Participant Name:_____Date:_____

Title of Study: Sodium-glucose transporter 2 inhibitor use in prediabetes: initial evaluation in Veterans

Principal Investigator: Beth Greck, PharmD VA Facility: Western North Carolina VA Health Care System

KEY SUMMARY INFORMATION ABOUT THIS STUDY

You are invited to take part in a research study funded by Veterans Integrated Services Network Mid-Atlantic (VISN 6). Before you decide, it is important for you to know why the research is being done and what it will involve. This includes any potential risks and benefits for you. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

The goal of this study is to find out if the medication empagliflozin (Jardiance®) can lower blood sugar levels in Veterans with prediabetes. We also want to understand how this medication affects your kidney function and weight.

Your involvement in this research will last approximately 12 weeks (3 months). This research aims to collect information on the safety and effectiveness of empagliflozin (Jardiance®). Empagliflozin (Jardiance®) is approved by the Food and Drug Administration (FDA) for type 2 diabetes, heart failure, and improving kidney function.

It is important to note that in this study, empagliflozin (Jardiance®) is used "off-label" for prediabetes. This means it has not been approved by the FDA for prediabetes. All side effects and complications are not known for people with prediabetes who take this medication. The reason for this study is to see if empagliflozin (Jardiance®) can potentially improve blood sugar levels, kidney function and weight in individuals with prediabetes.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You may want to be part of this study for a few reasons. First, by joining in, you help medical providers learn more about how to treat prediabetes. What is learned from this study could not only help you and your prediabetes but could also help other Veterans. Second, there is a chance the medicine being studied might help your blood sugar, your weight, and/or your kidney function. Third, you'll get regular check-ups as part of the study, which could help you keep a closer eye on your health. Some people might also just be curious about what it's like to be in a study. You help others by helping medical providers learn more about how to treat this condition.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

There could be a few reasons why you might not choose to join this study. First, you might be worried about the side effects of the medicine being tested, since it has not yet been proven to work for people with prediabetes. Second, you might not like the idea of having regular check-ups or tests that require your time. Third, you might be uncomfortable with the idea being in a study and that is perfectly okay. It's a personal decision. Finally, there is a chance you will be assigned to the "control group", the group that receives standard care and does not receive the study medication. Choosing to not participate will not affect any of your VA benefits or healthcare.

If you choose not to join this study, there are still other ways you can help manage your prediabetes. These often include changes to your lifestyle. For instance, eating healthier foods and getting regular exercise can often help. This means less sugar, less processed foods, and more fruits, vegetables, and whole grains. Regular exercise or other physical activities can also help. In some cases, a doctor might also recommend education to help prevent diabetes, in addition to healthy eating and exercise. It is best to discuss these options with your doctor or healthcare provider.

DO YOU HAVE TO TAKE PART IN THE STUDY?

You do not have to take part in this study. If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits, or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Beth Greck, PharmD, BCACP, CDCES, at the Western North Carolina VA Health Care System (Charles George VA Medical Center). If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study, her contact information is (828) 298-7911 ext. 1-5356.

DETAILED INFORMATION ABOUT THE STUDY

WHAT IS THE PURPOSE OF THIS STUDY?

By doing this research project, we hope to learn how empagliflozin (Jardiance®) affects people with prediabetes. Our goal is to learn if this medication can help prediabetes. Sixty Veterans in the WNCVAHCS will be enrolled in this study. Thirty participants will be randomly assigned to one of 2 groups: one group, called the "control" group, or a second group, called the "exposure" group. The study will look at how blood sugar levels, weight, and kidney function are affected in both groups. If you are assigned to the control group, you will receive education, but you will not receive the study medication. The results of the study will help us understand if this medication may be a way to help treat prediabetes.

HOW LONG WILL I BE IN THE STUDY?

If you join the study, your participation will last approximately 3 months. The total length of the study is expected to be about 6 months.

WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

1. Eligibility screening

   The eligibility screening is done by both the study coordinator and the provider in charge of the study n to see if you are eligible to enroll. This will include:

   - Blood draw: 2 tubes of blood will be collected to check your blood glucose, kidney function, and HbA1c (to confirm your diagnosis of prediabetes). If these blood tests were done within 7 days prior to your enrollment, those test results may be used, and a new blood draw may not be necessary.

   - History: A study coordinator will look at your medical history in your health record to make sure you are eligible to enroll in the study. This will include a review of history with empagliflozin or similar medications, diagnosis of prediabetes or diabetes, if you could be or become pregnant, and lab results.

- Medical examination: The provider in charge of the study (called the investigator) will review your labs and history to be sure you meet eligibility for the study. This should be no longer than 30 minutes.

If during this screening process you are found to have a condition that makes you not eligible, you will not be enrolled in this study. However, you will still receive the same level of care from the VHA and will not lose any of the benefits, rights, or services offered by the VHA.

2. Randomization Procedure

- This study is a randomized study that will consist of two groups:
  1) A group taking the medication empagliflozin (Jardiance®), also called the exposure group. Empagliflozin is also known as the "study medication".
  2) A group who will not be taking any medication, also called the control group.

- You will be randomly assigned to a group. The study coordinator or investigator will not decide your group assignment. Your group will be assigned by complete and random chance.

3. Study visits and medication

- Once you complete screening and randomization, including having labs done, you will begin the study. You will receive information about prediabetes and ways to help manage prediabetes, such as diet and exercise.

  If you are randomized into the group that receives the study medication:

  1) You will be given the medication before leaving the visit.

  2) The medication will be prescribed and given to you by the study team during each visit.

  3) You will be asked to bring the study medication to each visit

  4) The study coordinator will also schedule your next visit. This first visit will take 1-2 hours.

If you are randomized into the group that does NOT receive the study medication:

1) You will not receive any study medication at any visit

2) The study coordinator will schedule your next visit. This visit will take 1-2 hours to complete.

- There will be two visits following the first visit: one at 2-4 weeks after the first visit, and the third visit around 12 weeks after the first visit. During each visit the study team will gather study measurements and talk to you about symptoms or side effects. Each visit will last about 1 hour.
- During the study, the study team will monitor you whether you are in the study medication group or the control group. If there is a concern for your safety or health, you can choose to withdraw, or you may be withdrawn by the investigator. This can happen any time in the study, no matter which group you are assigned to. Also, if you miss a visit, you may be withdrawn from the study.

Table 1: The timeline and study measurements

Visit	Weight	Lab Work (Chemistry Panel)	Lab Work (HbA1c)	Blood Pressure	Side Effects Questions	Visit Time
Baseline (first visit)	X	X	X	X		1.5 – 2 hours
2-4 weeks after first visit	X	X		X	X	1 hour
12 weeks after first visit	X	X	X	X	X	1 hour

4. Study measurements

While participating in the study, each visit will include a blood draw, and we will record your weight and blood pressure. Also, you will speak with the study coordinator and the

study investigator. You will be asked questions at each visit to see if you have any health changes during your enrollment in the study. If you feel uncomfortable with the blood draw or choose to not have your weight and blood pressure recorded, you may be withdrawn from the study.

WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?

- Take the study medication as you are told by study staff.
- Keep the study medication in a safe place for your use only and away from children.
- Keep your study appointments. If you miss an appointment, please contact the research staff to reschedule as soon as you know you will miss the appointment.
- Complete all study-related labs.
- Ask questions as you think of them.
- While in this study, do not join any other research study without talking to the investigator. This is to protect you from possible injury from things such as extra blood work, extra testing, or possible medication interactions. Joining other research studies without first talking to the investigator of this study may affect the results of this study.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any procedure or medication has possible risks, discomforts, or side effects. The procedures or medication in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Because the study medication is not approved by the FDA for prediabetes, it is “off label” when taken without a diabetes diagnosis. While the FDA has approved this medication for treating diabetes, there may be side effects or risks associated with this medication in people with prediabetes.

The safe use of empagliflozin in pregnant women and nursing mothers is not known so there may be risks to you (or to your embryo or fetus) if you are or may become pregnant. Women who are pregnant or may become pregnant will not be enrolled in this study. Women are considered of childbearing potential unless they have been surgically sterilized (for example tubal ligation or hysterectomy) or are post-menopausal, that is, no menstrual period for more than 6 months. Nursing mothers will not be enrolled in this study.

If you have a medical emergency, please call 9-1-1. If you have an injury or become sick because of being in this study, the Department of Veterans Affairs (VA) will make sure treatment is made available at a VA y or non-VA hospital, if needed. If you were following study instructions, the costs of such treatment will be paid by the VA. If you were NOT following study instructions, the costs of treatment may be covered by the VA or you or your insurance may have to pay, just like other medical costs, depending on several factors. The VA and a study sponsor do not usually give any other type of payment for injury or illness. For more information about this, call the study team at the phone number(s) given to you.

There is always a chance that any procedure can harm you. The procedures in this study are no different. You may experience a previously unknown risk or side effect that is not listed above.

1. Medication Risks

If you are part of the study medication group, you may be at risk of experiencing side effects. These can be minor such as a headache to more serious side effects such as risk of hospitalization or death. During the study, the study team will be monitoring you and will be available by phone between visits if you have side effects that are possibly due to the medication. The following potential side effects are based on reported side effects in people with type 2 diabetes taking the medication (empagliflozin).

Common risks: In approximately 1,000 people, 5 to 10 people may experience these risks: urinary tract infection, genital mycotic infection (yeast infection) in females.

Less common risks: In approximately 1,000 people, 1 to 4 people may experience these risks: increased thirst, increased urination, respiratory tract infection, genital mycotic infections in males, changes in cholesterol, nausea, joint pain.

Rare but serious risks: angioedema (swelling of face/neck), necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis (blood infection), hypoglycemia (low blood sugar)

2. Blood Draw Risk

The risks of drawing blood include bruising or infection at the site of infection, temporary faintness, possible loss of consciousness due to a fall in blood pressure, commonly called a "vasovagal episode".

3. Privacy Risk

Also, there is a possible risk of health care information being seen by a person who does not have permission. This is called a breach of confidentially and while rare, could be possibly serious. Steps are taken to reduce this risk to the best of our ability and is described below.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this research consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

Your information, including your blood results, that is collected as part of the study, will not be used for future research studies even if your identifying information is removed. Your blood will not used for any type of genome sequencing (looking at your DNA).

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

We do not know if you will get any benefits from taking part in this research study. However, possible benefits may include:

- lower blood sugar (glucose) levels
- lower HbA1c level
- decreased weight
- improvement in kidney function
- lower blood pressure

Additionally, the results of this study will be used to provide more information on the effectiveness of the study medication in prediabetes and possibly the prevention of type 2 diabetes. This information may help you and other Veterans with prediabetes in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

If you decide to not participate in this study, your primary care provider may suggest other things to treat prediabetes. These may be changes to improve your diet, increase your physical activity, and lose weight. Your provider may suggest you join a class or visit with a dietician to help with these changes. There are no FDA approved medications to treat prediabetes.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

During this study, all information related to the study including your diagnosis, lab results and health information will be stored on secure VA computer servers and in your VA electronic medical record. Also, identifying information such as social security number, age, race, sex, gender, and date of birth will be collected and stored the same way.

If you do not feel comfortable giving information such as your social security number, you will not be able to enroll in the study. This information is critical for enrollment and viewing medical records.

The research team and medical staff will make every effort to keep your participation and information confidential. All information will be kept in locked cabinets within a locked office. All digital information of your medical records will be kept in an encrypted system managed by the VA information technology department which has several ways to keep the information secure.

Once you join the study, you will be assigned a random code so that your measurements and results will be linked to the code rather than your name. This will ensure that anyone reading this information besides the study team will not be able to connect you to your information.

The study team will put a note in your medical record to tell others you are in a study and so that they do not prescribe medications during your study participation that might affect the results. This is not to prevent prescribing of any medication in times of emergency. Medications will still be available to you if a health provider sees it is needed. There may be times your records may be shown to other people such as Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, the Food and Drug Administration (FDA), or other members of the research team that help with management or storage of information that may identify you.

There may be times when we have to provide information without your permission. For example, if information about child, or elder abuse or neglect is given to us, this information will be reported to the authorities.

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

The results of the study will not be given directly to you or the other participants. However, you may view the website above for a summary of results when they are available. You can request

your own study results, such as lab results, the same way you would to see results that are part of your usual care at the VA.

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You and your insurance will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study. If you participate in this study and are assigned the group receiving study medication, you will not pay for this medication. If you have insurance for medications, other than the VA, that company will also not be charged for this medication. Participation in this study is completely voluntary. There will be no payment to you for your participation in this study.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

If you are injured because of taking part in this study, the VA will provide necessary medical treatment at no cost to you or your insurance unless the injury is due to you not following study procedures or instructions.

If you have a medical concern or get hurt or sick because of taking part in this study, call:

DURING THE DAY:

Dr./Mr./Ms. _____ at _____ and

AFTER HOURS:

Dr. /Mr./Ms._____ at _____._____

Emergency Room _____

If there is an emergency, please contact or go to the local VA medical center emergency room. The Charles George VA Medical Center's emergency room number is 828-298-7911. Otherwise go to the local nearest emergency room.

DO I HAVE TO TAKE PART IN THE STUDY?

Participation in this study is voluntary. If you do not want to take part in the study, your normal VA healthcare or access to VA services will not be affected in any way. You will not be

penalized for not participating in this study if choose not to enroll. If you are an employee or student of the VA, choosing to not participate will not affect your employment or career related to the VA.

If you have family within the VA, or family that relies on care within the hospital, your choice to not participate, or to withdraw at any time, will not affect their care.

You may stop participation in the study at any moment for any reason. The research team will not pressure you to participate nor will anyone within the VA make you participate. If you decide to stop the study, your care will not change, and you will continue to have full access to VA services.

If you decide to stop participation in the study, you may do so by contacting the study coordinator of the research team at extension (828)298-7911 extension 1-5230. They will confirm your choice to leave the study and will make no attempts to pressure you to stay. Once they have confirmed you are no longer participating in the study, a note will be made in your study file.

Any information collected before you leave or withdraw from the study will be stored in secure locations. Any blood samples collected cannot be withdrawn. We will not collect any further information from you after you leave the study. You may contact the study team at any time afterwards for questions about your time in the study, but you cannot join the study again.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

The investigator or study coordinator may end your participation in the study for any reason without your consent. Situations that may cause this include but are not limited to:

- Worsening health condition during study participation
- Unable to tolerate the study medication or experience medication adverse event (if in the medication group)
- Missing study visits in the required time frame
- Unable to take the study medication correctly and consistently
- Diagnosis of diabetes

If you are no longer in the study, your care will not be affected, and you will still have access to all VA care facilities.

Participant Name:_____Date:_____

Title of Study: Sodium-glucose transporter 2 inhibitor use in prediabetes: initial evaluation in Veterans

Principal Investigator: Beth Greck, PharmD VA Facility: Western North Carolina VA Health Care System

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may call the Institutional Review Board (IRB) at the Charles George VA Medical Center at (828) 298-7911 extension 1-2102. This is the Board that is responsible for the safety of Veterans participating in research studies. You may call the Committee Coordinator, extension 1-2102, if you have questions, complaints, or concerns about the study or if you would like information or to give input.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Sometimes during a research study, new information becomes available about the study medication that might change a person's decision to stay in the study. If this happens, the study staff will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your study staff will arrange for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form. The study staff could also decide it is in your best interest to withdraw you from the study. If so, they will explain the reasons and arrange for your usual medical care to continue.

If, during the study, any of your blood test results show important information related to your health and wellbeing, you will be told as soon as possible by the study team. If they feel these results are concerning or do not feel like it is medically safe for you to participate, you may be withdrawn from the study. Also, if you feel concerned after the results of the tests, you may speak to any member of the study team and/or you may choose to stop participation in the study. Your medical care will not be affected if you choose to leave the study at any given time.

If you have any questions concerning information given to you during the study, you may contact the study team to ask those questions. You will also get a copy of the consent forms with signatures at the end of the first visit.

WHO COULD PROFIT FROM THE STUDY RESULTS?

This study is funded by a career award grant that allows for the money to be spent on this research study following the rules of the VHA and local committee (IRB, EOC (Environment of Care), and Research & Development (R&D)) guidelines. The investigator and staff receive no financial benefit from the results of this study.

Participant Name:_____Date:_____

Title of Study: Sodium-glucose transporter 2 inhibitor use in prediabetes: initial evaluation in Veterans

Principal Investigator: Beth Greck, PharmD VA Facility: Western North Carolina VA Health Care System

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms._____ _____ has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record.

I agree to participate in this research study as has been explained in this form.

FOR IRB USE ONLY

PI/SC Approval Date:
CGVAMC IRB 8/27/2024

Participant Name:_____Date:_____

Title of Study: Sodium-glucose transporter 2 inhibitor use in prediabetes: initial evaluation in Veterans

Principal Investigator: Beth Greck, PharmD VA Facility: Western North Carolina VA Health Care System

Participant's Name (Print)	Participant's Signature	Date of Signature
Name of Person Conducting the Consent Discussion (Print)	Signature of Person Conducting the Consent Discussion	Date of Signature

FOR IRB USE ONLY

PI/SC Approval Date:
CGVAMC IRB 8/27/2024