when in direct sunlight or with artificial UV light (e.g. tanning booths), is not known. As a general precaution, it is advised to use appropriate protective measures (e.g. long sleeve shirts and pants, hat, umbrella) to minimize exposure to direct sunlight during the treatment period and for at least 30 days after the last dose of duvelisib.

Vaccinations: Tell your study doctor if you have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines after starting duvelisib. Vaccinations while on duvelisib may not work or could result in infection. Tell your doctor if anyone in your household is scheduled to receive a vaccination.

Drug-drug interactions: If you start any new medications (prescriptions, herbal and/or over the counter), inform your doctor. Drug-drug interactions can decrease how well your medications work, may increase minor or serious unexpected side effects, or even increase the blood level and possible toxicity of a certain drug.

Ibrutinib

To be eligible for this study, you must be currently taking ibrutinib. Ibrutinib is an U.S. FDA approved for treatment of CLL. The table below lists the most common side effects seen in patients who have taken ibrutinib.

Most Common (≥ 20%)	Very Common (≥ 10%)	Less Common (≥ 1%)
• Increase in frequency of loose or watery stools (diarrhea) • Bruises • Muscle and bone/joint pain (musculoskeletal pain) • Nausea • Rash	• Swelling of the hands or feet (peripheral edema) • Sinus infection (sinusitis) • Common cold (upper respiratory infection) • Fever • Constipation • Joint aches (arthralgia)	• Dizziness • Urinary tract infection • Low white blood cells with fever (febrile neutropenia) • Abnormal heart rhythm (atrial fibrillation) • Blurry vision

• Low white blood cell count, cells that help fight infection (neutropenia)	• Mouth sores (stomatitis) • Headache • Pneumonia • Vomiting • Muscle spasms • Severe infection throughout the body • Low platelet count, cells that help blood to clot (thrombocytopenia) • High blood pressure (hypertension) • Skin infection	• Increase in white blood cell counts (leukocytosis) • Breaking of the nails (onychoclasis) • Inflammation of the lungs that could lead to permanent damage (interstitial lung disease) • Nose bleed (epistaxis) • Non-melanoma skin cancer (basal cell and squamous cell carcinoma) • Severe infection throughout the body (sepsis) • Skin redness (erythema) • Increased level of uric acid in the blood (hyperuricemia) • Small purple or red spots caused by bleeding under the skin (petechiae) • Increase in lymphocyte count (lymphocytosis)

Blood Sampling

Risks associated with drawing blood or needle sticks include pain, bruising, bleeding, light-headedness, inflammation, temporary redness of the skin at the place the needle is put into your arm, fainting, and, on rare occasions, infection and/or local clot formation.

Bone Marrow Biopsy

A local anesthetic will be injected at the site of bone marrow biopsy. There may be a stinging or burning sensation from the injection. The biopsy needle will be placed through the skin and into the bone and may produce a brief, dull pain. As the bone marrow liquid is withdrawn from the bone, there may be a brief, sharp pain. Since the interior of the bone cannot be anesthetized, this procedure may cause some discomfort, however not all patients experience these symptoms. In some cases, the doctor may prescribe some medication used as conscious sedation. This is given to you to help you relax if the doctor feels it is necessary.

Some risks associated with this procedure include persistent bleeding and infection, pain after the procedure at the site where the bone marrow biopsy is done, and sometimes very infrequently a nerve may be injured during the procedure causing pain.

Lymph Node Biopsy (Optional)

There are several ways to do a lymph node biopsy.

In a fine-needle or core needle aspiration biopsy, a thin needle is used to remove cells from the lymph node. Patients will feel only a quick sting from the local anesthesia used to numb the skin and may feel some pressure from the biopsy needle. After a fine-needle aspiration biopsy or core needle biopsy, the site may be tender for 2 to 3 days.

In an open biopsy, the lymph node is removed through a cut in the skin. This can be done under local anesthesia. After the open biopsy, the biopsy site may feel tender, firm, swollen, and/or bruised. Subjects may be advised to not do any heavy lifting or other activities that stretch or pull the muscles around the area.

As patients are at risk of infection at the biopsy site, we will ask you to report any swelling, redness or discharge to the research team so that appropriate antibiotics can be started if necessary.

I give my permission for my lymph node biopsy:

_____ Yes _____ No

Initials Initials

CT Scans

Before the CT scan a contrast dye (iodine dye) may be injected into your vein. These injections may cause a slight discomfort, bruising, swelling and sometimes an allergic reaction, although this is rare. If an allergic reaction occurs, it can range from being mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). In addition, contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies, kidney problems, or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan.

Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when you are inside the scanner, or by lying in one position for a long time. The contrast material may make you feel discomfort when it is injected/given by mouth. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting, or a headache.

Lymphapheresis (Optional)

Blood will be taken from your body (from an IV in your arm) and sent through a machine to remove white blood cells. Blood without white blood cells will be returned to you (through an IV in your other arm).

If you choose to have lymphapheresis, you might feel lightheadedness or have bleeding from the sites where blood is taken or returned. Low blood pressure and muscle cramps can occur during the procedure. If you feel uncomfortable, you should tell the study team. There is also the chance for infection after the procedure.

I give my permission for my blood to be taken for lymphapheresis:

_____ Yes _____ No

Initials Initials

What are the risks related to pregnancy?

Duvelisib has not been tested to determine whether it may have an effect on pregnancy or a developing baby.

All patients enrolled in the study and their partners should agree to take effective measures in order to prevent a pregnancy from the screening visit up to 30 days after the last dose of duvelisib. You must also agree not to donate sperm during this period.

If you are pregnant or plan to become pregnant, you will not be allowed to participate in this study because of possible harm to you or your baby. Females who are capable of bearing children will be required to take a pregnancy test prior to entry into this study and during the study. If at any time during the study and up to 30 days after you take the last dose of duvelisib you suspect that you have become pregnant, please notify the study doctor immediately.

If you become pregnant, you will be permanently taken off study drug(s), but we will continue to follow you at regular intervals.

If you are a male study participant, you should agree to protect your partner from becoming pregnant before and during the study and for up to 30 days after your last dose of duvelisib. If your partner becomes pregnant while you are on study and for up to 30 days after discontinuing the study, you must immediately notify the research study staff. We can provide counseling about preventing pregnancy for either male or female study participants.

To participate in this study, you should agree to use an effective method of birth control to prevent pregnancy. Acceptable methods to prevent pregnancy during participation in this study and for 30 days after the last dose of duvelisib are:

- Total abstinence (no sexual intercourse).
- Surgical sterilization including tubal ligation (tubes tied) or hysterectomy (removal of uterus or womb) in women or a vasectomy in men.
- Oral contraceptives (birth control pills), intrauterine devices (IUD), implantable or injectable contraceptives in combination with barrier methods (such as a condom or diaphragm) used with a spermicide.
- Barrier methods (such as a condom or diaphragm) used with a spermicide.

The contraception methods described above may not protect against HIV infection (AIDS) and other sexually transmitted diseases. If you need more information about this, please ask your study doctor.

You should not nurse (breastfeed) a baby while on this study because duvelisib may enter breast milk and possibly harm your child.

What are the risks of radiation from being in the study?

You may have up to 4 CT scans during the first year of the study, one of which you may have already had as part of your screening visit. The CT scan done after completion of 3 month and 6 months of duvelisib is medically indicated. The other CT scans (at the completion of one year on duvelisib and once a year for as long as you remain on treatment), will be done for research purposes if not required for your medical care. The amount of radiation you will receive in this study is 1.3 rem per year for annual research scans, which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. Although it is important for this research, you may choose not to undergo the CT scans that are scheduled for research purposes. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer. Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body. If you are pregnant you will not be permitted to participate in this research study. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You will not benefit from being in this study.

However, the potential benefit to you might be that duvelisib will help treat your CLL/SLL. If you decide to participate in this study, your health will be monitored very closely which may provide a benefit to you.

In the future, other people might benefit from this study because you will give doctors more information about how well duvelisib works. It may help doctors understand your condition better and may help future patients with CLL/SLL.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because we will have better understanding how this medication can help other patients.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose to be treated by your home health care provider. Venetoclax (Venclexta®) is a Bcl-2 inhibitor approved for previously treated CLL/SLL. Idelalisib (Zydelig®), a PI3Kδ inhibitor, combined with rituximab (Rituxan®), a monoclonal antibody, and duvelisib (Copiktra®) is approved for CLL/SLL after 2 prior therapies. If you received ibrutinib as the first treatment for your CLL/SLL, chemotherapy combined with monoclonal antibody is also an option. Other experimental treatments may be available at other research centers.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

Clinically relevant research results will not be shared with you.

EARLY WITHDRAWAL FROM THE STUDY

Your participation is entirely voluntary. You may choose to stop at any time. If you stop because of side effects, you might be asked to return for additional tests until the side effects resolve. New information regarding safety and effectiveness of duvelisib may become available. Following discussion of that new information with the research team:

- You may decide to discontinue participation
- You may decide to continue in the study, if so we will ask you to sign an updated consent form
- The research team may decide it is not in your best interest to continue in the study

The principal investigator of this study (Clare Sun, MD), the Institutional Review Board (IRB), and Verastem, Inc. may stop this study at any time, for any reason, without your consent. For safety reasons, the Data Safety Monitoring Board may also recommend stopping this study without your consent.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide

additional information that will be helpful in understanding Lymphoma, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH until they are no longer of a scientific value, at which time they will be destroyed.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

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

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

This study will offer reimbursement for, or payment of, travel, lodging or meals according to NIH and NHLBI policies and guidelines.

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.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using duvelisib developed by Verastem, Inc. through a joint study with your study team and the company. The company also provides financial support for this study.

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 (NHLBI Division of Intramural Research)
- Qualified representatives from Verastem, Inc., the pharmaceutical company who produces duvelisib.

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

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 information that 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 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, Clare Sun, clare.sun@nih.gov, 301-402-1806. *Other researchers you may call are:* Pia Nierman, pia.nierman@nih.gov, 301-827-1094. 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

Parent/Guardian of a Minor Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I give permission for my child to take part in this study.

Signature of Parent/Guardian	Print Name of Parent/Guardian	Date

Signature of Parent/Guardian *(as applicable)*	Print Name of Parent/Guardian	Date

Assent: *(Use this section only when this process is approved by an IRB for older minors. Do not use if an IRB requires a separate assent form for this population.)*

I have had this study explained to me in a way that I understand, I have been given the opportunity to discuss it, and I have had the chance to ask questions. I agree to take part in this study.

Assent of Minor: *(as applicable)*

Signature of Minor	Print Name of Minor	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process with a non-English speaking subject and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

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: _____ .

PRINCIPAL INVESTIGATOR: Jomy George, PharmD

STUDY TITLE: Impact of Once-Weekly Rifapentine and Isoniazid on the Steady State Pharmacokinetics of Dolutegravir and Darunavir Boosted with Cobicistat in Healthy Volunteers

STUDY SITE: National Institutes of Health (NIH), Clinical Center (CC)

Cohort: Standard – Darunavir/cobicistat once daily (Study Arm B)

Consent Version: 04/28/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

Jomy George, PharmD
Phone: 301-496-2997
Email: jomy.george@nih.gov

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.

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?

People infected with the human immunodeficiency virus (HIV) often take several anti-HIV medications to control their disease. They may also need to take medications to treat a type of infection called latent tuberculosis (TB). There are a number of medications that can be used to treat latent TB. Most of these have to be taken multiple times a week or every day. However, there is a once weekly treatment for latent TB that would be easier for people with HIV to take.

The once weekly TB treatment consists of two drugs: isoniazid and rifapentine. Pyridoxine (vitamin B6) may also be given to prevent side effects from isoniazid. Isoniazid and rifapentine may increase or decrease the blood levels of some anti-HIV medications. These changes could

either increase drug side effects or make the anti-HIV treatment not work. However, since isoniazid and rifapentine are given only once a week, they may not affect the anti-HIV drug levels at all.

It is important to know how anti-HIV and anti-TB drugs affect each other so that people taking these drugs together can be treated safely. We plan to test this once weekly TB treatment together with different anti-HIV drugs in HIV-negative healthy people. We will study these combinations in 2 different groups of study participants. This consent form provides information for the second study group, which will take the anti-HIV medication called darunavir once a day. The form of darunavir that will be given in this study has been combined with another drug, called cobicistat, in one single tablet. Cobicistat helps increase the amount of darunavir in the body. Results from this study group may help doctors decide whether rifapentine and isoniazid can be given to HIV-infected patients on the combination of darunavir/cobicistat. We will test 15 healthy people in this part of the study.

All of the drugs used in this study are approved by the Food and Drug Administration (FDA) and are used as standard treatments for HIV or TB.

STUDY SCHEDULE

This study is split into 2 parts: a screening portion and the actual study portion. The screening portion consists of a single visit. This visit will last about 3-4 hours and can occur up to 90 days before starting the study portion. If the screening tests show that you can participate in the study, you will move on to the study portion. This part will last 32-44 days and consists of 11 study visits. This includes the baseline visit (before you start taking the drug) and follow-up visits (after you have finished taking the drugs). At the discretion of the principal investigator, some laboratory evaluations may be repeated. You will only take the study medications for a total of 19 days. The baseline visit will last about 2-3 hours, and will take place up to 7 days before you start taking darunavir/cobicistat. Three of the visits will last for about 12 hours (long days). The remaining 7 visits will last for approximately 1 hour (short days). All visits will take place at the NIH Clinical Center.

There are specific times when we need to collect blood samples for our study. Therefore, there is a strict calendar for when study visits will take place. We will give you a detailed study schedule to keep. The day you begin taking darunavir/cobicistat will be called Day 1. Full clinic visits (long days) will take place on days 4, 14, and 19. The short visits will take place on days 5, 6, 13, 15, 20, 22, and 34. Then you will be done with the study.

PROCEDURES

Screening visit: You will need to fast (not eat anything and drink only water) beginning at midnight the night before the screening visit. The screening visit will include the following:

- An initial medical history and a physical exam will be performed.
- Vital signs (e.g., blood pressure, pulse, breathing rate, and temperature) will be taken.
- If you are a woman of child-bearing potential, a blood or urine pregnancy test will be done.

- Blood will be taken from a vein in your arm for the following:
    - Routine laboratory tests. If any of these tests are abnormal during the screening portion of the study, you will be told to follow-up with your personal physician.
    - HIV test. HIV is the virus that causes AIDS. If you are infected with HIV, you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.
    - TB test. If your TB test is positive, you will not be able to participate in the study. We will tell you what the results mean and how to find care.
    - Hepatitis tests. Your blood will be screened for active infection with hepatitis A, B, and C. If you are found to be actively infected with any type of hepatitis, you will not be able to participate in the study. We will tell you what the results mean and how to find care depending on which type of hepatitis infection that you have.

Baseline visit: You will need to fast (not eat anything and drink only water) beginning at midnight the night before the baseline visit. The visit will include the following:

- Vital signs will be taken.
- Blood will be drawn for routine laboratory tests.
- If you are a woman of child-bearing potential, a blood or urine pregnancy test will be done.
- You will be given a bottle containing your darunavir/cobicistat tablets and instructions for taking them, including which day to start. You will take one darunavir/cobicistat tablet with breakfast every day for 19 days. You will receive a telephone call to remind you when you need to start the darunavir/cobicistat.
- You will get a diary card to record all of your daily medication doses and side effects while you are at home. You should bring this diary card and all study medication bottles to each study visit. You should also call your study coordinator or one of the investigators to discuss or report any side effects. The contact information for the investigators is provided later in this consent form.

Full clinic visits (long days): You will need to fast beginning at midnight the night before the visit. You will arrive to the clinic early in the morning on the day of the visit. You will be given breakfast and lunch in the clinic. We will also provide you with dinner if you prefer. You should not take your dose of darunavir/cobicistat before your visit because you will take it during the visit. The following will be performed:

- Vital signs will be taken.
- We will ask how you are feeling and if you have had any illness recently.
- If you are a woman of child-bearing potential, a blood or urine pregnancy test will be done.
- We will insert an intravenous (IV) line into a vein in your arm using a needle. We will use the IV line to take blood for routine laboratory tests and research tests 8 times throughout the day. After the last blood draw, we will remove the IV line and you will be allowed to go home.

- During your visit on Day 4, you will receive the medication supplies for isoniazid, rifapentine, and pyridoxine. You will take them once per week for 3 weeks. You will be told the appropriate days to take these medications. You will be reminded at your Day 5 clinic visit to take these medications after your blood is drawn. You will also receive a reminder phone call the day before and on the same day that you need to take the second doses of these medications (Day 12). The third once weekly dose of these medications will be given while you are in the clinic on Day 19. You will need to bring your medication supply with you to this visit.

Short visits: The short visits will take place in the morning, before you take your next dose of study medications. You will need to fast beginning at midnight the night before the visit and arrive to the clinic early in the morning on the day of the visit. The following procedures will be performed:

- Vital signs will be taken.
- We will ask how you are feeling and if you have had any illness recently.
- Blood will be drawn for research tests.
- At the last visit, you will need to return your medication bottles and any leftover medication.

Additional instructions: You are not allowed to take any other medicines while you are enrolled in this study. This includes prescription drugs, dietary supplements, over-the-counter drugs, and recreational drugs. You cannot take a daily multivitamin with minerals or mineral-containing supplements during the study. You also must not drink alcohol while you are taking the study drugs. If your doctor prescribes a drug for you, you should let him/her know that you are in this study. You should also call the study coordinator immediately. You can take acetaminophen (Tylenol®, max 2000 mg/day), ibuprofen (Motrin® or Advil®), naproxen (Aleve®), and/or loperamide (Imodium®) to manage side effects from the study drugs, or antihistamines if you need to do so. However, you cannot take these medicines on the days that you come to NIH for blood sampling. If you take any permitted medicines during the study period, we ask that you record the date and doses of the medicine, and the reason why it was taken.

STUDY RISKS AND DISCOMFORTS

Darunavir/cobicistat (Prezcobix®, Janssen Therapeutics): Darunavir is an anti-HIV medication. Cobicistat is a "booster" that helps increase the levels of darunavir in the body. These drugs are combined in a single tablet. They are used with other medications to treat HIV. The most common side effects of this therapy include diarrhea, nausea, rash, headache, abdominal pain, and vomiting. These occurred in more than 5% of people. A mild-to-moderate rash can also occur. This usually occurs within the first four weeks of therapy. Cobicistat can increase serum creatinine level. This is a measure of kidney function. However, this does not mean that kidney function has actually changed. Rarely (in less than 1% of people), darunavir/cobicistat has caused liver injury and severe skin reactions. In studies, the rates of side effects in healthy volunteers were similar to those seen in patients with HIV. You will take this medication once daily for 19 days. We expect that you may have similar side effects to those described above. We will monitor your labs and side effects throughout the study.

We do not know if darunavir/cobicistat will protect you from getting HIV. It is important that you avoid behaviors that would put you at risk for becoming infected with HIV. Such behaviors include having unprotected sex or sharing needles used to inject drugs. The study investigators will be happy to answer any questions that you may have about whether a certain behavior places you at risk for getting HIV.

Rifapentine (Priftin®, Sanofi-Aventis): Rifapentine is a medication used in combination with isoniazid to treat TB infection. The most common side effects of rifapentine include vomiting, nausea, diarrhea, headache, dizziness, decreases in red and white blood cells, increases in liver enzymes, and rash. Side effects are less common when rifapentine is given once a week. Rifapentine may also cause your body fluids (saliva, sweat, tears, urine) to turn red or orange. This goes away as the drug leaves the body, and it is not due to damage in the body. There is a possibility of developing a hypersensitivity or flu-like reaction with the combination of rifapentine and isoniazid. The symptoms of this type of reaction include headache, nausea, chills, fatigue, and muscle pain. This side effect was reported in one clinical study and caused <4% of study participants to stop treatment. This side effect was more common in people who were white, female, over the age of 35, and those with a lower body mass index (BMI). You will only take three once weekly doses of this drug on this study. We anticipate the main side effects to be vomiting, nausea, diarrhea, orange or red body fluids, and higher than normal liver enzymes on blood tests.

Combined Use of Darunavir/Cobicistat and Rifapentine: Darunavir is in a drug class called protease inhibitors. Rifapentine is in a drug class called rifamycins. Studies with drugs from these classes have been done in healthy volunteers. Severe side effects were seen. Most of the side effects were large increases in liver enzymes, indicating liver damage, nausea, vomiting, abdominal pain, and rash. The side effects went away once treatment was stopped. One of these studies used drug doses that were higher than the doses approved by the FDA. In the other two studies, the protease inhibitors significantly increased blood levels of the rifamycins being used. We do not expect to see these same side effects in this study for a number of reasons. First, we are using the FDA-approved drug doses. In addition, rifapentine will only be given once weekly, and not daily or every other day like the other studies. Furthermore, there is no evidence that darunavir/cobicistat will increase rifapentine levels. We will monitor your blood tests and watch for side effects throughout the study.

Combined Use of Anti-HIV Medications with Rifapentine and Isoniazid: Some anti-HIV medications have been studied with rifapentine and isoniazid. These anti-HIV medications include dolutegravir, efavirenz, and raltegravir. Dolutegravir was used in an earlier arm of this study, and 2 of 3 participants who completed the entire study developed drug reactions on the last day of study medications. An additional 4th participant enrolled in the study, but withdrew prior to the final dosing day and did not develop this reaction. These drug reactions included symptoms of nausea, vomiting, fever, and chills. Together, these symptoms are referred to as "flu-like syndrome". One participant required hospitalization for ~24 hours due to low blood pressure, which required IV fluids. In addition, these same participants also had higher than normal liver enzymes following these reactions. The flu-like syndrome lasted ~24-48 hours, but the liver enzymes took ~2-3 weeks to return to normal levels. Both participants were monitored until symptoms and safety labs returned to baseline. The reason for these reactions is unclear. These reactions have been reported with rifapentine and isoniazid, but are not common. These

reactions were not seen with the other anti-HIV medications, efavirenz or raltegravir, in combination with rifapentine and isoniazid. While you are on this study, we will monitor your blood tests and watch for side effects.

Isoniazid: Isoniazid is a medication that is used to treat TB infection. One of the most common side effects of isoniazid is higher than normal liver enzymes (10-20%). Peripheral neuropathy is another common side effect. This is nerve damage that causes numbness and weakness in the hands and feet. It is more likely to occur with higher drug doses and long-term therapy, and in people who are not healthy. This side effect can be prevented and reversed by taking pyridoxine. Isoniazid may cause severe and sometimes hepatitis (liver inflammation) that can be fatal. This side effect is rare, but can occur in older adults and in people who drink alcohol daily. Other side effects of isoniazid include nausea, vomiting and stomach pain. While you are on study, you will be limited to three once weekly doses and you should not drink alcohol. This should minimize the side effects that you may have. We expect that the most likely side effects that you will experience will be nausea, vomiting, and stomach pain, and/or higher than normal liver enzymes.

Pyridoxine: Pyridoxine is a vitamin B6 supplement. It is used to prevent peripheral neuropathy with isoniazid therapy. Vitamin B6 is a normal part of the human diet, so we do not expect any side effects with the doses that will be used in this study.

Combined Use of Study Drugs: The use of the study drugs may involve risks to you that we cannot predict. We will monitor your blood test results and side effects throughout the study.

Pregnancy and breastfeeding: We do not know if these study medications are safe to take during pregnancy. Therefore, you cannot be in this study if you are pregnant or plan to get pregnant. If you can get pregnant, you must agree to use an effective method of non-hormonal birth control during this study. Acceptable methods are condoms, a diaphragm with spermicide, or an intrauterine device (IUD) without hormones. You must tell the study team right away if you think you are pregnant. If you get pregnant during this study, you should stop taking all study medications and contact the study team. The risks of the study drugs for nursing infants are also not known, so mothers should not breastfeed during the study.

Blood Draw: The risks related to drawing blood or having an intravenous (IV) catheter include pain, bruising, bleeding, lightheadedness, and fainting. Infection is rare. An IV catheter can also cause inflammation of the skin and vein. The total amount of blood collected during this study will not exceed the guidelines for blood drawn for research purposes at the NIH Clinical Center.

GENETIC TESTING

Some of the blood drawn from you may be used for genetic testing to look at possible relationships between your genes and drugs that will be given during this study. These will be research tests and are not designed to reveal information about your health or risk for disease. Any genetic information collected or discovered about you or your family will be confidential. Records containing this information will be kept on password-protected computer systems and in locked and secured quarters within the Clinical Center. We will not release any information about you or your family to relatives, any insurance company, employer, or your primary care physician without your written permission. There may be a risk that genetic information obtained as a result of participation in research could be misused for discriminatory purposes. However, state and federal laws provide some protections against genetic discrimination. Researchers who

will have access to genetic information about you will take measures to maintain the confidentiality of your genetic information.

BENEFITS

You will not receive a benefit from being in this research study. The knowledge gained from this study may help in the future care of patients with HIV and latent TB infection.

ALTERNATIVES

You can choose not to participate in this study.

STORED SAMPLES / FUTURE STUDIES

We will store some of your blood samples for future research. We will label your stored samples with a code that only the study team can link to you. We will keep any information that can be traced back to you as private as possible. We might send your samples to other investigators for their research, without any information that can identify you. We might also share information such as your sex, age, health history or ethnicity. We will not sell your samples and you will not be paid for any products that result from the research. In general, future research that uses your samples will not help you, but it may help us learn more about drugs that are used to treat HIV, TB, and other medical conditions.

The greatest risk of allowing us to store samples will be an unplanned release of your identity from the samples due to release of this information from the stored sample database. The chances of this happening are very low.

If you agree to participate in this study, you agree to let us store your samples for future research. You also agree that we can contact you again in the future. If you decide not to participate, you may still participate in other studies at NIH. Even if you agree now to let us store your samples, you can change your mind later. If you do, please contact us and say that you do not want us to use your samples for future research. We will do our best to comply with your request, although we cannot guarantee that we will always be able to destroy all of your samples.

WITHDRAWAL FROM PARTICIPATION

You may stop participating in this study at any time. If you decide to stop participating, you will be asked to return for a final visit. You must also return all unused study drugs. The decision to no longer participate in this study will in no way affect your ability to receive care at the Clinical Center or to participate in other NIH studies. Refusal to participate or stopping participation at any time involves no penalty or loss of benefits otherwise entitled to you.

You may be removed from the study if you

- develop a health problem that may be related to one or more of the study drugs,
- become pregnant,
- develop a medical condition that requires medication,
- do not comply with the study requirements, or
- if it is felt by the study team to be in your best medical interest.

If you are removed from the study because of a safety concern, you will receive immediate medical care as necessary. Afterward, you will be followed medically by the study investigators

until your symptoms go away and/or your abnormal laboratory values return to normal (or to what they were before you started the study). If we feel that you should have further medical follow-up, you will do this with your personal physician.

If you are removed from the study because you become pregnant, we will keep in contact with you until you give birth. Your personal physician will provide your prenatal care. This will not be provided by the study investigators or other NIH personnel.

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.

REIMBURSEMENT

This study does not offer reimbursement for parents and participants, or payment of, hotel, travel, or meals.

PAYMENT

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

You will be compensated for the time and inconvenience or participating in the study. You will receive $50 for the screening portion of the study. If you complete the entire study portion, then you will receive an additional $1,450, making a total of $1,500. If the screening and baseline visit occur at the same time, you will be compensated $100 total. This is the same amount that you would have been compensated for separate visits. If additional visits and/or procedures are felt to be needed by the study staff to ensure your safety while participating in the study, you will receive additional compensation accordingly based on the extent of additional procedures and visits. If you do not complete the entire study for any reason, you will receive partial compensation according to this schedule:

Compensation schedule	
Screening	$50
Baseline	$50
Day 4	$300
Day 5	$100
Day 6	$50
Day 13	$50
Day 14	$300
Day 15	$100
Day 19	$300
Day 20	$100
Day 22	$50
Day 34	$50
Total	**$1500**

If you are unable to finish the study, you will receive compensation for the parts you completed. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year.

NEW FINDINGS

New information may become available that could affect your decision to stay in this study. In this case, we will discuss the new information with you.

CONFLICTS OF INTEREST

The National Institutes of Health reviews NIH staff researchers associated with this study at least yearly for conflicts of interest. You may ask your research team for additional information or for a copy of the "Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH". This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Guide but are not required to report their personal financial holdings to the NIH.

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

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

We will ask you to provide your social security number in order to compensate you. You can withhold your social security number and still participate in the research, however you will not be able to receive compensation.

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 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 Jomy George, PharmD, Building 10, Room 1C240M, Telephone 301-496-2997. 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

Witness to the oral short-form consent process only:

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: _____.