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COMIRB No: **23-1686**
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Study Title: **Prospective Evaluation of Sequencing from antiCD-20 Therapies to Ozanimod**

Key Information:

Please read all the information below and ask questions about anything you don't understand before deciding if you want to take part.

You are being asked to be in a research study. Participation in research is voluntary.

Purpose of this study: The purpose of this study is to learn more about the safety and efficacy of ozanimod, a once daily oral medication, as de-escalation therapy in patients with MS who have been clinically stable for several years on an anti-CD20 therapy.

Procedures: If you agree to participate, the following will happen:
- You will come to the research site for 1-2 visits in the month before you start the ozanimod (the first visit is to see if you are eligible for the study) and then 7 more visits occurring every 3-6 months after you start ozanimod for a total of 36 months. The study team will call you every 6 months to ask about signs and symptoms. Unscheduled visits may occur if determined necessary by the study team.
- Study participation includes taking ozanimod, blood draws for lab work, optical coherence tomography if indicated by study doctor, neurological assessments, MRI, and questionnaires.

Risks: Participation in this study involves risks, including the following:
- Feelings of claustrophobia, flashing light in eyes, warmth and redness of skin during the MRI; pain and bruising from blood draw; boredom from questionnaires and assessments; allergic reaction to study drug (rash, hives, or blisters or more serious difficulty breathing or swelling of the face, mouth, lips, gums, tongue or neck); other risks of the study drug include: common cold, runny nose, sore throat, and reduced white blood cell count (they fight infection), infection in your kidneys, urinary tract or bladder, headache, swelling in legs or hands, changes in liver function, elevation in blood bilirubin level (which may lead to the development of jaundice), high blood pressure, shingles (painful rash), herpes infection, slowing heart rate, decrease in blood pressure on standing, MS relapse, and abnormal breathing test results. See risk section for full list of possible risks.

Benefits: There is no guarantee that your health will improve if you join this study. This study may lead to information that could help patients and health care providers in the future.

Alternatives: You could continue your current treatment, change to a new treatment, or stop treatment. Please discuss standard treatment and care options with your doctor.

Detailed Consent:

Why is this study being done?

This study plans to learn more about how "de-escalation" therapy affects outcomes in patients with relapsing forms of multiple sclerosis (MS). For this study, "de-escalation" means switching from an anti-CD20 treatment (for example rituximab, ocrelizumab, and ofatumumab) to ozanimod (Zeposia®).

You are being asked to be in this research study because you have a relapsing form of MS, have been taking an anti-CD20 treatment for 2 years or more, and your disease activity is stable. Your doctor thinks that de-escalation to ozanimod might be a safe and effective next step in your treatment.

Other people in this study

Up to *16* people from your area will participate in the study.

Up to *24* people around the country will be in the study.

What happens if I join this study?

If you join the study, you will come to the research site for 1-2 visits within the month before you start ozanimod, and 7 more visits every 3-6 months after you start ozanimod.

The schedule of study visits and what will be done at each visit is described below:

Visit	Screening/baseline (<30 days before ozanimod start)	Month 3 (+/- 30 days)	Month 6 (+/- 30 days)	Month 12 (+/- 30 days)	Month 18 (+/- 30 days)	Month 24 (+/- 30 days)	Month 30 (+/- 30 days)	Month 36 (+/- 30 days)
Blood draw for inclusion criteria, safety monitoring, or biomarker evaluation, and biobank sampling^	X	X	X	X	X	X	X	X
Ozanimod dispensed	X (you may be asked to come in for a separate visit for this, if necessary)		X	X	X	X	X	
Electrocradiogram (EKG)	X							
Optical coherence tomography (OCT), if recommended by study doctor	X	X						
Neurological assessments	X		X	X	X	X	X	X
Magnetic resonance imaging (MRI)	X		X		X			X
Questionnaires about symptoms and quality of life	X		X	X	X	X	X	X

^optional biobank samples [option for storing blood in the University of Colorado Biorepository given below]

In addition, the study team will call you every 6 months to ask about symptoms and any signs of relapse, pregnancy, how you are tolerating the drug, and other health changes. If there is concern of a relapse, you

may be asked to come in for an additional unscheduled visit which may include exams, questionnaires, and bloodwork.

Your symptoms and signs of relapse will be monitored by your doctor, and your treatment may be switched or changed if needed. Even if you change treatment, you will be asked to continue to come in for study visits per the above.

Optional Consent for Data and Specimen Banking for Future Research

The study doctor would like to keep some of the blood that is taken during the study but is not used for other tests. If you agree, the samples and your study data will be kept and may be used in future research to learn more about neuropathy and other diseases. The research that is done with your data and samples is not designed to specifically help you. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

The choice to let us keep the data and samples for future research is up to you. No matter what you decide, you can still participate in this research study. If you decide now that your data and samples can be kept for research, you can change your mind and contact your study doctor to let him or her know, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until the study doctor decides to destroy them.

When your data and samples are given to other researchers in the future, we will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and samples are used for genetic research (about diseases that are passed on in families). Even if your data and samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and samples will only be used for research and will not be sold. The research done with your data and samples may help to develop new products in the future, but there is no plan for you to be paid.

We may share data from our research with other researchers or data banks. One such data bank is called dbGAP, which collects genetic and other data and is sponsored by the National Institutes of Health. By broadly sharing data in data banks like this, we can make our discoveries more accessible to other researchers. Information which directly identifies you will not be sent to these data banks.

Because your genetic information is unique to you, there is a small risk that someone could connect the information back to you. Also, genetic research and broadly sharing data may involve risks to you or people like yourself that are unknown at this time.

The possible benefits of research from your data and samples include learning more about what causes diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. We will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage.

Please think about your choice and check “yes” or “no.” If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and samples, you may still take part in the study.

I give my permission for my data and blood to be stored in a central tissue bank at University of Colorado Anschutz Medical campus for future research:

_____ YES _____ NO _____ Initials

What are the possible discomforts or risks?

Discomforts you may experience while in this study include boredom or discomfort while completing the questionnaires and neurological assessments.

MRI
In this study we will take Magnetic Resonance Images (MRI's) of your head. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working. You should NOT have an MRI if you have metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices. The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces. The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes. If you are pregnant, be sure to tell the person giving you the MRI.

Blood Draws
In this study, we will need to get about 6-8 tablespoons of blood from you at each timepoint. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise under the skin.

MS Relapse
Because we are putting you on a medication that lowers your immune system less, you may experience new or worsening of your MS symptoms concerning for a relapse. Please discuss with your study team any new neurological symptoms so that they can be evaluated to determine if a relapse is occurring.

Ozanimod
The study drug, ozanimod, is being studied in people with multiple sclerosis (MS), Crohn's disease (CD) and ulcerative colitis (UC). MS is a chronic disease that can affect your brain, spinal cord, and the optic nerves in your eyes. It can cause problems with vision, balance, muscle control, and other basic body functions. UC and CD are chronic inflammatory disorders of the bowels that can cause diarrhea, rectal bleeding, weight loss, abdominal pain, and fever.

As of 19-May-2023, there are about 6057 people who have received ozanimod in human studies.

There is always a risk involved in taking any drug, but you will be carefully watched for any side effects. There may be risks or side effects that are unknown or cannot be foreseen at this time. You are encouraged to report anything that is bothering you to your study team.

You may ask your study doctor at any time for more information about side effects and other possible risks. Your study doctor may give you medicines to help lessen the side effects. Your study doctor may adjust the study drug to try to reduce side effects. Some side effects go away soon after you stop the study drug. In some cases, side effects can be serious and long lasting. Sometimes they never go away or may cause death.

All medications have a risk of an allergic reaction. In some cases, the reaction could be life- threatening if not treated quickly. Seek immediate medical help if you have any of the following signs of a serious allergic reaction:

trouble breathing or swelling of the face, mouth, lips, gums, tongue, or neck. Other allergic reactions may include rash, hives, or blisters. Tell your study doctor as soon as possible if any of these reactions happen.

Because these medications work by reducing the number of certain cells in your body's immune system called lymphocytes, you may have an increased risk for infections or cancers. Ozanimod treatment may cause vaccines to be less effective. Tell your study doctor right away if you get sick or have an infection.

The side effects associated with ozanimod treatment are listed below.

Very common (occurring in at least 1 out of 10 people):

- Common cold, runny nose and sore throat [nasopharyngitis, respiratory tract infection viral, pharyngitis]
- Reduced blood lymphocyte count (a type of white blood cell that fights infection) [lymphopenia]

Common (occurring in at least 1 out of 100 and less than 1 out of 10 people):

- Urinary tract infection (infection of your kidneys, urinary tract or bladder) [urinary tract infection]
- Headache [headache]
- Swelling of the legs or hands [oedema peripheral]
- Elevations in liver enzymes, abnormal liver function test (changes in your liver functioning) [alanine aminotransferase increased, gamma-glutamyltransferase increased]
- Elevation in blood bilirubin level [blood bilirubin increased]
- High blood pressure [hypertension]
- Painful rash known as shingles [herpes zoster]
- Herpes infection (a viral infection) [herpes simplex]
- Slowing of heart rate [bradycardia]
- Blood pressure decrease on standing [orthostatic hypotension]
- Breathing test results altered [pulmonary function test abnormal]

Uncommon (occurring in at least 1 out of 1,000 and less than 1 out of 100 people):

- Allergic reactions, including skin rash or hives [hypersensitivity (including rash and urticaria)]
- Macular edema (fluid build-up at the back of the eye that may distort vision) [macular oedema]

Rare (occurring in at least 1 out of 10,000 and less than 1 out of 1,000 people)

- Progressive multifocal leukoencephalopathy (PML) is a rare viral disease of the brain caused by inflammation and damage which can cause severe disability or death. It is important that you tell your doctor right away if you have any new or worsening medical problems that last for several days. This can include weakness on one side of the body, clumsiness of the arms and legs, vision problems, speech difficulty, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Other conditions have been observed but it is not known if they are caused by ozanimod.

A case of temporary coma in one patient in a multiple sclerosis study from Posterior Reversible Encephalopathy Syndrome (PRES)]. PRES is a medical condition of the brain with symptoms of severe headache, confusion, seizures and vision loss. Tell your doctor right away if you experience these symptoms. The symptoms of PRES are usually reversible but may lead to blocked blood flow in the brain [ischemic stroke] or bleeding in the brain [cerebral hemorrhage].

Cancers (including breast and skin cancers - uncommon). You should also minimize sun exposure, use appropriate sun protection and monitor your skin for any changes. Tell the study doctor or staff if you have any concerns or skin changes.

One case of an uncontrolled growth of white blood cells or lymphoproliferative disorder was reported in a patient in an ulcerative colitis study.

A case of acute liver failure resulting in liver transplant occurred in a patient with evidence of underlying liver problems in the post-marketing setting. The patient was taking multiple medications and experienced symptoms approximately 10 days after starting ozanimod. Tell your doctor right away if you experience: unexplained nausea, vomiting, stomach area [abdominal] pain, tiredness, loss of appetite, jaundice, or dark colored urine.

In addition, the following side effects have been seen with other medications that work in a similar way to ozanimod:

- Very rare fatal cases of chicken pox in patients with MS treated with other drugs that work like ozanimod in combination with high-dose steroids for treatment of an MS relapse.
- Fungal infections (sometimes serious) were seen with other medications that work like ozanimod.
- Worsening of MS that was severe after stopping drugs that work like ozanimod (disease rebound).

Risks Associated with Pregnancy

The risks to an unborn child or nursing child from ozanimod are not known at this time. Ozanimod should not be taken by pregnant or nursing women.

Studies in animals have shown that ozanimod can harm a fetus, and it is possible the study treatment may harm a nursing child or may cause a miscarriage.

If you are a woman

If you are pregnant, planning to become pregnant, or you are nursing a baby, you should not take part in this study. The study doctor will discuss effective birth control methods with you if you are able to become

pregnant. This is to make sure that you do not become pregnant while in the study. Your chosen form of birth control must be effective by the time you receive your first dose of study drug. For example, birth control pills should be started at least 28 days before your first dose of study drug.

If you can become pregnant,

- pregnancy will be assessed during the study
- you must avoid any sexual activity that may lead to pregnancy or
- you must use one of the approved options for birth control while taking the study drug and for at least 90 days after your last dose of study drug.

Approved options are any one of the following highly effective birth control methods:

- Hormonal contraception (for example, birth control pills, intravaginal ring, transdermal patch, injection, implant);
- intrauterine device (IUD);
- tubal ligation (tying your tubes);
- a partner with a vasectomy; or
- completely avoiding sexual intercourse.

Certain other drugs may reduce the effectiveness of hormonal birth control treatments during and up to 30 days after discontinuation of these concurrent therapies. Please talk to your doctor for further information about birth control treatments.

You must inform the study doctor, if at any time during the study:

- your birth control method changes, or
- you experience a problem with your current birth control method

If your ability to become pregnant changes (for example, you have an IUD removed, accidently miss taking any of your birth control pills, or enter menopause), you must inform and discuss with the study doctor or nurse about other birth control methods.

If you suspect that you have become pregnant during the study or within 90 of the last dose of study drug, you must tell the study doctor right away. Your study doctor must then require you to stop taking the study drug. Your study doctor will want to check on you during the pregnancy and ask you questions about the pregnancy.

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the effects of de-escalation therapy on MS.

This study is not designed to treat any illness or to improve your health.

Are there alternative treatments?

There may be other ways of treating your MS, please discuss this with your treating neurologist; options could include continuing your current treatment, changing to a new treatment or stopping treatment.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study

This research is being sponsored by Bristol Myers Squibb, the manufacturer of ozanimod.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

You will not be charged for the study drug or any of the study procedures or office visits for the study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Alvarez immediately. His phone number is 303-724-2187

In the event of an illness or injury resulting from your participation in this study, you should seek appropriate medical care. However, you and/or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Enrique Alvarez. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Alvarez at 303-724-2187. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Alvarez with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

What happens to data collected in this study?

The data we collect will be used for this study but may also be important for future research. Your data may be used for future research or distributed to other researchers for future study without additional consent if information that identifies you is removed from the data.

Who will see my research information?

The University of Colorado Denver | Anschutz Medical Campus (the University) and its affiliated health systems have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver | Anschutz Medical Campus
- University of Colorado Health

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Enrique Alvarez, MD
12469 E. 17th Ave room 201
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- The Institutional Review Board that is responsible for overseeing this research

- The study doctor and the rest of the study team.
- Bristol Myers Squibb, who is the company paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records

What happens to Data and Blood that are collected in this study?

Scientists at the University and the health systems involved in this study work to find the causes and cures of disease. The data and blood collected from you during this study are important to this study and to future research. If you join this study:

- The data or blood given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data and blood collected from you.
- If data or blood are in a form that identifies you, the University or the health systems involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures (banking of data and samples for future research). You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Participant Signature:_____ Date:_____

Participant Print Name:_____

Consent form explained by:_____ Date:_____

Print Name:_____

----------Use the following only if applicable----------

A signature of a witness is required for consent of non-reading subjects and consent using a short form.

Witness of Signature ☐

Witness of consent process ☐

Witness Signature: _____ Date:_____

Print Name:_____