Official Title: Study of Nasal Insulin to Fight Forgetfulness - Combination Intranasal Insulin and Empagliflozin Trial

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Wake Forest®
School of Medicine

Department/Section of Internal Medicine – Gerontology & Geriatric Medicine

"STUDY OF NASAL INSULIN TO FIGHT FORGETFULNESS (SNIFF) – COMBINATION INTRANASAL INSULIN AND EMPAGLIFLOZIN"

Informed Consent Form to Participate in Research

Suzanne Craft, PhD – Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research study is to determine the effects of Empagliflozin (brand name JARDIANCE®) in combination with an intra-nasal (in the nose) insulin administered with the Aptar CPS device in adults with mild memory impairment or early-stage Alzheimer's disease compared to placebo. The use of Empagliflozin or in combination with intranasal insulin has not received approval from the Food and Drug Administration (FDA) for how it will be used in this study.

You are invited to be in this study because you have expressed an interest in participating in a research study. Your participation in this research may involve up to 6 in-person visits and 1 telephone visit, which will last about 30 minutes to 3 hours each over the next 8 weeks.

Participation in this study will involve using a device to administer insulin or placebo through your nose in combination with taking a 10 milligram (mg) capsule by mouth of Empagliflozin or placebo. All research studies involve some risks. Some risks to this study that you should be aware of are a drippy nose, urinary tract infections, increased urination, volume depletion (extracellular fluid volume reduction), and genital yeast infections, especially in females.

You are not expected to benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. Some other choices may include not participating in this study and continuing to follow up with your doctor. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Suzanne Craft, PhD. If you have questions, suggestions, or concerns regarding this study or want to withdraw from the study, her contact information is [redacted].

If you have any questions, suggestions, or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have mild memory impairment or early-stage Alzheimer's disease. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to find out what effects (good and bad) the study medications (insulin administered as a spray in the nose four times daily and Empagliflozin capsules taken by mouth once daily) have by themselves or in combination with each other on adults with mild memory impairment or early Alzheimer's disease compared to placebo.

Placebo is a substance that is not thought to have any effect on your disease or condition. Placebos are used in research studies to see if the drug being studied really does have an effect. For the placebos, this study will use fluid used to dilute insulin (diluent) and a cellulose capsule containing no active ingredients.

Insulin is a hormone that is produced in the body. It works by lowering levels of glucose (sugar) in the blood. We also know that it may have beneficial effects on the brain and on memory. Empagliflozin, sold under the brand name JARDIANCE®, is commonly used together with diet and exercise to treat Type 2 diabetes. Insulin and Empagliflozin are both approved by the US Food and Drug Administration (FDA). However, using them separately or together to treat mild memory impairment or early Alzheimer's disease is experimental. In addition, the use of insulin administered intra-nasally using the Aptar CPS device is also experimental but has been previously used in research here at Wake Forest Baptist Medical Center to administer insulin intra-nasally.

During this study, we will determine the effects of the study treatments on memory, blood, and cerebrospinal fluid biomarkers. Spinal fluid is a clear, colorless fluid that protects your brain and spinal cord.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 60 people will take part in this research study here at Wake Forest Baptist Medical Center. In order to identify the 60 subjects needed, we may need to screen as many as 120 people because some will not qualify to be included in the study.

WHAT IS INVOLVED IN THE STUDY?

Your participation in this research study will involve coming to the Sticht Center for Healthy Aging and Alzheimer's Prevention at Wake Forest Baptist Medical Center up to 6 times over the next 8 weeks. During this time, you will complete the series of measurements and procedures listed below. More details about these measurements and procedures will be provided in the next section of this consent form. If you have had an evaluation with the Sticht Center within the last 3 to 12 months, you may not need to repeat certain procedures, and you may require only 5 visits. During your visits, you will be asked to:

- Give blood samples (up to 4 times)
- Have vital signs (blood pressure, heart rate, and temperature) and weight taken (up to 6 times)
- Have a physical exam (up to 1 time)
- Have a nasal exam (up to 5 times)
- Take tests of memory/thinking and answer questions about your daily activities (up to 5 times)
- Undergo a lumbar puncture (LP) (2 times)
- Have an electrocardiogram (ECG) (up to 1 time)
- Undergo a Magnetic Resonance Imaging (MRI) scan (up to 2 times)
- In-home sleep assessments (2 times)
- Continuous glucose monitoring (CGM) assessment (2 times)

You will be also be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have a one in four chance of being placed in any of the following groups:

Study Group 1: INI + EMPA Placebo	• 40 IU of intra-nasal insulin administered using the Aptar CPS device 30 minutes prior to eating and 30 minutes before bedtime for a total of four (4) times daily • Placebo capsules taken by mouth 30 minutes before breakfast once daily
Study Group 2: EMPA + INI Placebo	• Empagliflozin 10 mg capsules taken by mouth 30 minutes before breakfast once daily • 40 IU of intra-nasal insulin diluent (placebo) administered using the Aptar CPS device 30 minutes prior to eating and 30 minutes before bedtime for a total of four (4) times daily
Study Group 3: INI + EMPA	• 40 IU of intra-nasal insulin administered using the Aptar CPS device 30 minutes prior to eating and 30 minutes before bedtime for a total of four (4) times daily • Empagliflozin 10 mg capsules taken by mouth 30 minutes before breakfast once daily

Study Group 4: Placebo	• 40 IU of intra-nasal insulin diluent (placebo) administered using the Aptar CPS device 30 minutes prior to eating and 30 minutes before bedtime for a total of four (4) times daily • Placebo capsules taken by mouth 30 minutes before breakfast once daily

Neither you nor the investigator will know which study treatment you are receiving. This is done so that a fair evaluation of results can be made. In addition, this information is available to the researchers if needed in an emergency.

As a part of the study, we can provide you with the ECG and blood test results, which you may give to your physician. These tests can reveal more information about your heart, blood sugar, cholesterol levels, liver function, and kidney function. We will advise you to consult with your physician if your tests suggest that you have a medical problem.

DESCRIPTION OF STUDY VISITS

If you have participated in a research study with the Alzheimer's Disease Research Center (ADRC) at Wake Forest Baptist Medical Center within the last 3 to 12 months, you may not have to repeat all of the study procedures. Data used during the completion of the previous study will be used to avoid duplicating those procedures.

You will be asked to fast (no food or drinks except water) for 8 hours prior to 3 visits during your participation in this study.

During your participation, we may need to request medical records from your primary care doctor. Therefore, we will ask you to sign a medical records release form giving us permission to request these records if needed.

Study visits include the following:

SCREENING VISIT 1

This visit will last between 1 and 2 hours. You will be asked to fast (no food or drinks except water) for 8 hours prior to this visit. Once you complete the blood collection at this visit, you will receive a snack before we begin any other study activities. After a review of this consent form, you will have the opportunity to ask questions about this study. After your questions have been answered, you will be asked to sign this consent form.

If this information has not previously been collected within the past 12 months, we will complete the following:

DEMOGRAPHICS: At your first screening visit, we will ask you basic questions about yourself, such as your age, occupation, and level of education.

MEDICAL HISTORY: We will ask you questions about your general medical history, including questions about your family history of Alzheimer's disease and any current problems. At future visits, we will ask you about anything that might have happened during the time between visits, such as a change in your health, any injury or illness, or any reactions to the study drugs or procedures.

MEDICATION HISTORY: We will collect a list of your past and current medications. The study investigator must be told about any medications, vitamins, and/or herbal substances that you take or any medication that you may plan to start taking during the study. If any of these change during the course of your participation, you should tell the study investigators, ideally before the changes are made.

VITAL SIGNS/HEIGHT/WEIGHT: Your vital signs (blood pressure, heart rate, and temperature), height, and weight will be recorded.

PHYSICAL, NEUROLOGICAL AND NASAL EXAMS: A brief physical, neurological and nasal exam will be performed. These are similar to what you receive during a routine checkup with your family doctor/clinician.

ELECTROCARDIOGRAM (ECG): An ECG will be used to measure the electrical signals from your heart. If specific abnormalities of the electrical function of your heart are detected, you may not be able to participate in the study. You may have mild irritation, slight redness, or itching at the sites on your skin where the recording patches are placed.

MEMORY AND THINKING TESTS: You will be given various memory and thinking tests, most of which include remembering information, naming and drawing pictures, connecting symbols, and other similar tasks. You can skip any questions you do not want to answer and take breaks as needed.

BLOOD COLLECTION: Approximately 2 ½ teaspoons of blood will be drawn from a vein for routine laboratory tests to ensure that no other medical conditions might interfere with your participation. In the event any of your lab results fall just outside of the required range, you may be asked to return to the clinic for a repeat blood collection. A portion of your blood sample will also be stored for future research. In order to participate in this study, you must be willing to provide samples for future research. This is discussed in more detail later in the "Future Research & Storage of Biological Samples" section of this consent form.

About 1 teaspoon of blood will be drawn for DNA storage and to determine your apolipoprotein (ApoE) genotype. Previous studies have shown that the ApoE gene may be linked to how well some people do on memory tests **and** can also identify volunteers who may have an increased risk of developing Alzheimer's disease (AD). However, this test alone does not predict who will or will not develop AD as there are many other factors involved. The ApoE test is for research

purposes only; you will not receive the results, and they will not become part of your medical record.

VISIT 2 (BASELINE)

This visit will take approximately 2 hours to complete.

We will review your current medications and any changes in your health since your last visit. The following procedures will also be performed during this visit:

VITAL SIGNS/WEIGHT: Your vital signs (blood pressure, heart rate, and temperature) and weight will be recorded.

NASAL EXAMINATION: A brief exam of your nose will take place.

STUDY DEVICE TRAINING: The Aptar CPS device will be used in this study to administer the insulin or placebo intra-nasally (in the nose). This device is investigational and has not been approved by the FDA to administer intra-nasal insulin. However, this device has been previously used in research here at Wake Forest Baptist Medical Center to administer insulin intra-nasally.

During this visit, you will be given instructions and training on how to administer the insulin or placebo (diluent) using the Aptar CPS device. During your first week of using the device, you will be given a sample of saline to use with the Aptar CPS device for training. You will also be trained by the study team on how to record your use of the device.

MEMORY AND THINKING TESTS: You will be given various memory and thinking tests, most of which include remembering information, naming and drawing pictures, connecting symbols, and other similar tasks. You can skip any questions you do not want to answer and take breaks as needed.

QUESTIONNAIRES: We will ask you questions about your daily functioning and behavior. Some of these questions can be sensitive, such as whether you have been experiencing feelings of depression, thoughts of taking your own life, or have recently harmed yourself. If you are found to have thoughts of harming yourself, a study doctor will talk with you to determine the best course of action. You can skip any questions that you do not want to answer, and you can take breaks if needed.

IN-HOME SLEEP ASSESSMENT: You will be asked to complete an in-home sleep assessment using a wearable device called the Empatica E4. You will be given instructions and training on how to use the Empatica E4 device at this visit. The Empatica E4 is a non-invasive device that is worn around your wrist like a watch. This test will monitor your breathing, pulse rate, and activity or movement throughout the night. A study team member will give you a call the night of your sleep test to review how to use the device and the morning after with a reminder to complete the Post-Empatica E4 questionnaires.

CONTINUOUS GLUCOSE MONITORING: You will have a continuous glucose (blood sugar) monitoring (CGM) device called the Libre Freestyle Pro placed on the back of your upper arm by the study team at this visit. A CGM device measures the glucose level in the fluid under the skin. It consists of a sensor, a transmitter attached to the sensor, and a display device. The sensor is a disposable piece that attaches to the skin. It has a tiny filament on the bottom that reads the sugar in the body tissue just underneath the skin. It is about the size of a quarter. Every 15 minutes, the transmitter sends your glucose readings to the display device. The display device stores the readings.

BLOOD COLLECTION: Approximately 3 teaspoons of blood will be drawn from a vein during your participation. Your blood will be used for routine laboratory tests and stored for future research.

MAGNETIC RESONANCE IMAGING (MRI) SCAN: You will undergo an MRI scan (unless you have had one done in the past 3 months). An MRI scanner uses a large magnet and computer equipment to take electronic pictures of your brain. You will lie on your back and enter the MRI machine for the scan, during which time you will hear loud knocking noises as the magnet does its work. People with pacemakers, aneurysm clips, cochlear implants, or metal/foreign objects in their eyes are not permitted to undergo brain MRI studies. During the scan, you must remain as still as possible. Every effort will be made to make you as comfortable as possible during your scan. Each brain MRI will last about 1 hour.

VISIT 3 (BASELINE)

This visit will take approximately 2 hours to complete and will occur 1 week after Visit 2. You will be asked to fast (no food or drinks except water) for 8 hours prior to this visit.

We will review your current medications and any changes in your health since your last visit. The following procedures will also be performed during this visit:

VITAL SIGNS/WEIGHT: Your vital signs (blood pressure, heart rate, and temperature) and weight will be recorded.

CONTINUOUS GLUCOSE MONITORING: The Libre Freestyle Pro will be removed at this visit.

IN-HOME SLEEP ASSESSMENT: The Empatica E4 and sleep questionnaires will be collected.

INSULIN/PLACEBO: You will receive either insulin or placebo to be administered with the Aptar CPS device. However, <u>everyone will receive a dose of insulin (40 International Units) and not placebo at this visit, including those participants who have been randomized to other treatment groups.</u>

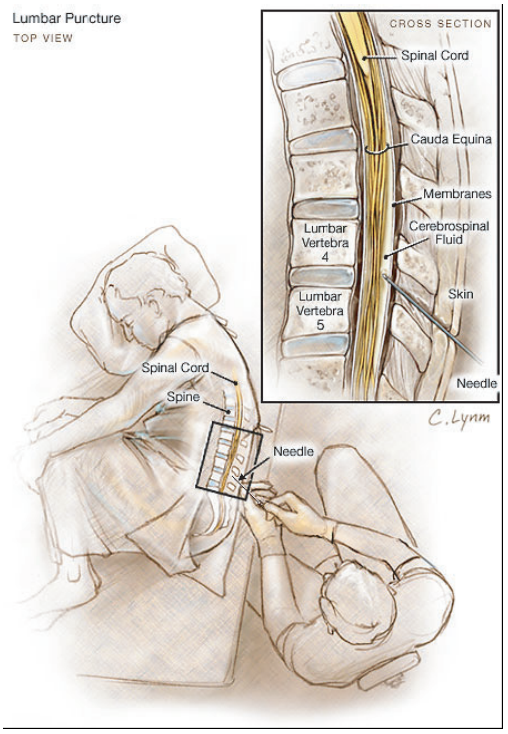
The study team will also go over any issues you may have encountered using the device and

answer any questions that you may have about the device.

EMPAGLIFLOZIN/PLACEBO: You will receive Empagliflozin or placebo capsules during this visit and will be given instructions and training on how to take Empagliflozin or placebo capsules. You will also be trained by the study team on how to record your use of the medication.

BLOOD COLLECTION: Approximately 3 teaspoons of blood will be drawn from a vein during your participation. Your blood will be used for routine laboratory tests and stored for future research.

LUMBAR PUNCTURE (LP): An LP is a procedure in which a small amount of the fluid surrounding the brain and spinal cord is removed from the lower back. You will be asked not to eat or drink anything other than water for at least 8 hours before the lumbar puncture visit. However, because you will need to be well hydrated, please drink plenty of water. You will be positioned sitting up and bent forward or lying on your side, and your lower back will be cleaned with antiseptic. Local anesthetic (lidocaine, 1%) will be injected into the skin of your lower back. When the area is numb, a very thin needle will be inserted into the spinal canal in the lower back, well below the level where the spinal cord ends. About 25 milliliters (less than 2 tablespoons) of cerebrospinal fluid (CSF) will be removed. Your body replaces this spinal fluid within 1-2 hours.



During your LP, a sample of CSF will be obtained (10 milliliters or about half a tablespoon). You will then receive a dose (40 International Units) of insulin with the Aptar CPS device. Two more CSF samples will be taken, totaling about 15 milliliters (about 1 and ½ tablespoons).

After the LP is complete, you will remain in the clinic while resting quietly for about half an hour. You will be given something to eat and drink, and detailed instructions on self-care after the LP will be provided. Specifically, you will be asked to avoid any strenuous physical activity for 24 hours. Study staff will call you the following day to see how you are.

VISIT 4 (RE-SUPPLY)

This visit will take approximately one hour to complete.

We will review your current medications and any changes in your health since your last visit. In addition, the following procedures will also be performed during this visit:

VITAL SIGNS/WEIGHT: Your vital signs (blood pressure, heart rate, and temperature) and weight will be recorded.

INSULIN/PLACEBO: During this visit, the Aptar CPS Device and any remaining insulin or placebo will be collected and reviewed with you, as well as your device use logs. You will receive new vials of either insulin or placebo to be administered with the Aptar CPS device.

EMPAGLIFLOZIN/PLACEBO: During this visit, any remaining Empagliflozin or placebo will be collected, as well as your study drug use logs. You will receive Empagliflozin or placebo capsules during this visit and will review the instructions and on how to take Empagliflozin or placebo capsules and record your use of the medication in the provided logs.

VISIT 5 (POST-TREATMENT)

This visit will take approximately 2 hours to complete.

We will review your current medications and any changes in your health since your last visit. In addition, the following procedures will also be performed during this visit:

VITAL SIGNS/WEIGHT: Your vital signs (blood pressure, heart rate, and temperature) and weight will be recorded.

NASAL EXAMINATION: A brief exam of your nose will take place.

MEMORY AND THINKING TESTS: You will be given various memory and thinking tests, most of which include remembering information, naming and drawing pictures, connecting symbols, and other similar tasks. You can skip any questions you do not want to answer and take breaks as needed.

QUESTIONNAIRES: We will ask you questions about your daily functioning and behavior. Some of these questions can be sensitive, such as whether you have been experiencing feelings of depression, thoughts of taking your own life, or have recently harmed yourself. If you are found to have thoughts of harming yourself, a study doctor will talk with you to determine the best course of action. You can skip any questions that you do not want to answer, and you can take breaks if needed.

IN-HOME SLEEP ASSESSMENT: You will be asked to complete an in-home sleep assessment using a wearable device called the Empatica E4. You will be given instructions and re-training on how to use the Empatica E4 device at this visit. The Empatica E4 is a non-invasive device that is worn around your wrist like a watch. This test will monitor your breathing, pulse rate, and activity or movement throughout the night. A study team member will give you a call the night of your sleep test to review how to use the device and the morning after with a reminder to complete the Post-Empatica E4 questionnaires.

CONTINUOUS GLUCOSE MONITORING: You will have a continuous glucose (blood sugar) monitoring (CGM) device called the Libre Freestyle Pro placed on your shoulder by the study team at this visit. A CGM device measures the glucose level in the fluid under the skin. It consists of a sensor, a transmitter attached to the sensor, and a display device. The sensor is a disposable piece that attaches to the skin and has a tiny filament on the bottom that reads the sugar in the body tissue just underneath the skin. It is about the size of a quarter. Every 15 minutes, the transmitter sends your glucose readings to the display device. The display device stores the readings.

MAGNETIC RESONANCE IMAGING (MRI) SCAN: You will undergo an MRI scan (unless you have had one done in the past 3 months). An MRI scanner uses a large magnet and computer equipment to take electronic pictures of your brain. You will lie on your back and enter the MRI machine for the scan, during which time you will hear loud knocking noises as the magnet does its work. People with pacemakers, aneurysm clips, cochlear implants, or metal/foreign objects in their eyes are not permitted to undergo brain MRI studies. During the scan, you must remain as still as possible. Every effort will be made to make you as comfortable as possible during your scan. Each brain MRI will last from 1 to 1 ½ hours.

VISIT 6 (POST-TREATMENT)

This visit will take approximately 2 hours to complete and will occur 1 week after Visit 5. You will be asked to fast (no food or drinks except water) for 8 hours prior to this visit.

We will review your current medications and any changes in your health since your last visit. In addition, the following procedures will also be performed during this visit:

VITAL SIGNS/WEIGHT: Your vital signs (blood pressure, heart rate, and temperature) and weight will be recorded.

INSULIN/PLACEBO: During this visit, the Aptar CPS Device and any remaining insulin or placebo will be collected, as well as your device use logs.

Everyone will also receive a final dose of insulin (40 International Units) and not placebo at this visit, regardless of what treatment group you were randomized to.

EMPAGLIFLOZIN/PLACEBO: During this visit, any remaining Empagliflozin or placebo will be collected, as well as your study drug use logs.

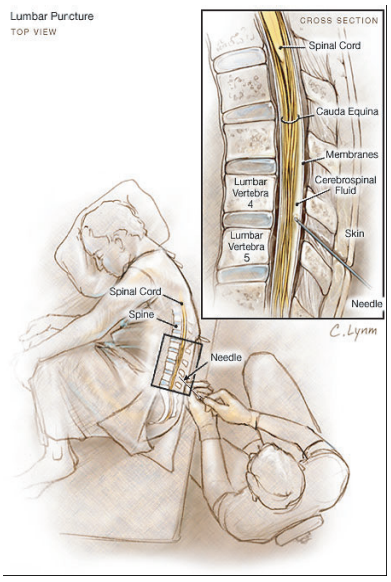
CONTINUOUS GLUCOSE MONITORING: The Libre Freestyle Pro will be removed at this visit.

IN-HOME SLEEP ASSESSMENT: The Empatica E4 and sleep questionnaires will be collected.

BLOOD COLLECTION: Approximately 3 teaspoons of blood will be drawn from a vein during your

participation. Your blood will be used for routine laboratory tests and stored for future research.

LUMBAR PUNCTURE: An LP is a procedure in which a small amount of the fluid surrounding the brain and spinal cord is removed from the lower back. You will be asked not to eat or drink anything other than water for at least 8 hours before the lumbar puncture visit. However, because you will need to be well hydrated, please drink plenty of water. You will be positioned sitting up and bent forward or lying on your side, and your lower back will be cleaned with antiseptic. Local anesthetic (lidocaine, 1%) will be injected into the skin of your lower back. When the area is numb, a very thin needle will be inserted into the spinal canal in the lower back, well below the level where the spinal cord ends. About 25 milliliters (less than 2 tablespoons) of fluid will be removed. Your body replaces this spinal fluid within 1-2 hours.



During your LP, a sample of CSF will be obtained (10 milliliters or about half a tablespoon). You will then receive a dose (40 International Units) of insulin with the Aptar CPS device. Two more CSF samples will be taken, totaling about 15 milliliters (about 1 and ½ tablespoons).

After the LP is complete, you will remain in the clinic while resting quietly for about half an hour. You will be given something to eat and drink, and detailed instructions on self-care after the LP will be provided. Specifically, you will be asked to avoid any strenuous physical activity for 24 hours. Study staff will call you the following day to see how you are.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about 2 months. You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. There are no known risks associated with receiving the study placebo. Risks and side effects related to your participation in this study are outlined below:

NASAL INSULIN ADMINISTRATION

No serious adverse reactions to insulin given through the nasal passages have been observed in similar studies. Insulin given in this manner has not been associated with low blood sugar in our previous studies.

A few participants in previous studies complained of “drippy nose” after being given the study drug. Still, these symptoms did not persist beyond the initial use of the study drug. As

with any medication, there may be unexpected side effects that we are not aware of.

RISKS ASSOCIATED WITH THE USE OF THE NASAL DEVICE

Some risks may occur from the use of the nasal device. However, these are not expected to be serious. You will be shown how to use the device by study personnel present during its use. Risks may include discomfort to your eyes, face, and/or nose. These risks are not long-lasting and will subside without medical treatment.

RISKS ASSOCIATED WITH EMPAGLIFLOZIN

The most common side effects of Empagliflozin are urinary tract infections, increased urination, volume depletion (extracellular fluid volume reduction), and genital yeast infections, especially in females.

Other rare but serious side effects associated with the use of Empagliflozin are ketoacidosis (increased ketones in your blood or urine) and low blood pressure. Ketoacidosis has occurred in a subset of people who had Type 1 or Type 2 diabetes during treatment with Empagliflozin. Low blood pressure has happened in people with low systolic blood pressure or those who are taking diuretics or fluid pills.

RISKS ASSOCIATED WITH COMBINED USE OF INSULIN AND EMPAGLIFLOZIN

The combined therapy of insulin and Empagliflozin was associated with rare but increased risk of ketoacidosis (increased ketones in your blood or urine) in a subset of Type 2 diabetic patients who had reduced insulin secretory capacity. Low levels of blood sugar (hypoglycemia) have also been noted with combined administration.

BLOOD COLLECTION

Removal of blood by a needle and syringe poses a small risk of pain or bruising at the needle stick site, but this is temporary. Some people may experience fainting or dizziness, and there is also a slight risk of infection at the needle stick site. To minimize these risks, experienced medical personnel will collect all blood, and sterile conditions will be maintained. About 10 teaspoons of blood will be taken during the entire course of this study, and your body will readily produce new blood to make up for the loss.

MEMORY AND THINKING TESTS

Memory tests may be slightly frustrating or produce fatigue and boredom.

QUESTIONNAIRES

Psychological questionnaires may cause some individuals to become anxious, upset, frustrated, or tired. Therefore, you have the right to refuse to answer any questions and may ask to stop testing at any time for any reason.

LUMBAR PUNCTURE (LP)

During and after the procedure, you may have temporary pain or discomfort at the insertion site in your back. You may feel faint. You may experience a mild headache, backache, or sore muscles in your neck from the positioning required for the procedure.
Rarely, a low-pressure headache may develop after the procedure due to leakage of spinal fluid. If this headache persists, it may require additional treatment. Uncommonly a blood patch may be required. To create a blood patch, a small amount of your blood will be injected between the lumbar vertebrae in the epidural space of your spinal canal near the site of the previous LP. As the blood clots, it forms a "patch" that seals the site and stops the spinal fluid leak. This typically relieves the headache immediately. Because we use a very small, specialized needle in our study, the possibility of a low-pressure headache after an LP occurs in about 1-4% of participants.

Although very rare, it is possible that you may have an allergic reaction to the local anesthetic (lidocaine 1 %) used for the LP. This would cause swelling and a rash on your skin where the anesthetic was injected. Please tell us if you had ever had a reaction to a local anesthetic before (such as when you were visiting the dentist). Potential but very rare risks of an LP include infection of the skin or in the spinal fluid space (meningitis), bleeding, or damage to nerves in your back. The risk of these is very small. To minimize these risks, the LP procedure will be performed by experienced medical professionals who are specifically trained to carry out this procedure.

BRAIN MAGNETIC RESONANCE IMAGING (MRI)

There are no known biological risks associated with a brain MRI scan. However, an MRI scan may cause anxiety for some people due to the loud noises made by the machine and the confined space of the testing scanner. There is also a risk of injury if a metal is brought into the imaging room, which might be pulled into the MRI magnet. People with pacemakers, aneurysm clips, artificial heart valves, ear implants, or metal/foreign objects in their eyes are not permitted to have an MRI. You will be asked to complete an MRI screening form to identify these objects before each scan to ensure your safety.

CONTINUOUS GLUCOSE MONITORING (CGM)

Potential risks from using a CGM include:

- Discomfort when the sensor is inserted into the skin (common)
- Itchiness, redness, bleeding, and bruising at the insertion site (unlikely to rare)
- Tape allergies (rare)
- Infection at the site of sensor insertion (rare)

IN-HOME SLEEP ASSESSMENT

Rarely, skin irritation may occur in reaction to the wristband or sensors.

LOSS OF PRIVACY

There is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure, and allowing only authorized people to access research records, will be made to keep your information safe.

OTHER POTENTIAL RISKS

There also may be other side effects that we cannot predict. You should tell the research staff about all the drugs, vitamins, supplements you take, and any medical conditions you have. This may help avoid side effects, interactions, and other risks.

FUTURE RESEARCH & STORAGE OF BIOLOGICAL SAMPLES

If you agree to participate in this study, blood and spinal fluid will be stored and used for future research to learn more about other diseases. Your samples will be obtained in the Sticht Center at Wake Forest Baptist Medical Center. The samples will be stored at Wake Forest Baptist Medical Center. Your samples may be shared with other researchers. Your samples will be given only to researchers approved by Suzanne Craft, PhD. An Institutional Review Board (IRB) must also approve any future research study using your tissue sample. In order to participate in this study, you must be willing to provide samples for future research.

The National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genetic studies, especially when the research looks at all or large sections of an individual's genetic code. This is often called whole-genome sequencing. Genomic information relates to the structure and function of all of the genetic material in the body. These central banks will store your genetic information and give them to other qualified and approved researchers to do more studies. The data that we share with federal repositories will be coded in such a way that you would not be able to be identified. For example, we will not share your name, birth date, or any other information that could directly identify you. The link to the code would be kept securely at Wake Forest Baptist Health. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

We do not think that there will be further risks to your privacy and confidentiality by sharing your genetic information with these banks. However, we cannot predict how genetic information will be used in the future. The genetic data could be used to study a wide variety of diseases.

Your blood and spinal fluid samples will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of

commercial value. There are no plans to share any of the profits with you, which may occur due to the research.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There is no benefit to you from participating in this study. The study results will be used to guide the development of future studies of intranasal insulin as a therapy for Alzheimer's disease and memory loss.

WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. You may choose not to participate.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All study costs, including any study drugs and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive $50 each for completing baseline visits 1 and 2 and post-treatment visits 1 and 2, for a total of $200.

To receive payment, you must provide your social security number, name, and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS, we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information, you can still participate in this study, but you will not be paid.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the Alzheimer's Association. The sponsor is providing money or other support to the researchers to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure, and allowing only authorized people to access research records, will be made to keep your information safe. We will do our best to protect your confidential information.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. Some of the information we will collect for this research study includes:

- demographic information
- social security number (required in order to receive payment)
- emergency contact information
- medical record release form (required if we need to request your medical records)

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or

recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.
You can tell Dr. Suzanne Craft that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Dr. Suzanne Craft
Wake Forest School of Medicine
Alzheimer's Disease Research Center
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study. By signing this form, you give us permission to use your Protected Health Information for this study.

A description of this clinical trial will be available on http://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.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be due to unexpected reactions to the study drug, failing to follow instructions or if the study is stopped early.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year.

The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated does not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Suzanne Craft, PhD at [redacted] (after hours number [redacted], ask for the Geriatrician on call and reference the SNIFF study).

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

PARTICIPANT STATEMENT OF CONSENT

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Do you request that we send important medical findings from your study ECG and/or laboratory tests to your personal physician?

[ ] Yes [ ] No _____Initials

Participant Name (Printed):_____

Participant Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm

Legally Authorized Representative Name (Print):_____

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify health care power of attorney, spouse, parent, etc.)

_____
Relationship to the Participant

_____ _____am pm
Signature of the Legally Authorized Representative Date/Time

PARTICIPANT STATEMENT OF ASSENT – IF APPLICABLE

The study has been explained to me and I have had the opportunity to ask all of my questions. I understand that it is my choice to be in the study and that no one will be upset with me if I say "No". By signing below, I agree to participate in this study.

_____
Name of Participant (Print)

_____ _____am pm
Signature of Participant (as able) Date/Time

Legally Authorized Representative Name (Print):_____

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify health care power of attorney, spouse, parent, etc.)

_____
Relationship to the Participant

_____ _____am pm
Signature of the Legally Authorized Representative Date/Time

Statement of Person Conducting Assent Discussion:

- I have explained all aspects of the research to the subject to the best of his or her ability to understand and information provided was given in language that was understandable.
- I have answered all questions so far of the subject relating to this research.
- The subject agrees to this research.
- I believe the subject's decision to enroll is voluntary.
- The study doctor and study staff agrees to respect the subject's physical and emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

_____
Name of Person Conducting Assent Discussion (Print)

_____ _____am pm
Signature of Person Conducting Assent Discussion Date/Time