THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

The GW Medical Faculty Associates

Informed Consent for Participation in a Research Study

IMPACT OF SEMAGLUTIDE (LONG-ACTING GLP1 AGONIST) ON PERIPHERAL BLOOD DERIVED CD34+ ENDOTHELIAL PROGENITOR CELLS (EPCS) AND SUBCUTANEOUS FAT DERIVED MESENCHYMAL STROMAL CELLS (MSCS) IN TYPE 2 DIABETES SUBJECTS

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Informed Consent for Participation in a Research Study

Key Information:

You are being asked to take part in a research study about a special sort of cells called Endothelial Cells. This page will give you key information to help you decide whether or not you want to participate in this study. More detailed information can be found on the next pages. Ask the research team questions during the consent process, and use the contact information on this form to ask questions later.

COVID19 Addendum: *If you are uncomfortable with coming on site to take part in his study we will offer a virtual format. The study visit will be done via zoom. The study drugs will be shipped to your home address and a mobile phlebotomist will meet you at your residency to collect blood and urine sample.*

WHAT IS THE PURPOSE, PROCEDURES, AND DURATION OF THIS STUDY?

By doing this study, we hope to learn whether the drug semaglutide will improve your overall cardiovascular health by increasing the number of a special cells in your body called Endothelial progenitor Cells. Endothelial cells protect the inner lining of your blood vessel and this medication might help them survive in the high sugar environment of diabetes. Your participation in this research will last about 8 months.

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

By being in this study your diabetes might improve, you might lose some weight and the overall health of your blood vessels might get better. For a complete description of benefits please refer to the Detailed Consent.

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

There are few medication side effects such as nausea, vomiting, diarrhea, constipation and abdominal pain. You might also not be comfortable with a required collection of fat tissue sample from your belly area. This study also involves blood draw. For a complete description of risks please refer to the details below.

DO YOU HAVE TO TAKE PART IN THIS STUDY?

You do not have to take part in this research. It is your choice whether or not you want to take part. You can agree to take part and later change your mind. If you choose not to take part or choose to stop taking part at any time, there will be no penalty to you or loss of benefits to which you are otherwise entitled.

WHAT IF YOU HAVE QUESTIONS OR CONCERNS?

The person in charge of this study is Dr. Saby Sen. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study you can contact Dr. Sen at 202 994 8560.

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to them at 202-994-2715 or via email at ohrirb@gwu.edu if:

- You have questions, concerns, or complaints that are not being answered by the research team or if you wish to talk to someone independent of the research team.
- You have questions about your rights as a research subject.

Informed Consent for Participation in a Research Study

Detailed Consent Form:

COVID19 Addendum: *If you are uncomfortable with coming on site to take part in his study we will offer a virtual format. The study visit will be done via zoom. The study drugs will be shipped to your home address and a mobile phlebotomist will meet you at your residency to collect blood and urine sample.*

Why am I being invited to take part in a research study?

You have been invited to participate in a research study. You are being asked to take part in this research study because you: 1) have type 2 diabetes 2) are taking only metformin as anti-diabetic therapy 3) diabetes is not under control 4) do not have any disease of the heart vessels but you do have some risk factors to it. We will be enrolling male and female subjects who are 30-70 years old.

What should I know about a research study?

- Someone will explain this research study to you. You may ask all the questions you want before you decide whether to participate.
- Participation is voluntary; whether or not you take part is up to you.
- You can agree to take part and later change your mind.
- Your decision not to take part or to stop your participation will not be held against you.
- Your decision will not affect the medical care you receive from GW. If you decide not to take part, you can still receive medical care from GW.
- You may take this document home to read or to discuss with your family members or doctor before deciding to take part in this research study.

ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. 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 website at any time.

Who can I talk to if I have questions?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the Principal Investigator, Dr. Sabyasachi Sen at *202 994 8560 or email at* **ssen1@gwu.edu.**

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to them at 202-994-2715 or via email at ohrirb@gwu.edu if:

- You have questions, concerns, or complaints that are not being answered by the research team or if you wish to talk to someone independent of the research team.
- You have questions about your rights as a research subject.

Informed Consent for Participation in a Research Study

Why is this research being done?

Type 2 diabetes is a national epidemic. Diabetes has undesirable effects on blood vessels which may contribute to heart disease. The inner lining of your blood vessels are protected by a type of special cells called Endothelial Cells. They form a barrier so your blood doesn't touch the inner part of the body. Those endothelial cells form from another type of cells called endothelial progenitor cells. Endothelial Progenitor Cells (EPCs) are found in the blood. These cells die when they are exposed to high sugar environment. Research has shown that improving the survival of these special cells, by reducing sugar in the body, may decrease the harmful effects of diabetes on blood vessels and reduce or reverse heart disease. Semaglutide is an FDA (Food and Drug Administration) approved prescription medicine used along with oral medications to lower blood sugar in people with Type 2 diabetes. Other than improving the survivability of the special EPC cells it might also reduce inflammation in the fat cells of your body which would mean weight loss something this medication is already known to do.

The medication we will be using in this research is called, Semaglutide, it is already FDA approved for diabetes and we will be using it to control your diabetes as well. It is **once a week injection**, which comes in a pen form like some of the commercially available insulin. This drug is not insulin.

This is a placebo controlled study, which means there is a 50% chance you will get a placebo, which will also be like the pen injection, but without the actual medication in it. The placebo will contain saline only. If you are taking the placebo medications, it is as if you are taking no medication at all. That's why we will not take you off your metformin because we want your blood sugar to be under control. This study will have 4 visits total. The screening visit, Visit 1 at week 0, Visit 2 at Week 8 and Visit 3 at week 24.

If you decide to take part in this study, your diabetes might get better if you are in the treatment group of this study, also you might lose some weight. It is also possible you will get no direct benefit from this study, but the data we will collect will be used to further our understanding of science. If you decide that you will not be taking part in this study, no more procedures will be performed as you withdrew consent.

There will be 4 phone calls made to you to inquire about your wellbeing, as part of this study.

How long will I be in the study?

We expect that you will be in this research study for 32 weeks. There will be 4 visits total, where you will need to travel to The GW Medical Faculty Associates, including the screening visit. There will also be telephone calls as part of this study. Details of the visit schedule is below.

Your participation in this study may be stopped if the study doctor thinks (1) it is in your best interest to stop, (2) if you do not follow the study requirements, or (3) or if the study is stopped for any reason. The study doctor will tell you about new information that might affect your health or could change your decision to be in this study. If this occurs, you may be asked to sign a new consent form.

How many people will take part in this research study?

We expect about 40 people will take part in the entire study. The research is being conducted only at GW Medical Faculty Associates.

What happens if I agree to be in this research?

You have already completed the pre-screening, in which your initial eligibility was determined by the research staff. The first visit of this trial will be a screening visit, where we will determine if you are fully eligible to be part of this research study.

What will be done in the Screening Visit?

- A medical history and physical exam will be performed, to make sure it is safe for you to participate.
- Your heart rate, blood pressure, temperature, weight, height and BMI (Body Mass Index) will be measured
- Lab tests including urine and a blood draw of **22ml (1.5 tablespoons)** will be done to check the following:
    - Complete Blood Count (CBC) and Sedimentation Rate (Infection, anemia, and others)
    - Hemoglobin A1C (HbA1C) (Blood sugar)
    - ALT/AST (Liver function)
    - Lipid Panel (Cholesterol)
    - Blood Urea Nitrogen (BUN) (Kidney function)
    - Electrolytes (Kidney function)
    - Fasting Glucose (Blood sugar)
    - Thyroid Stimulating Hormone (TSH) (Thyroid Function)
- Urine Sample**:**
    - To get a Pregnancy test (if applicable)
    - Micro-albumin / Creatinine Function (Kidney function)

Also you will be asked to not change your current eating habits, including alcohol intakes because we want to see if any weight loss that might happen was caused by the study medication.

If the results of the screening tests show that you are eligible for this study, you will be randomly assigned (randomized) into one of the two study groups by chance. There is a 50% chance you will receive the study medication. We will be doing this because we want to compare the group that would have received the study medications to the ones who will not. The treatment you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get.

Based on everything we gather from the screening visit, you may not be eligible for the study. This may be due to your medical history, current list of medications, laboratory results, vitals, or another reason that, at the discretion of the study doctor, makes you not suitable for the study.

If Eligible, What Will Be Done In Visits 1, 2, and 3?

- Lab tests involving a urine sample and a fasting blood draw of approximately **95 milliliters, (6.5 tablespoons**, less then when giving blood**)** will be done at study Visits 1, 2, and 3. We will use these samples, send out to LabCorp, to check for your diabetes status (sugar levels), kidney function, lipid levels, and more. Some of the blood will be given to our laboratory staff at The George Washington University so they can check the number and function of your EPC
- Vitals: your heart rate, blood pressure, weight and height will be measured
- Your waist and hip circumference measurements will be done.
- Your weight and body composition will be measured with bare feet on the body composition scale. This scale sends a mild electrical current through your body when you step on it. The electrical current is so small that you will not feel it. This is a research related procedure only and is not usually done as part of a physical exam.
- Arterial Stiffness measurements (like a mini ultrasound) of the blood vessels (pulse) in your wrist, neck, and groin area. This is a research related procedure, not routinely done in clinical setting. This procedure will tell us if your blood vessels are elastic or not as elasticity of the vessels are correlated with their health, as hardened vessels are not healthy.
- Fat Biopsy (only in Visit 1 and 3): In order to detect any inflammation in your fatty tissue we will need about 2-3 grams sample of your belly fat. You will lie down on an exam table. Physician performing the biopsy will do a quick abdominal exam followed by application of topical anesthetics. A small incision will be made (less than half an inch), and a biopsy needle will be inserted. Once the needle is in the fatty layer of your belly, a fat sample will be extracted using suction. Then a larger needle will be used to get some more fatty tissue. After this procedure, the incision will be closed using either suture or sterile tape. If suture was used to closed the incision, you will need to be back in a week for suture removal.

The following will happen to everyone in the study (in all groups):

When	What happens
Screening (Week -4)	Today's visit • Consent form, list of current medications, and review of inclusion/exclusion criteria • Screening lab tests: Urine and Blood Draw • Medical history and physical exam • Vital signs (Blood Pressure, Heart Rate, and Temperature)

	• Height, weight, BMI
Study Visit 1: Beginning Treatment (Week 0)	• Randomization: *Get randomly assigned to one of 2 groups* • *Determine if you are experiencing any side effects.* • Vital signs (Blood Pressure, Heart Rate, and Temperature) • Weight/body composition (Tanita Scale), and hip and waist measurements • Fasting Lab work: Urine and Blood • Arterial Stiffness measurements • Subcutaneous Fat Biopsy • Dispense Study medication or placebo. ***Begin taking study medication or placebo at home next day. Week 0 to week 4, take 0.25 mg/week. Week 4 to week 8, take 0.5mg/week.***
Follow Up Phone Call (Week4)	• Adverse Event Assessment
Study Visit 2 (Week 8)	• Vital signs (Blood Pressure, Heart Rate, and Temperature) • *Determine if you are experiencing any side effects.* • Weight/body composition (Tanita Scale), and hip and waist measurements • Fasting Lab work: Urine and Blood • Arterial Stiffness measurements • Return unused study drug and packaging from visit 1 • Compliance Check • Dispense study medication or placebo • ***Continue taking study medication or placebo at home. From Week 8 to week 24, take 1 mg/week.***
Follow Up Phone Call (Week16)	• Adverse Event Assessment
Study Visit 3: End of Treatment (Week 24)	• Vital signs (Blood Pressure, Heart Rate, and Temperature) • *Determine if you are experiencing any side effects.* • Height, weight/body composition (Tanita Scale), and hip and waist measurements • Fasting Lab work: Urine and Blood • Arterial Stiffness measurements • Subcutaneous Fat Biopsy • Return unused study drug and packaging from visit 2 • Compliance Check
Follow up telephone call	• Determine if you are experiencing any side effects after stopping the study medication

(Week 28)	

You might not find out what treatment you received during this study until the whole study has been completed. Which might be few years from when you complete the study.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to take all the study medications on time, and listen to the study staff regarding any instruction. You also have to make sure the Study medications are refrigerated.

What other choices do I have besides taking part in the research?

Instead of being in this research study, your choices may include:1) You could take part in another study 2) You could choose no treatment 3) You could take Semaglutide on your own, not as a part of the research, if prescribed by your Physician.

What happens if I agree to be in research, but later change my mind?

Taking part in this research study is entirely voluntary, and you may decide to leave the study at any time. If you decide to leave the research, please contact the investigator or any study personnel as soon as possible. If you stop being in the research, data already collected will remain part of the study compiled data, but no new information will be collected about you.

Is there any way being in this study could be bad for me?

General Risks: You may experience risks or discomfort as a result of being in this study. As with any research study there may be risks to you that are not known at this time. The known risks are described below.

Blood Draw: This may result in discomfort at the site of the needle entry or bruising at the site. There is also a remote risk of fainting or local infection associated with drawing blood.

Urine collection: You will be asked at some visits to give a urine sample. Some people do not like the idea of providing a urine sample and may experience difficultly with the collection as a result.

Medical Information: You will be asked to provide a medical history. Some participants may find this uncomfortable or embarrassing. We have minimized this risk by making sure people could not have access to your identity other than the research team members. Your information will be locked safe with us, but there is always a chance of data loss.

Tanita Body Composition Scale may cause interference with electrical devices inside your body such as a pacemaker to malfunction.

Subcutaneous fat biopsies: Collection of subcutaneous adipose tissue biopsies may result in pain, bruising, blood pooling inside, infection, and scarring. The procedure will be performed under sterile technique to minimize the chances of infection. Local anesthetic will be used to minimize pain. Ice will be applied to the site immediately after the procedure to limit bruising, swelling and tenderness. After each biopsy, you will be monitored by the study physician. Post-biopsy the incision site will be cleaned and closed with adhesive wound closures and covered with gauze and dressing tape. You will be instructed to report to the study phyisician any changes at the biopsy site including bleeding, redness, pain, puss formation etc.

Study Medication: semaglutide. The following warnings and precautions are listed:

- The most common adverse reactions, reported in ≥ 5% of patients treated with semaglutide, are: Nausea, Vomiting, Diarrhea, Abdominal pain and Constipation.
- Pancreatitis has been reported in clinical trials. If pancreatitis is suspected, study medication will be discontinued immediately.
- Diabetic Retinopathy Complications have been reported in a clinical trial. We will monitor patients with a history of diabetic retinopathy.
- Thyroid C-cell tumors were found in mouse. It is unknown if semaglutide causes C-cell tumors in humans (including MTC).
- Acute Kidney Injury: There have been some reports kidney injury in patients treated with medication similar to this. Kidney function will be checked throughout the study, especially in patients reporting severe abdominal reaction.
- You should not become pregnant while taking Semaglutide as it is not known if Semaglutide can harm your unborn baby. You should stop using Semaglutide 2 months before you plan to become pregnant."

You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

What happens if I believe I am injured because I took part in this study?

The researchers have taken steps to minimize the known or expected risks. In spite of all precautions, you still may experience medical complications or side effects from participating in this study. You should promptly notify the study doctor in the event of any illness or injury as a result of being in the study.

If you believe that you have been injured or have become ill from taking part in this study, you should seek medical treatment from GWU Hospital and/or the GWU MFA or through your physician or treatment center of choice. Care for such injuries will be billed in the ordinary manner to you or your

insurance company, unless your injury is due to a defect in the design or manufacturing error of the study drug or placebo.

Novo Nordisk agrees to pay for reasonable costs of medical care and treatment required if an injury, illness or condition is caused by or derived from a defect in the design or manufacturing error of the study drug or placebo.

You do not waive any liability rights for personal injury by signing this form.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include

- Improvement in diabetes condition
- Improved cardiovascular health and possible decrease in body weight.
- Continual monitoring of their diabetes progression and overall health through standard of care labs.
- Information gained from this research study may help other people with diabetes in the future.

What happens to my information collected for the research?

To the extent allowed by law, we limit your personal information to people who have to review it. We cannot promise complete secrecy. The IRB and other representatives of this organization may inspect and copy your information.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

Federal law requires that hospitals, researchers, and other healthcare providers (like physicians and labs) protect the privacy of health information that identifies you. This kind of information is known as "protected health information" or "PHI." This section tells you your rights about your protected health information in the study. This section also lists who you let use, release, and get your protected health information if you participate in the study. You are free to not allow these uses and releases by not signing this form. If you do that though, you cannot participate in the study.

If you sign this document, you give permission to all health care providers at The GW Medical Faculty Associates (GW MFA) to use or disclose (release) your health information that identifies you for the research study described in this consent form.

The health information that we may use or disclose (release) for this research includes:

- This consent form;
- Demographic information (like your name, address, date of birth, etc.);
- All information from you medical records about your medical history, including historical exams/testing;
- Information obtained from you to be used in the Study as a result of tests or procedures;
- Results of physical examinations
- Laboratory results obtained on specimens collected from you (like blood, urine, tissue);
- Admissions information;
- Health care expenses and health insurance coverage information;
- Questionnaires/surveys you complete;
- Interviews with you conducted by members of the Research Team;
- Other data created or collected during this study.

The health information listed above may be used by and/or disclosed (released) to:

- Researchers and their staff
- Research collaborators participating in this multi-site study at other institutions (Data receiving center(s) responsible for collecting, monitoring and /or analyzing data from all the sites participating in this study);
- GWU Institutional Review Board ("IRB") or its authorized representatives, as well as representatives of the Office of Human Research Protections (OHRP) who may review your records to ensure that your rights as a research subject are protected;
- Accrediting agencies;
- Your health insurer and/or other potential payment source to discuss payment or get paid for services that are not paid for by the research;
- Clinical staff who are not involved in the study who may become involved in your care, if it might be relevant to your care; and
- Other members of the GWU, GWU Hospital or GW MFA workforce who are directly, or indirectly, supporting the research;

The GW MFA are required by law to protect your health information. By signing this document, you authorize The GW MFA to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

You do not have to sign this Authorization, but if you do not, you may not participate in the research study. The GW MFA may not withhold or refuse to treat you based on whether you sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time, except to the extent that The GW MFA has already acted based on this Authorization. If you revoke this Authorization, you will no longer be allowed to participate in the research described in this Authorization. To revoke this Authorization, you must write to:

Sabyasachi Sen, MD, PhD

The George Washington University School of Medicine and Health Sciences

2300 I Street, Ross Hall 450 Washington DC, 20037 ssen1@gwu.edu

202-994-8560

Even if you revoke this Authorization, The GW MFA may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research.

This Authorization does not have an expiration date.

Your health information will be used or disclosed when required by law. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations or interventions.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

Access to your study records will be limited to those who need the information for purposes of this study, as well as your health care providers if they need access to the information. All records will be kept in a secure location and access will be limited to research study personnel.

You generally will not have access to your personal health information related to this research until the study is complete. At the conclusion of the research and at your request, you generally will have access to your health information that The GW MFA maintains in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at The GW MFA to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by The GW MFA. If it is necessary for your care, your health information will be provided to you or your physician.

Are there any costs for participating in this research?

Clinical services provided during a research study are either research-related or related to usual medical care. Research-related services are not the responsibility of you or your insurance. Your medical care at these visits for this study is research-related and you will not have to pay for it.

Will I be paid for my participation in this research?

If you agree to take part in this research study, we will pay you your time and effort. You will receive $50 for Screening Visit, $150 for Visit 1, $50 for Visit 2 and $150 for Visit 3, totaling $400 for the whole trial.

What else do I need to know?

This research is being funded by Novo Nordisk.

Signature Block for Adult

By signing below, you agree that the above information has been explained to you and you have had the opportunity to ask questions. You understand that you may ask questions about any aspect of this research during the course of the study and in the future. Your signature documents your permission to take part in this research. Your signature documents your permission to take part in this research.

_____

Printed name of subject

_____ _____

Signature of subject Date

_____ _____

Signature of person obtaining consent Date and Time