Research Subject Information and Consent Form

Title: **Role of Linagliptin in Improving Renal Failure by Improving CD34+ Cell Number, and Gene Expression in Renal Function Impaired Type 2 Diabetes Patients**

Sponsor: Medical Faculty Associates, George Washington University
Funding Source: Boehringer Ingelheim (BI)

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WHY ARE YOU BEING ASKED TO TAKE PART IN THIS RESEARCH?

You have been invited to participate in a research study. You are being asked to take part in this research study because 1) you have type 2 diabetes 2) mild form of kidney disease 3) taking a stable injectable form of Insulin, stable dose of Metformin, or stable dose of both, and are not taking any other oral diabetic medications 3) have not yet achieved the level of glucose control that is best for you. We will be enrolling male and female subjects who are 30-70 years old.

Whether or not you take part in this study is up to you. If you choose not to participate in the study it will not affect the quality of medical care you will receive. Your academic standing/employment status will not be affected in any way should you choose not to take part or to withdraw at any time.

This form gives you important information. Please read it carefully and ask questions before you make a decision. You may want to talk about this research study with your family, your friends, and your other health care providers. Please take your time. You should not sign this form until all of your questions are answered.

WHY IS THIS RESEARCH STUDY BEING DONE?

Type 2 diabetes is a national epidemic. Diabetes has undesirable effects on blood vessels which may contribute to heart disease. Endothelial Progenitor Cells (EPCs) are found in the blood. Research has shown that improving the survival of these special blood cells may decrease the harmful effects of diabetes on blood vessels and reduce or reverse heart disease. Linagliptin is an FDA (Food and Drug Administration) approved prescription medicine used along with insulin or with oral medications to lower blood sugar in people with Type 2 diabetes. It is in a class of diabetes medication called DPP-4 inhibitors. DPP-4 inhibitors have been shown to increase EPCs in patients with Type 2 diabetes. The

purpose of this research study is to explore the effect of Linagliptin in addition to a stable dose of Insulin, stable dose of Metformin, or stable dose of both in patients diagnosed with type 2 diabetes with creatinine clearance less than 90 and above 29 (or with microalbinuria), on the EPCs. A creatinine clearance is a test that compares the amount of creatinine (a breakdown product from muscle) in your urine to the amount in your blood. This is used to test how well the kidneys are working. In this study, Linagliptin will be compared to placebo used together with Insulin/Metformin/Both (which you are already taking). Linagliptin is a medication in pill form taken once a day. The placebo is a pill that looks like Linagliptin but will have no active ingredients. If you take the placebo medication it will be like taking no medication at all.

HOW IS THIS RESEARCH STUDY BEING FUNDED?

This research is being funded by an Investigator Initiated Independent Study Grant funded by **Boehringer Ingelheim (BI)**, the maker of Linagliptin.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

The research is being conducted only at GWU Medical Faculty Associates. We expect to enroll 40 subjects in this study.

HOW LONG WILL YOU BE IN THIS STUDY?

Your participation in this research study is expected to last for 18 weeks. You will need to visit the research department four (4) times, including the screening visit. Each visit is anticipated to last approximately 90 minutes.

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.

PARTICIPATION IN THIS STUDY IS VOLUNTARY

Taking part in this study is voluntary. You may choose not to take part or to leave the study at any time. Your decision will not affect your relationship with your doctor or with GWU and will not result in any penalty or loss of benefits to which you are otherwise entitled.

You can stop taking part in this study at any time. Tell the study doctor or research coordinator if you are thinking about stopping or have decided to stop. The study doctor may also ask you to have some follow up care or tests done.

WHAT WILL YOU DO IN THIS STUDY?

Screening:

To make sure that you are eligible for this research study you will need to have the following exams, tests, and/or procedures. This process is called "screening". If you had some of these done recently, they may not need to be repeated.

- A medical history and physical exam will be performed, to make sure you don't have anything that could keep you out of the study, such as a heart disease or medical conditions that make it unsafe for you to exercise.
- You will receive exercise counseling by the study coordinator, a registered dietician, or a diabetes educator.

- Your heart rate, blood pressure, temperature, respiratory rate, weight and height will be measured
- Lab tests will be done to check different things in your body. They include:
    - Complete Blood Count(CBC) and Sed 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)
    - Microalbumin/Creatinine Ratio (Kidney function) - URINE
    - Pregnancy test (if applicable) - URINE

If the results of the screening tests show that you are found to be eligible for this study, you will be randomly assigned(randomized)into one of the two study groups by chance (like flipping a coin). You will have an equal chance (50%) of being in either group. Half of the people will get a placebo and half will get the study drug, Linagliptin. The same tests and procedures will happen to both study groups. After the first two weeks of changes to your diet and exercise, you will begin to receive the study medication, either placebo or Linagliptin. Neither you nor the study team can choose or know which group you are in.

If you are accepted into the study you will have the following exams, tests or procedures:

- Lab tests will be done at study Visit 1, 2, and 3 for research purposes. This includes a fasting blood draw, and a urine sample. We will be looking at many things including a check of your blood sugar level called HbA1C, and many other lab tests including cholesterol. **The amount of blood drawn will be approximately 85 milliliters, but may be up to 95 mL for visit 2 and visit 3.**
    - Your heart rate, blood pressure, weight and height will be measured
    - Your waist and hip circumference measurements will be done.
    - Your weight and body fat will be measured with bare feet on the Tanita Body Composition Analyzer 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.
- You will need to do mild to moderate exercise (~150 minutes/week), in order to maintain a healthy life style.
- You will be required to wear an Actigraph for 7 continuous days after visit 1 and 7 continuous days after visit 2. This device is worn on the hip with a belt or clip either under or above your clothing and will measure your activity during the day. You will take it off before you go to bed and put it back on when you wake up. It cannot get wet, so if you bathe or swim during the day, you will need to remove it. This device will help us monitor your level of physical activity. This is a research related procedure. It is not routinely done.
- Vascular flow and wave 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.
- Resting Metabolic Rate (RMR) will be measured using a machine called ReeVu. This is a non-

invasive procedure. You will breathe through a simple mouthpiece and all the exhaled air is collected and analyzed. Because there is a direct relationship between oxygen used and calories burned an accurate measurement of oxygen use is an effective measurement of calories burned. The machine uses a one-way valve in the disposable (MetaBreather) mouthpiece. This draws in fresh room air with each inspiratory breath and eliminates concerns about cross contamination. The disposable mouthpiece is thrown away. This procedure is not routinely done for the care of diabetic patients.

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

When	What happens
Screening (Week -2)	Today's visit (described just before this table) • Consent form, inclusion/exclusion checklist, list of current medications • Screening lab tests, including pregnancy test (if applicable) • History and physical exam • Vital signs (Blood Pressure, Respiratory Rate, Heart Rate, and Temperature) • Height, weight, and hip and waist measurements • Diet and exercise counseling
Study Visit 1 (Week 0)	• Randomization • Vital signs (Blood Pressure, Respiratory Rate, Heart Rate, and Temperature) • Height, weight/body composition (Tanita Scale), and hip and waist measurements • Resting Metabolic Rate measurement using ReeVue device • Dietary advice • Actigraph device given and exercise motivation • Fasting Lab work • Vascular flow and wave measurements • General diabetes education • Begin taking study medication or placebo • Urine Sample from patient
Study Visit 2 (Week 6)	• Vital signs (Blood Pressure, Respiratory Rate, Heart Rate, and Temperature) • Height, weight/body composition (Tanita Scale), and hip and waist measurements • Resting Metabolic Rate measurement using ReeVue device • Dietary advice

	• Actigraph device given and exercise motivation • Fasting Lab work • Vascular flow and wave measurements • General diabetes education • Return unused study drug and packaging • Dispense study medication or placebo • Urine pregnancy test (if applicable) • Urine Sample from patient
Study Visit 3 (Week 12)	• Vital signs (Blood Pressure, Respiratory Rate, Heart Rate, and Temperature) • Height, weight/body composition (Tanita Scale), and hip and waist measurements • Resting Metabolic Rate measurement using ReeVue device • Dietary advice • Actigraph device and exercise motivation • Fasting Lab work • Vascular flow and wave measurements • General diabetes education • Return unused study drug and packaging and Actigraph device • Dispense study medication or placebo • Urine pregnancy test (if applicable) • Urine Sample from patient
Follow up telephone call (Week 16)	• Determine if you are experiencing any side effects after stopping the study medication

OPTIONAL: Urine Exosome Study
As a part of the Linagliptin study, you will be providing a urine sample. This urine will be used for urine pregnancy tests (if applicable), and tests for microalbumin/creatinine ratio. There will be extra urine left over. If you want, you can be a part of a sub-study in which your extra urine will undergo a urine exosome analysis.

Exosomes are bubbles that form from cells, and travel between parts of the body to communicate information. They also are used to get rid of "garbage" in the cell. The information in these bubbles can tell us more about someone's kidney function, and also about how some diseases (such as chronic kidney disease) may be changing.

You have the option at the end of this consent form to either opt in or opt out of this sub-study.
If you opt in, then the excess urine will be used for exosome analysis. There will be no additional compensation provided, and you will not be notified about these results.

If you do not wish to partake in this sub-study then you can simply circle "no" at the end of this consent

form. This will not affect your care or involvement in the Linagliptin study.

WHAT RISKS OR PROBLEMS COULD YOU HAVE BY BEING IN THIS STUDY?

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 know at this time. The known risks are described below.
Having your blood drawn can be uncomfortable and can sometimes cause a bruise. In some people, it can cause fainting. In very rare cases, an infection may occur. Only trained people will draw your blood. Let your doctor or study coordinator know if you have had any problems with blood draws.

The Tanita Body Composition Scale may cause a pacemaker or similar device to malfunction. ***It should not be used by people with pacemakers or other similar devices***. It is important that you tell the study doctor if you have a pacemaker or other similar devices.

Linagliptin is a medication that is on the market now and has FDA approval. However, like all medications it may have side effects or risks from taking it. These risks include:

- Low blood sugar (Hypoglycemia), particularly with taken with insulin or other insulin secreting medications.
- Acute pancreatitis (pain in your stomach area that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. Pancreatitis could be potentially fatal.
- Bullous Pemphigoid, a rare skin condition which involves fluid filled blisters forming on the skin
- Mouth ulceration (like canker sores), or stomatitis (an inflamed mouth)

If you have any of these symptoms you should contact your study doctor or study staff immediately.
In less than 5% patients (taking linagliptin alone or in combination with insulin)

- Upper respiratory tract infection (naso-pharyngitis)
- Diarrhea
- Cough
- Constipation
- Swelling of your ankles (angio-edema), pain in joints (arthralgia), pain in muscles and extremities, which could be severe and disabling.

Allergic reactions
Include: skin rash, itching, flaking or peeling, raised red patches on your skin (hives), swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing, difficulty with swallowing or breathing.

If you have any of these symptoms, stop taking the study medication and contact your doctor or go to the nearest hospital emergency room right away.

General Statement

Tell your study coordinator if you have ever had inflammation of your pancreas (pancreatitis), stones in your gallbladder (gallstones), a history of alcoholism and high blood triglyceride levels.

You need to supply us the entire list of your medications, importantly other diabetes medications. Please mention if you are taking any medication for tuberculosis such as Rifampicin. You should immediately contact your study coordinator if you start any prescription drug or other medication (including over-the-counter drugs and herbal supplements) not prescribed by the study physician-investigator.
You must not be pregnant or breastfeeding, and you should not become pregnant or breastfeed while you are taking the study treatments. You must use an adequate method to avoid pregnancy for the duration of this study. You should immediately contact your study coordinator if there is a change in your method to avoid pregnancy.

Risks to Reproduction, Unborn Babies and Nursing Infants Unforeseeable Risks
There may be unknown risks to you, your unborn baby or nursing infant if you are or become pregnant during this study or are breastfeeding during this study.

Pregnancy
Pregnant subjects are advised to not use Linagliptin. Suitable contraceptives, such as the double barrier method of contraception, are suggested while the female patients of child bearing age are enrolled in this study. Hormonal preparations of contraception should be avoided. Estrogen and progesterone may have an effect on EPCs or mature endothelium or there may be a possible interaction between estrogen preparations and endothelium. If you have any questions about methods of birth control, please discuss them with your study doctor.

Use of a Study-Prohibited Contraceptive Method
You should notify your study physician/ coordinator if hormonal preparations are started as a form of contraception during the course of this study.

Requirements for Pregnancy Testing
During this study you may have a number of pregnancy tests. Pregnancy will be determined on the basis of a urine test.

Occurrence of Pregnancy or Suspected Pregnancy
If you become pregnant, suspect pregnancy or if you missed your period or it is late, or if you have a change in your usual menstrual cycle (e.g., heavier bleeding during your period or bleeding between periods), you should immediately contact your study doctor.

Discontinuation from the Study
Should you become pregnant during this study, you will be immediately withdrawn from the trial or have the investigational product(s) discontinued (as stated in the protocol) and will be referred for obstetric care. The sponsor has not set aside any funds to pay for any aspects of obstetric, child or related care and does not plan to pay for them.

Pregnancy Reporting
In case of a pregnancy, your pregnancy and its outcome will be reported to the study sponsor.

Information for Men with Partners of Childbearing Potential
Linagliptin, as per currently available medical literature does not appear to pose a risk to a woman who

becomes pregnant while her male partner is a study subject, using linagliptin. However, you are asked to inform your study doctor if your partner becomes pregnant while you are enrolled in this clinical trial, and you and your partner will be asked to provide information about the pregnancy outcome. The sponsor has not set aside any funds to pay for any aspects of obstetric, child or related care and does not plan to pay for them.

WILL YOU BENEFIT FROM BEING IN THIS STUDY?

- You may benefit from the nutritional counseling and exercise motivation
- You may have improved cardiovascular health and possibly a decrease in weight and/or blood Pressure
- Your diabetes could improve, stay the same or get worse
- You may not benefit directly but your participation could benefit society. What we learn from this research study may help other people with pre-diabetes or diabetes in the future.

WHAT OPTIONS OTHER THAN THIS STUDY ARE AVAILABLE TO YOU?

If you do not want to be in this study, other treatments may be available to you such as:

- You could take part in another research study
- You could choose to exercise and diet on your own, or with your own doctor
- You could choose no treatment

WILL THERE BE ANY COSTS TO YOU?

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 YOU RECEIVE ANY COMPENSATION?

You will receive $50 per visit to cover your time and expenses such as transportation, parking and babysitting.

You will receive up to $200 for all 4 visits. You will be paid with a VISA gift card (or similar).

WHAT HAPPENS IF YOU HAVE A COMPLICATION?

It is possible that you could have complications or injuries that are directly related to your participation in this study. If this happens, you will be offered medical treatment at the responsibility of yourself or your insurance company. GWU Medical Faculty Associates, GWU, GWU Hospital or the sponsor does not have a program to provide compensation or free medical treatment for research-related injury. You do not lose any of your legal rights by signing this form.

HOW WILL YOUR PRIVACY BE PROTECTED?

We will protect your privacy as a participant in this research study and the confidentiality of your research information. Information obtained from the research will be recorded in a separate file from your Hospital Medical Record and confidentiality will be maintained by assigning you a code number. Your study file will be stored in a secure area in the Clinical Research Division, GWU Medical Faculty Associates. While the study is ongoing, an electronic database of your study data will be kept using

RedCap, which is an online protected database that is stored at Children's National. The information that identifies you will be kept separate from the RedCap database, and will be kept in a password protected excel document (only accessible to the study staff) that is stored on the MFA network. We may be required by law to report some information (for example; certain infectious diseases, suspected abuse) to a state agency for public health or safety reasons.
If we publish information from this research study or use it for teaching, your name will not be used.
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

INFORMATION ABOUT THE PRIVACY OF PROTECTED HEALTH INFORMATION

GWU Medical Faculty Associates, its employees, and its affiliates are required by law to protect the privacy of information that identifies you. If you enroll in this research study, your protected health information (referred to as **PHI** in the rest of this section) may be used and shared with others as explained below.

What PHI will be used and shared with others for this research study?

- Information gathered from your medical records.
- New information created as a result of this study (for example, from study exams, tests, procedures, surveys, etc.).

Why will your PHI be used and shared?

- We need to use and share your PHI in order to conduct this research study, monitor your safety and the safety of the study as a whole, and to ensure that the research meets legal, institution, and accreditation standards.
- We may also need to use and share your information for treatment purposes, payment, or for health care operations.

Who may use and share your PHI?

- The study doctors and the staff helping them conduct the research.
- Other people within GWU Medical Faculty Associates and its affiliates such as those who oversee research, process bills and payments, conduct quality assurance, and provide legal advice.
- Other doctors, medical centers, and research staff taking part in this study as necessary.
- Insurers and their agents as necessary.
- Organizations that accredit hospitals and research programs.
- **Boehringer Ingelheim (BI)**, the funding source of the research study.

In order to check that we are conducting research properly, government agencies may access information that could identify you. For example, the following people/groups may inspect research records:

- The Office of Human Research Protections in the U.S. Department of Health and Human Services.
- State agencies such as the Department of Public Health.
- Other domestic and foreign government agencies if required.
- Representatives of Federal regulatory agencies such as the U.S. Food and Drug Administration (FDA) Once your PHI has been released it may no longer be protected by

federal law.

Can you see your research records?

- You can ask to see your research records but sometimes that can only happen after the research study is completed. If you would like to see your research records please discuss this with your study doctor or call: Sabyasachi Sen, MD at 202-994-8560.

How long will your PHI be used and shared for this research study?

- Since research is an ongoing process, there is no scheduled date at which your PHI will be destroyed.

What if you decide that you no longer want your PHI used or shared for this research study?

- You can withdraw your permission at any time for us to use and share your PHI by contacting your study doctor. We will not be able to take back any information that has already been used or shared. You will not be able to continue in the research study once you withdraw your permission.

If you have any questions about this study, please contact: Dr. Sabyasachi Sen, MD at 202-994-8560 or Fiona Dore at, GWU Medical Faculty Associates, 2150 Pennsylvania Ave NW, Suite 3-325, and Washington, D.C. 20037, e-mail- fdore@mfa.gwu.edu 202-741-2489
If you experience a complication or injury that you believe may be related to this study, please contact Dr. Sabyasachi Sen at 202-994-8560. Indicate you are participating in a research study and suspect you have a complication for which you need to speak directly to Dr. Sen, the Principal Investigator.

If you would like to discuss your rights as a research participant, or wish to speak with someone not directly involved in the study, please contact the George Washington university Office of Human Research at 202-994-2715, this is your representative.

OPTIONAL URINE-EXOSOME SUB STUDY

I would like to partake in the optional urine exosome sub-study. I understand that I do not need to undergo any additional procedures in order to partake, and that it is just my excess urine sample that will be analyzed. I understand that there will be no additional compensation provided, and that I will not get the results from this sub-study.

I would like to participate in the OPTIONAL urine exosome sub-study:

YES _____ (Initials) NO _____ (Initials)

STATEMENT OF VOLUNTARY CONSENT

By signing below, I am volunteering to be in this research study.

Participant's Name (Print): _____

Signature: _____ Date: _____

STUDY REPRESENTATIVE STATEMENT

I have explained the purpose of the research, the study procedures, the possible risks and discomforts, the possible benefits, and have answered all questions to the best of my ability.

Study Representative's Name (Print): _____

Signature: _____

Date: _____ Time: _____