VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	**Optimizing Stage 2 T1DM Management: Assessing the Impact of GLP-1Ra on Metabolic Outcomes in Patients Receiving Teplizumab**
Version Date:	**February 5, 2024**
PI:	**Justin M. Gregory, M.D., M.S.C.I.**

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:

Thank you for considering joining our research study. We are studying a type of medication called glucagon-like peptide-1 receptor agonists (GLP-1Ras) to see if it can help people with a type of diabetes called stage 2 Type 1 Diabetes Mellitus (T1DM). Patients in our study will receive or have already received a treatment called teplizumab (TZIELD®). Normally, GLP-1Ras are used to treat type 2 diabetes, but we think they may also help people with stage 2 T1DM.

These drugs may make your blood sugar levels better and could also improve your blood vessel health. By joining our study, you could help us learn more about how to treat T1DM better. If these drugs help, people with stage 2 T1DM may not need to take insulin as soon.

If you decide to join, you will need to visit our research center two or three times. If you have already received TZIELD®, you will have two post-TZIELD® visits. If you have not yet received TZIELD®, you will have one pre-TZIELD® and two post-TZIELD® visits. Each visit will last about five hours. At these visits, you will undergo a mixed meal tolerance test (MMTT). This test involves drinking a protein shake provided by us. We will then draw blood at various times to check your blood sugar levels to see how your body responds. There are also some rules we will ask you to follow. For example, you might have to stop taking certain medications, not eat before a visit, or follow a special diet for a few days before each visit.

The drug we are studying is called semaglutide (Rybelsus ®), a type of GLP-1Ra. This drug is already approved by the FDA for treating type 2 diabetes in adults, but not yet for type 1 diabetes. We will give you this drug one time. You will receive this drug before one of the two post-TZIELD® MMTTs. Before the other post-TZIELD® MMTT, you will receive a placebo (a pill or capsule that has no drug and does not do anything). The first of these two post- TZIELD® studies

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will occur three to five months after receiving TZIELD®. These two studies will occur approximately one to two months apart from each other. You will receive Rybelsus ® or placebo before the MMTTs in random order. Some participants may also have an additional pre-TZIELD® MMTT.

After receiving Rybelsus ®, some people may feel sick, vomit, or have diarrhea. A serious but rare side effect is a disease called pancreatitis. We will watch your health closely throughout the study to ensure your safety.

You do not have to pay anything to be part of this study. We will cover all the costs of treatments and tests that are part of this study. You can decide not to join or leave the study at any time without it affecting your regular healthcare. We are here to answer any questions. Thank you for considering joining our research study!

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have stage 2 Type 1 Diabetes Mellitus (T1DM) and have received or will be receiving a treatment called TZIELD®. We are researching a way to make managing your type of diabetes easier and possibly improve overall health in people with stage 2 T1DM. There are two problems we want to investigate, which is the body making less and less insulin, a hormone needed to manage blood sugar, and the body producing too much glucagon, a hormone that raises blood sugar levels.

We are using a type of medicine called GLP-1Ras, which has shown promise in addressing both of these issues. However, there is much we still do not know about how this medicine works in people with your type of diabetes. It is possible that this medicine might help your body better control blood sugar levels and improve the health of your blood vessels. By doing so, it might make it easier to manage diabetes, possibly delay the need for taking insulin, and lead to better health outcomes. But, to find all this out, we need people like you to take part in our study.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some

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research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

Venipuncture and placement of IV: the placement of a small tube into a vein for drawing blood can cause bruising, bleeding, discomfort, and infection. Sometimes people may feel nauseous, lightheaded, or even faint during this procedure. We will attempt to lessen these possibilities by cleaning the skin and having you lie down or sit during this procedure.

Risk of loss of confidentiality: our study team believes our participants are entitled to privacy and confidentiality. Blood and tissue samples taken during the study will not use your name. Instead, a specific participant code will be used that does not reveal your identity. Only the study team will be able to link your identity to the study code.

Common side effects (>10% of people) from Rybelsus ®**:** These are the side effects that many people who use Rybelsus ®experience. However, because you will only receive a single, low dose, these effects are less likely and if they do occur, they are unlikely to persist.

- Nausea
- Vomiting
- Diarrhea

Common side effects (>10% of people) from nitroglycerin: We will use a medicine called nitroglycerin when we measure your blood vessel health. Nitroglycerin is routinely given before measuring blood vessels in the body. Nitroglycerin causes a decrease in blood pressure. When blood pressure decreases, people commonly feel the following symptoms:

- Headache
- Lightheadedness
- Dizziness

Although these symptoms are common, they usually go away within five minutes. To decrease the symptoms of low blood pressure, we will only give nitroglycerin after making sure your blood pressure is not already low.

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Common side effects from acetaminophen (Tylenol)

- Nausea
- Vomiting
- Stomach pain
- Loss of appetite
- Constipation

Uncommon side effects (<10% of people) from Rybelsus ®: These side effects do not happen to everyone and are less common, particularly with a single dose.

- Headache
- Indigestion or heartburn: This might happen because Rybelsus ®slows down how quickly food moves through your stomach.

Rare side effects (<1% of people) from Rybelsus ®: These side effects are very rare, but they can be serious.

- Pancreatitis: Pancreatitis, or inflammation of the pancreas, is a serious but rare side effect. Signs include severe stomach pain that might move to your back, along with nausea and vomiting. You should get emergency medical help if you have these symptoms.
- Gallbladder problems: GLP-1 Ra therapy has been associated with increased risk of gallbladder and biliary diseases including cholelithiasis and cholecystitis. Symptoms of this may include upper stomach pain, fever, clay-colored stools, and jaundice (yellowing of the skin or eyes).
- Kidney problems: In very rare cases, Rybelsus ®can affect your kidneys. This is more likely if you already have kidney disease.
- Severe allergic reactions: Symptoms might include a rash, itching, trouble breathing, or swelling of the face, lips, tongue, or throat.

If you take part in this study, we will watch you closely for any side effects. If we learn anything new about the side effects of Rybelsus ®during the study, we will let you know.

Risks that are not known:

Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

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Other Risks:

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only the Principal Investigator and a limited number of key study personnel working in the laboratory will have access to your name and study samples.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Good effects that might result from this study:

The benefits to science and humankind that might result from this study:

Your participation in this study may contribute to scientific research on early-stage Type 1 Diabetes Mellitus (T1DM), known as stage 2 T1DM. Your involvement could help researchers better understand the potential benefits of a class of drugs called GLP-1 receptor agonists (GLP-1Ras) in managing this specific stage of T1DM.

At this stage of diabetes, effective interventions could slow down disease progression and potentially delay the need for insulin injections. One of these potential interventions is the use of GLP-1Ras, which has shown promise in managing blood sugar levels and improving the health of blood vessels.

However, our understanding of these drugs in the context of stage 2 T1DM is limited. This study will help us discover how GLP-1Ras work in people with early-stage T1DM and whether they can delay the need for insulin therapy. This knowledge could improve treatment strategies, making the management of diabetes easier and less intrusive for these individuals in the future.

Procedures to be followed:

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1. **First Visit:** The first time you come in, we will administer an MMTT. This test involves you drinking a protein shake and a dose of liquid Tylenol. Then, we will take several blood samples to see how your body processes the shake. We will also measure the amount of Tylenol in the blood to see how quickly your body digests the shake. This will happen before you receive a 14-day infusion of TZIELD® from your endocrinologist's office. Before the MMTT you will receive a placebo.

   In some cases, participants who have already received teplizumab (TZIELD®) may not have this first visit. They will begin this study with the "second and third visits" described below.

2. **Second and Third Visits:** Three to five months of receiving teplizumab, you will come back for two more visits. You will repeat the MMTT during these visits. However, in addition, we will also give you either the medicine called GLP-1Ra or a placebo. We will not know which one you are getting, and you will not know either. This is to make sure the test is fair.

3. **Getting Ready for the Visits:** To make our tests as accurate as possible, we will ask you to do certain things before each visit. This includes avoiding hard exercise, eating a diet with a normal amount of calories for three days, and following a special diet the day before each visit. You will also need to avoid certain things like vitamins, certain pain medicines, caffeine, vigorous exercise, and smoking.

4. **What Happens at Each Visit:** During each visit, a nurse will place a small tube in your vein (IV). We will take several blood samples before and after you drink the shake. Depending on the visit, as previously described, you will either get the GLP-1Ra medicine or the placebo.

   Additionally, we will do a test called Flow Mediated Dilation (FMD). This test lets us look at the blood flow in your arm. We use a small blood pressure cuff to temporarily stop the blood flow for five minutes and then we use a machine to measure the size of an artery in your arm.

5. **HLA haplotyping:** During the first study, we will examine certain genes called the human leukocyte antigen (HLA) genes. These genes play a role in the immune system. These specific genes influence how the body responds to various diseases and treatments. You are being asked to provide a blood sample for genetic research that will include HLA haplotyping. HLA haplotyping is a type of genetic test that helps us understand the unique make-up for your immune system. This information can provide

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insights into how your body might react to certain treatments. What we learn from this HLA haplotyping test will not be put in your health record. We will not release these results to anyone outside of the research.

Payments for your time spent taking part in this study or expenses:

The study will compensate you for your participation. We will ask for your social security number and address before the compensation forms are processed. You will be mailed a check equal to the dollar amount below.

- Study visits: the study will compensate participants $125 for each of three completed mixed-meal tolerance test studies. These studies will each last approximately five hours.

You are not allowed to accept any money for taking part in this study if you are not eligible to receive money from a U.S. person or company or the U.S. government because of U.S. national security and/or foreign policy laws. You can still take part in the study; however, you will not be paid if you are a resident of a country restricted by the U.S. government's comprehensive territorial sanctions or if you are listed on the U.S. Treasury Department's Office of Foreign Assets Control's Specially Designated Nationals (SDN) list of prohibited individuals. You do not have to say why you choose not to be paid.

Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Justin Gregory, M.D., M.S.C.I. at (615) 322-7427. If you cannot reach the research staff, please page the study doctor at (615) 835-9612.

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For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:

While we want everyone to finish the study, there are some reasons why the study doctor might need to take you out of the study early. Here is what they are:

1. **Your Health Changes:** If your health gets worse or if you get a new health problem, the study doctor may decide it is safer for you to stop the study. This could be because the new health problem affects the results of the study, or because it is not safe for you to stay in the study.

2. **You are Not Following the Study Rules:** It is very important to follow the study rules. These rules help us to keep you safe and to make sure our study results are accurate. If you do not follow these rules, like not taking the study medicine or not coming in for your visits, the study doctor may take you out of the study.

3. **The Study is Stopped:** Sometimes, studies are stopped early. This could be because the study medicine is not working, because of safety issues, or for other reasons. If this happens, the study doctor will take you out of the study.

4. **Pregnancy:** If you become pregnant during the study, the study doctor will take you out of the study. This is because we do not know how the study medicine might affect a baby.

What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:

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

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Confidentiality:

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Only research associates in our laboratory or individuals directly involved in the study will have access to data or protected health information. Blood samples will be stored in our locked freezers for an indefinite amount of time. Samples will be coded with a unique identifier. This unique identifier can only be linked to patient identity through a secure database. Research records and data with personal identifiers will be stored in our locked offices or on a secure data collection program (REDCap). Only the study doctor and key personnel on the research team will be able to access study patients' names or other identifying data. Data from the study will be maintained in HIPAA-compliant, password-protected databases. Urine samples from the pregnancy test will be immediately discarded.

Privacy:

Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us, or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

At any time, you may ask to have your sample destroyed. You should contact the study team at metabolism@vumc.org to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample, such as

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those from previously completed study visits. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Study Results:

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use, or share the information?

The people who may request, receive, or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

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Do you have to sign this Authorization?

You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?

You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

Consent for Genetic Research

One goal of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. We will not release these results to anyone outside of the research.

A single vial of blood will be obtained and used for this test.

Blood samples – You may feel bothered or pained from the needle stick. You may have a bruise, or the site may get infected. It is rare, but some people faint.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples.

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To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Justin Gregory and key study personnel will have access to your name.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Your sample will be used to make DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for gene research

At any time, you may ask to have your sample destroyed. You should contact Dr. Justin Gregory at (615-322-7427) to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for gene research in this study.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research in diabetes.

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☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research for other health problems (such as cancer, heart disease, etc.).

☐ Yes ☐ No

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Patient/Volunteer Name

_____
Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Printed Name and Title

_____
Signature

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