Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

Who is funding this study?

This study is being funded by the National Institutes of Health.

Key Information About This Research Study

Principal Investigator:	Rita Basu, MD Department of Medicine-Division of Endocrinology University of Virginia Health System Fontaine Research Park 560 Ray C Hunt Drive, Room 3108 P.O. Box 800831 Charlottesville, VA 22908-0831 Telephone: 434-924-5183
Sponsor:	National Institutes of Health (NIH)

You are being asked to take part in a research study. You do not have to take part in this study.
You should only agree to take part in this study after reading this consent form and discussing it with the study team.
You may also discuss this with your family, friends, health care providers or others before you make a decision.

What problem is this study trying to solve?

The purpose of this study is to examine the effects of three different diabetes treatments to determine if they improve night-time blood sugars.

Investigators at the University of Virginia have shown in prior research that individuals with type 2 diabetes have higher blood sugar throughout the night than individuals without type 2 diabetes. However, researchers still don't know if this rise in blood sugar can be controlled using medications. The results of this study may

allow researchers to learn how much glucose is made and stored overnight and after a meal and its relationship with medications like metformin, insulin and dorzagliatin.

Why would you want to take part in this study?
You will not be helped by being in this study, but the information gained by doing this study may help others in the future.. The data we gather from you will be shared with you and you can get better insight into your daytime as well as nighttime blood sugar patterns. You can share this data with your primary care physician if you choose to do so after you complete the study, and they can utilize this information to optimize your treatment for type 2 diabetes.

Why would you NOT want to take part in this study?
You might not want to take part in this study because of the risks involved while you are in the study, which include the risk of worsened blood sugar control due to the discontinuation of your antidiabetes medications for a short duration 4-14 days, , the risk of blood drawing, needle sticks, hormone infusions with Food and Drug Administration (FDA) approved medications insulin, glucagon or somatostatin which has been allowed for use by the FDA. If you get randomized to the dorzagliatin medication, you may also get radioactive trace substances of glucose but the smallest possible dose is used which has low risk of harmful effects. Complications such as allergic reactions, infection, bruising, or discomfort at the site of the plastic needle (venipuncture site) are very low and will be decreased by using sterile precautions. You will be required to remain in bed (study 2 and 3) and use a bedpan/bedside commode or have an in and out urinary catheter.

What will I have to do if I take part in this study?
Full details of all the procedures are found later in this form. If you take part in this study, you will

- Agree to discontinue your antidiabetic medication.
- Take the study diabetes medications which are either approved by the (FDA) for treatment of Type 2 diabetes which are metformin, insulin (glargine) also known as Lantus or an investigational medication that the FDA has allowed to be tested for treatment of diabetes called dorzagliatin for up to 8 weeks. This medication can only be used in a research study such as this one and is not approved for the treatment of Type 2 diabetes. It has been proven to be safe and helpful in many prior human studies conducted elsewhere and in the United States (Phase II, III clinical trials).
- Come to the UVA Fontaine Research Park for study visits. Each study visit may last about 15-18 hours. Come for placement of a continuous glucose monitor (CGM) which is a FDA approved device, for monitoring of your blood sugar. This device will be provided free of charge. Alternatively, you can monitor your blood sugar with a glucose meter. If you do not have a glucose meter one will be provided by the study along with glucose test strips at no charge.
- Monitor your blood pressure if you are on dorzagliatin arm of the study as described later in the form.

What is the difference between being in this study and getting usual care?
If you take part in this study, the following things will be done differently than if you do not take part in this study. You will:

- May have placement of a Continuous Glucose Monitor (FDA approved Device to measure glucose).

- Receive stable, nonradioactive or radioactive trace substances of glucose in small amounts.
- Receive either insulin glargine, metformin, or dorzagliatin.

What other treatments may I receive if I decide to not take part in this study?
You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment for management of diabetes even if you choose not to be in this study. You may be prescribed the following treatments by your healthcare provider:

- Lifestyle therapy
- Oral or injectable antidiabetic medications
- Insulin therapy

You are being asked to be in this study, because you have been diagnosed with type 2 diabetes and are a potential subject who matches our inclusion and exclusion criteria for this study.

Up to 45 people will be in this study at UVA.

How long will this study take?

Your part in this study will require study visits over a period of 6-8 weeks. All study procedures will take place at the Clinical Research Unit (CRU) at the UVA Fontaine Research Park

What will happen if you are in the study?

Note: All tests, procedures and assessment discussed in this consent are being done solely for research purposes.

SCREENING (visit will last about 4 hours)

Visit 1 (week 1)

If you agree to be in this study, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period.

You will come to the Clinical Research Unit (CRU) at UVA Fontaine after fasting (nothing but water after midnight the night before).

If you typically take your diabetes medication with food, you will be asked to come to the visit fasting and to bring your morning dose of the diabetes medications with you. We will offer you a small snack to eat after the fasting blood has been drawn and you can take your morning dose of diabetes medications at that time.

During the screening visit, you will have the tests and procedures to make sure you are eligible, and it is safe for you to continue study participation. These include the following:

- Review medical history and medications. There are certain medications you are not able to take during the course of your study participation. The study doctor will review this list with you.

- Review your dietary history.
- Physical Exam, blood pressure, heart rate, temperature, height.
- An electrocardiogram (EKG) if not done in prior 3 months to see the electrical activity of your heart.
- Blood tests (about 1 tablespoon of blood) to check your blood counts, your liver, kidney and your blood sugar.
- Urine sample to assess for urinary glucose.
- Pregnancy test (if you are a female of childbearing age) that must be negative in order to participate.
- Step on a scale to measure total body weight, body fat and lean body weight.

If these tests show you are eligible, you will return to the CRU Fontaine Research Park for the next study visit in approximately two (2) weeks.

You will be asked to withdraw your anti-diabetes medications for 4-14 days prior to the first study visit and to monitor your glucose levels regularly during this period. You will either need to wear a CGM or check finger stick glucoses three times each day including a fasting glucose. The study staff will contact you every 48 hrs during the 2-week withdrawal of medications. If you record ONE value of fasting CGM or fingerstick glucose > 250 mg/dL you will be immediately withdrawn from the study and you will be asked to resume your anti-diabetes medication.

During the next two weeks:

1. You will be asked to refrain from unusual or unaccustomed physical activity during the study period.
2. You will wear a Fitbit (provided by the study) for monitoring of your own activity during the course of your study participation as regular activity will help you maintain your blood sugar and blood pressure better. However, the study will NOT be collecting the Fitbit data.
3. You will also answer some questions related to your daily habitual activity with a questionnaire. You do not have to answer all questions if you are unsure. Participation in the study will not be affected if you do not answer all questions.
4. Dietary advice will be provided by the study doctors to help maintain your body weight during this study. You will be asked about dietary preferences for the meals that you will eat during your study visit. Maintaining a healthy diet will help you manage your blood sugar, blood pressure and levels of fat in your blood.
5. You will be asked to withdraw your anti-diabetic medications for 10-14 days prior to the next study visit and to monitor your glucose levels regularly during this period. You will need to check finger stick glucoses a few times each week. If three successive finger-stick fasting glucose values exceed 250 mg/dl, you will be asked to resume your anti-diabetic medication and be withdrawn from the study.

RANDOMIZATION and STUDY PROCEDURES

You will be randomly assigned to 1 of 3 study groups during the 2 weeks you are off your anti-diabetic medications. You have an equal chance of being assigned to any one of the groups. Neither you nor your study physician can choose to which group you are assigned. **You will receive your allocated treatment for 6-8 weeks after completing the baseline visit(s) and if on metformin or insulin glargine arm a dose titration**

period or study run in phase of 2 weeks. At the end of the run-in phase if your fasting blood glucose does not stabilize to between 70-180 mg/dl you will be withdrawn from further study participation after discussion with study doctor and the study monitoring panel of doctors who are overseeing subject safety (data and safety monitoring board-DSMB).

GROUP 1: Insulin. You will be instructed on self-injecting insulin glargine once-daily in the morning. The dose will be increased by the study team to avoid hypoglycemia and to maintain fasting blood glucose concentrations between 70 to 180 mg/dl**.**

GROUP 2: Metformin. You will start metformin (500 mg tablet twice daily) with meals. After 72 hours and in the absence of side effects, you will increase the dose to 500 mg with breakfast and 1,000 mg with supper. After a further 72 hours and in the absence of side effects, you will increase the dose to 1,000 mg twice daily with meals and continue until the end of the trial. The dose will be adjusted by the study team to maintain fasting blood glucose concentrations between 70 to 180 mg/dl.

GROUP 3: Dorzagliatin. Dorzagliatin dose will be a 75 mg tablet twice daily. Anticipate that your fasting glucose concentrations will be between 70 to 180 mg/dl since we cannot titrate the dose of this medication.

****For the purpose of this study, we will refer to insulin, metformin and dorzagliatin as the "study medication"**

You will need to pick up your study medications from the CRU. You will take your assigned study medication for approximately 8 weeks.

Glucose monitoring during study treatment:

You may have a continuous glucose monitor (CGM) device placed before starting your study medication at the end of the first inpatient visit. We will place the device during your IPV and teach you how to monitor your glucose readings. This device is known as the Abbott Freestyle Libre and is approved by the Food and Drug Administration (FDA) for monitoring blood glucose in people with diabetes. The CGM placement involves introducing a probe underneath the skin on the back of the arm. The device will be paired wirelessly to a reader. This device will not interfere with arm movement or cause any discomfort. The study team will insert the device and provide necessary instructions about the use of this device. You may need to have the sensor replaced every 14 days if needed for monitoring blood sugar. If you are uncomfortable using a CGM you may opt to use a glucose meter and check fingerstick glucoses instead. Glucose meters and lancet devices will be provided.

If you report fasting glucose less than 70 mg/dl or greater than 180 mg/dl on 2 successive occasions with either fingerstick or CGM after the run in phase is over for the ~ 6-8 week on study medication, you will be withdrawn from the study with notification and discussion with DSMB.

In-patient Visits (IPV Baseline and Post-treatment):

Two weeks after the screening visit, you will return to the CRU to begin the first of two identical inpatient admissions. You will perform the following in-patient visit, two times, once before and once after your 8

weeks study medication treatment. You will refrain from smoking and drinking alcohol during the inpatient visits.

For subjects assigned to Insulin and Metformin (week 2 and week 10):

- You will arrive at CRU Fontaine Research Park at around 5PM.
- The study team will record your blood pressure, heart rate, temperature, weight, medications you are taking and collect a urine sample from you for a pregnancy test (if applicable), that must be negative in order to continue with study participation.
- You will consume a standard mixed meal (10 kcal/kg: 50% carbohydrate, 20% protein, 30% fat) at around 5:30 PM.
- You will not consume anything except water after the evening meal until the end of study.
- You will ingest 1.67 g/total body weight deuterated water for estimation of new sugar being formed in the body at divided doses at around 5:30, 7:00 and 8:30 PM.
- At 9 PM you will have one IV catheter placed in the vein of your forearm (near the elbow).
- Another IV will be started in the back of your hand/forearm. An IV catheter is a thin tube inserted into the vein using a needle. Once the catheter is in place, the needle is removed but the tube remains in the vein. The needle is replaced by a small cap above the tube which, allows blood to be drawn from the vein and for agents to be administered through it.
- The IV in your forearm will have a nonradioactive trace substance of glucose infused throughout the night starting at about 9:30 PM. This IV may be replaced, if needed.
- Throughout the night, the IV in your other forearm/hand will be used for drawing blood samples periodically to measure your blood sugar levels and hormones.
- At 10PM, you will be asked to go to bed, and lights will be turned off.
- All infusions and blood draws will be stopped at 7 AM, catheter removed, a breakfast meal provided and you will be able to leave.

You will have to provide urine samples either using a urinal, bedside commode or if you prefer a urinary catheter will be placed in your bladder and urine will be collected throughout the study.

For subjects assigned to receive Dorzagliatin (week 2 and week 10)

If you are randomized to receive dorzagliatin, you will have two study visits separated by 1-3 days, before and after the 8 weeks of study medication treatment. (Total of 4 visits).

High glucose study day (visit will be completed twice):

You will arrive at CRU Fontaine Research Park at around 5PM. Study team will record your blood pressure, heart rate, temperature, weight, medications you are taking and collect a urine sample from you for a pregnancy test (if applicable) which must be negative to continue study participation.

- You will consume a standard mixed meal (10 kcal/kg: 50% carbohydrate, 20% protein, 30% fat) at around 5:30 PM. You will not consume anything except water after the evening meal until the end of study. You will ingest 1.67 g/total body weight deuterated water for estimation of new sugar being formed in the body at divided doses at around 5:30, 7:00 and 8:30 PM.
- At 9 PM you will have one IV catheter placed in the vein of your forearm (near the elbow).
- Another IV will be started in the back of your hand/forearm. An IV catheter is a thin tube inserted into the vein using a needle. Once the catheter is in place, the needle is removed but the tube remains in the vein. The needle is replaced by a small cap above the tube which, allows blood to be drawn from the vein and for agents to be administered through it.
- The IV in your forearm will have a nonradioactive trace substance of glucose infused throughout the night starting at about 9:30 PM. The IVs may be replaced, if needed.
- The IV in your other forearm/hand will be used for drawing blood samples periodically to measure your blood sugar levels and hormones.
- At 10PM, you will be asked to go to bed, and lights will be turned off.
- At about 5AM an infusion of a radioactive trace substance of glucose will begin in-order to measure how much glucose is being taken up by the liver and this will continue until end of the study at 10AM.
- An infusion of another trace substance of radioactive glucose will start at about 6 AM and continue until the end of the study at ~ 10 AM which will measure how much fat (glycogen) is stored in the liver. The infusion of the nonradioactive trace substance of glucose will be discontinued at about 7 AM.
- An infusion of somatostatin (natural occurring hormone, allowed by the FDA to be used in this study) will be started at the established rate until end of study and you may need some small amounts of insulin and glucagon to maintain your blood sugar at about 165 mg/dL which is often the level of sugar seen in the blood after one eats a meal.
- You will be asked to empty your bladder at ~ 6:55 AM and then ingest 2 g of Tylenol.
- You will have to provide urine samples either using a urinal, bedside commode or if you prefer a urinary catheter will be placed in your bladder and urine will be collected throughout the study to check for urinary glucose.
- A 50% dextrose infusion containing radioactive trace substance of glucose will also begin at ~ 7 AM, and will continue over the next 3 hours.
- All infusions and blood draws will be stopped at 10 AM, cannulae removed, a meal provided, and you will be able to leave.

Meal study day (visit will be completed twice):

You will arrive at CRU Fontaine Research Park at around 5AM. Study team will record your blood pressure, heart rate, temperature, weight, medications you are taking and collect a urine sample from you for a pregnancy test (if applicable) which must be negative to continue study participation.

- At ~5:30 AM you will have an IV cannula inserted in a forearm.
- You will receive a trace substance of non-radioactive glucose through the IV starting at 6 AM.

- At 8AM, a plastic tube will be inserted into one of your hands for periodic blood draw sampling. The hand will then be placed in a heated plexiglass box (at about 55 C°) or covered with heating pad heated at 42 C° to enable periodic blood draws during this time.
- You will eat a meal at ~ 9 am. The meal will consist of Jell-O that has small amounts of non-radioactive labeled glucose, and you will also eat some scrambled eggs with Canadian bacon (with the option of steak, hard cheeses etc.) and a small glass (100ml) of water.
- With the first bite of the meal, an infusion of a small amount of a nonradioactive glucose will also be started.
- Following the last blood draw at ~ 12 noon, all infusions will be stopped and all IV catheters will be removed.
- You will be provided a snack if you wish, and you will be able to leave.

Study Schedule

	Visit 1 (Screening)	**IPV (baseline) Insulin and Metformin**	**Dose titration or run-in phase**	**IPV (post-treatment) Insulin and Metformin**	**IPV Baseline (high glucose and meal) Dorzagliatin**	**IPV post-treatment High glucose and meal Dorzagliatin**
Study Week	0	2	2-4	10	2	10
Informed Consent	x					
Review study eligibility	x					
Medical History	x					
Review of Medications	x	x		x	x	x
Vital signs	x	x		x	x	x
Physical Exam	x					
Urine pregnancy test (if applicable)	x	x		x	x	x
Blood draw (lab work)/safety tests	x				x	x
Urinalysis	x					
Glucose monitoring		x	x	x	x	x
Nonradioactive glucose tracer infusion		x		x	x	x
Radioactive trace substance of glucose, somatostatin, insulin and glucagon infusion					x	x
IV Line placements		x		x	x	x
Research blood draws		x		x	x	x

What are your responsibilities in the study?

You have certain responsibilities to help ensure your safety.

- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Please let the study doctor know if you are taking any of the following medications: ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, indinavir, ritonavir, saquinavir, telithromycin, boceprevir, nelfinavir, telaprevir, conivaptan, nefazodone, carbamazepine, phenytoin sodium, rifampicin.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over-the-counter), including herbal supplements and vitamins. The study doctor will let you know if you can take these medications while participating in the study.

Blood Testing

We will take (or "draw") up to 37 tablespoons (~ 1 unit) of blood over a period of up to 6 weeks.
The blood we take will be tested to measure the amount of red blood cells, the amount of white blood cells, how well your kidneys/liver work, the amount of sugar, the levels of hormones (Insulin and Glucagon) and the amount of glucose taken up by the body and amount of glycogen stored by the liver in this study.

If you want to know about the results before the study is done:

During the study your study team will let you know of any test results that may be important to your health. In addition, as the research moves forward, your study team will keep you informed of any new findings that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time you can ask for more information about the study results.

Collection of Samples and Health Information for Specimen Banking

What Sort of Research Will Be Done On Your Sample(s)?

You are being asked to give samples of your blood to be used for future research. Along with samples, researchers will need to collect some health information about you. Combining information from the samples with information from your health records may be useful for this research. For this research, the following types of information could be included: age, sex, weight, medications, and how long you have had diabetes.

In addition, if you agree, samples collected for research will be added to a research specimen bank. The purpose of a specimen bank is to process, and store samples until researchers need them for future research. The long-term goals of the samples collected in this bank will be mainly used for physiology research (the study of how a normal body functions). It is not possible, however, to list every research project that will include the samples because we cannot predict all of the research questions that will be important over the coming years. As we learn more, new research questions and new types of research may be done.

What will you have to do to give samples for research?

We will obtain blood samples from you for measuring your blood sugar levels and hormones during the course of the study. After completion of the study procedures, there may be samples left over. Normally, these leftover samples would be thrown away. We are asking you to allow us to collect this leftover material for specimen banking.

How Will Your Sample(s) Be Labeled?

Dr. Basu and her research team will be responsible for storing your sample and for protecting your privacy. Your sample will not have your name or other personal information linked to it. No one will be able to tell that you gave us the sample. The only information we will keep with the sample is information like your age and what disease/condition you have. Because we will not keep your name or other identifying information when we use your specimen, you will not be able to have the sample removed from the bank at a later time.

Which researchers can use your samples and what information about you can they have?
Your sample may be shared with researchers at the University of Virginia and at other institutions. Dr. Rita Basu will not give your name to other researchers who want to use your sample, but will only give them information like your age and what disease/condition you have. Those who would see the information would include researchers and the others listed under "Who will see your private information?" section of this consent document.

Some of the people who receive your information may not have to follow the privacy laws and may share or release your information because they do not have to follow the privacy laws.

What Are the Benefits To Donating Your Samples For Specimen Banking?
The specimen banking that is done with your sample is not meant to help you. But, doctors hope that in the future it will help people who have other diseases or conditions.

It is very unlikely that any future research performed using your specimens would benefit you directly, but it may provide important medical knowledge that could help other patients with your medical condition or other medical problems in the future.

What Are The Risks of Donating Your Samples For This Study?

Risks to Privacy from Specimen Banking:
The main risk of allowing us to store and use your samples and certain limited health information for research is a potential loss of privacy. One of the risks to you is the release of information from your health records. The University of Virginia will do its best to protect your records so that facts about you and your health will be kept private. The chance that information identifying you will be given to someone else is very small. However, we cannot *guarantee* it will be safe. To further safeguard your privacy, information obtained from future research will not be placed in your medical record.

There are certain risks of having health information given to other people by mistake. In the unlikely event that this happens, it could cause discrimination or mental harm to you or your family members if others were to see this information. The results could be that you may not be able to get or keep certain kinds of insurance. It could also hurt family relationships.

Will You Find Out the Results of the Research on Your Samples for Specimen Banking?
Neither you, your health care provider**,** nor anyone in your family, will receive the results of any research done on your sample(s). The results will not be put in your health records. Therefore, results from any research done on your samples will not affect your medical care. This helps protect you and other members of your family from harm that might be caused by this information.

What If You Change Your Mind About Donating Your Samples for Specimen Banking?
If you change your mind about donating your sample, you may contact Dr. Basu whose contact information is found at the front of this consent document.

Will You Be Paid For Donating Your Samples Specimen Banking?
You will not be paid to donate your samples for specimen banking.

Will Donating Your Sample(s) Cost You Any Money?
There is no cost to you to have your samples collected for specimen banking.

Specimen Banking Options:

You do not have to participate and agree for specimens to be collected for specimen banking in order to be in the main part of this study. No matter what you decide to do, your decision will not affect your medical care. You can tell us your choice by placing your initials in one of the options below:

SPECIMEN BANKING:

Please indicate your choice by placing your initials below:

___ YES	**Your sample(s) may be saved for future research and stored in a specimen bank.**
___ NO	**Your sample(s) may not be saved for future research and stored in a specimen bank.**

What are the risks of being in this study?

Risks from hormone infusions:

Somatostatin hormone is naturally present in the body. Giving somatostatin in the vein may cause nausea and rarely vomiting. If you develop nausea, we will either stop the study (if you wish) or give you a medication to control nausea. This risk is very low, and we have only observed in 1 out of 10,000 people who were given this hormone. There is a potential risk of hypoglycemia (low blood sugar) during any insulin infusion, but in this study, we plan to keep blood sugars at a level that is seen typically after meals by infusing sugar through your veins and we will be checking blood sugars frequently every 5-10 minutes. Glucagon hormone is also naturally present in your body and will be given in small amounts to raise your blood sugar to what is commonly observed after a meal.

Risks of Metformin

Common side effects include nausea, vomiting, abdominal pain and diarrhea which improves with time and if dose is increased slowly to the desired level.

Risks of Insulin (glargine)

Common side effects with insulin glargine include hypoglycemia (low blood sugar),injection site reactions, pruritus (itching), rash, and long-term use can result in lipodystrophy (loss of fatty tissue at the injection site), edema, and weight gain.

Risks of Dorzagliatin:

Dorzagliatin is an investigational drug. It was found to be safe and well tolerated in phase II and phase III trials in humans.

Common side effects with dorzagliatin are as follows:

- A very small risk of hypoglycemia (low blood sugar)
- Mild and temporary increase in blood triglycerides (fats)
- Mild and temporary increase in liver enzymes
- Mild increase in blood pressure

If you are on dorzagliatin, we will require that you check your blood pressure every 2 weeks at home or at a local pharmacy or come to the CRU to have it checked. You will maintain a diary to record your blood pressure throughout the study. If your blood pressure is more than 140/90 mm Hg on two or more occasions we may need to verify if you are regularly taking your blood pressure lowering drugs if you are on them, and maintaining a low salt diet. We may need to withdraw you form the study after discussion with the DSMB. Serum Triglycerides, liver enzymes and uric acid will be measured at the end of the treatment period and if elevated will be managed appropriately with your PCP after discussion with the DSMB. **However, based on the safety profile of the drug we do not anticipate that your blood pressure, triglycerides, liver enzymes or uric acid will remain elevated at the end of the 8-week study.**

Allergic reactions are a possibility with any medication/infusion. Symptoms of an allergic reaction include skin rash, hives, itching, runny nose, watery eyes, nausea, abdominal cramps and diarrhea. Severe reaction may include shortness of breath, tightness in the throat, swelling of lips, tongue or throat, weak pulse and drop in blood pressure. However, all medications and infusions are safe and well tolerated and will be administered in the CRU under the supervision of a licensed physician.

Blood Donation

If you participate in this study, it will affect your ability to donate blood. From the time that you are enrolled in this study to completion of the study you must not donate any blood. Following completion of this study you should wait for 12 weeks before donating blood or participating in another research study, which might involve blood withdrawal. This is very important because of the amount of blood drawn for this study.
If you have any questions call the organization where you donate blood and talk to one of their nurses

Risks of having your blood drawn:

Having blood drawn may cause:

- ✓ pain (common),
- ✓ a bruise (sometimes),
- ✓ fainting or passing out (not very often), and
- ✓ infection (rare).

Risk of Repeated Sticks:

- ✓ Sometimes the catheter stops working. In order to get the blood we need, we may have to stick you again with another needle.

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested. The tests might check for:

- ✓ hepatitis,
- ✓ HIV (Human Immunodeficiency Virus), or
- ✓ other infections.

You and the person exposed would be told the test results. However, your name would be kept private. If your test is positive for hepatitis or HIV, we will tell you the results and help you understand what the results mean for you.

Risks of high blood sugar as a result of discontinuation of your antidiabetes medications:

It is anticipated that you may experience high blood sugar as a result of discontinuation of your antidiabetes medications. You will be required to wear a CGM sensor to track your glucose continuously or monitor your blood sugar using fingertick glucose at least 3 times daily including a fasting measurement. Study staff will review CGM data or fingerstick glucose data every 48 hours during the 2-week withdrawal of medications. If you record a fasting CGM or fingerstick glucose > 250 mg/dL you will be immediately withdrawn from the study.

Risk of Low and High Blood Sugar:

It is not anticipated that you will experience low or high blood sugar, as we frequently check your blood sugar levels during the study and adjust dextrose infusion as needed to keep your blood at ~ 165 mg/dL.

Risk of Low Blood Sugar (hypoglycemia):

Symptoms of low blood sugar include, sweating, rapid pulse, shaking, dizziness, weakness, blurred vision, headache, difficulty concentrating. However, we will closely monitor your blood glucose during study with either CGM or finger stick checks.

Risk of High Blood Sugar (hyperglycemia):

Symptoms of high blood sugar include dry parched mouth, extreme thirst, frequent urination, weakness, fruity breath odor. However, we will closely monitor your blood glucose during study with either CGM or finger stick checks.

Risk of urinary catheter (if needed):

A urinary catheter will be placed in your bladder. This could cause discomfort, irritation, bleeding, and/or painful spasm of the bladder and rarely infection. Any adverse effects related to the catheter will be appropriately managed.

Risk of the HOT BOX:

The temperature inside the box where your hand will be placed is maintained at about 55°C. With prolonged exposure to continuous heat, there is a potential risk of local skin irritation/redness. If this occurs, it will be treated appropriately. However, we have used this technique for the past 25 years and have had no instances of hot box related burns or injuries.

Risks for women:

Pregnancy and Contraception

The drug(s) dorzagliatin and radioactive trace substance of glucose used in this study can harm an unborn or nursing baby. Therefore, you cannot be in this study if you are pregnant or nursing a baby. A POC urine pregnancy test will be done at screening and at each in-patient visit before starting this study if you are a woman able to become pregnant. You must use contraception and MUST NOT become pregnant during the course of your study participation and for up to ***four weeks*** after your last dose of drug.

You and your partner must use an approved form of birth control during this study. Examples of birth control you may use are:

- Norplant
- IUD (intrauterine device)
- Depo-Provera
- Birth Control Pills
- Birth Control Patch
- Sterilization

The birth control methods listed below are less effective. They may be used if combined with other birth control methods:

- Condoms
- Jellies or foam
- Withdrawal
- Sponge
- Diaphragm
- Rhythm
- Cervical cap

If you become pregnant during this study, you must tell your doctor right away. Your doctor will discuss your treatment and the effect on the pregnancy. If you have questions about birth control, please ask the study leader or your primary care physician.

Risks for men:

We also do not know the effects of these drugs on male sperm. If you are a male, you should not father a baby during the course of your study participation and ***for four weeks*** after your last dose of the drug. You MUST use contraception during this entire period. You should also not donate to a sperm bank during this time. To do so may hurt your unborn baby. Use an effective method of birth control during this time.

You and your partner must use an approved form of birth control during this study. Examples of birth control you or your partner may use are listed below.

- Norplant
- IUD (intrauterine device)
- Depo-Provera
- Birth Control Pills
- Birth Control Patch
- Sterilization

The birth control methods listed below are less effective. They may be used if combined with other birth control methods

- Condoms
- Jellies or foam
- Withdrawal
- Sponge
- Diaphragm
- Rhythm
- Cervical cap

Risks from Stable (non-radioactive) and radioactive isotope glucose Infusion:

There is no known risk of stable isotopes of glucose as these are naturally occurring substances and present in the body.

Risks from radioactive glucose tracer:

You may be exposed to radiation from the glucose infusions in the study if you are in the dorzagliatin group. The amount of radiation you will receive has a low risk of harmful effects.

Risks and side effects related to the continuous glucose monitor (CGM) insertion include:

Likely

- Failure or lack of sensitivity of the continuous glucose monitor sensor that requires replacement / insertion of new sensor

- Discomfort from insertion of sensor

Less Likely

- Bruising less than one half inch
- Bleeding less than one fourth of a teaspoon
- Sensitivity to adhesives with use of continuous glucose monitor resulting in skin irritation, redness and swelling at the insertion site

Other unexpected risks:

You may have side effects that we do not expect or know to watch for at this time. Call the study team if you have any symptoms or problems.

Could you be helped by being in this study?

You will not benefit from being in this study. However, the information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study.
If you are an employee of UVa your job will not be affected if you decide not to participate in this study.
If you are a student at UVa, your grades will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?

You will be paid $1800 if you are in the metformin or insulin glargine arm and $2500 if in the dorzagliatin arm for finishing this study by check. The compensation is based on time and inconvenience associated with participation. If you start the study but do not finish the amount will be prorated based upon your participation as follows.

Each in-patient study visit is compensated at $500 each and the 6-8 week drug treatment period is compensated at $800, which is a total of $1800.

Those randomized to the dorzagliatin have to spend extra daytime hours during their overnight visits along with 2 additional meal study visits. Each of the daytime extension period will be compensated at $100 and each of the meal study visits are compensated at $250 hence total is $1800 plus $700 which amounts to $2500.
You should get your payment about 1 month after finishing the study. The income may be reported to the IRS as income.

If you complete the screening visit, but the study team determines you are not eligible to participate, you will be paid $25 by check. You should get this payment about 1 month after the visit.

If you are staying in a local hotel overnight prior to the study visit, you will be reimbursed for your hotel stay and food (receipts for actual expenses) while travelling and mileage as per UVA guidelines (calculated and confirmed *via Mapquest).

By agreeing to be in this study, you are donating your blood samples for research, and giving up any property rights you may have in them. The results of this research using your donated materials may have commercial value. However, you will not receive any payments.

Will being in this study cost you any money?

Being in this study will not cost you any money. The following procedures/tests, which are being done for research purposes, will be provided at no cost to you or your health insurance.

- Tests performed during the screen visit.
- Pregnancy tests
- CGM placement and use
- All infusions, tests and procedures done during the study visit 2 and 3 outlined in this form.

Your travel and parking costs will also be reimbursed. See the "Will you be paid for being in this study?" section of this form for more information.

What if you are hurt in this study?

You do not give up any legal rights, such as seeking compensation for injury, by signing this form. If you feel you have been injured as a result of this study you may contact the Principal Investigator or the IRB (phone numbers are located near the end of this form). If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.
The study team may also discontinue your participation in the study.

Any data collected about you up until the time you leave the study must be kept in order to determine the results of the study.

How will your personal information be shared?

The UVA researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

Some of the people outside of UVA who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

Information and samples obtained from you during this study may be used in future research. Your information and samples may be shared with other researchers inside or outside of the University of Virginia. They will not be sent with information that could identify you such as name, address or phone number.

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.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

A copy of this consent form will be put in your medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your medical records will be able to find out that you are in this study. This is done so your regular doctors will know what you receive as part of this study. If you have other health problems during the study, they will be able to treat you properly.

Your information, collected for this study, will be protected by a Certificate of Confidentiality from the federal government. If UVA receives a subpoena or court order demanding information from the study records that would identify you, we will use the Certificate to resist the demand. However, UVA will not use it in the following cases.

- You have agreed in writing to allow UVA to share the information with your employer, your insurance company for billing purposes, or someone else
- Reports to authorities where there is a danger that you may harm yourself or others, or if there is evidence of probable child or elder abuse or neglect.
- Reports to authorities if you have an infectious disease that health care providers are required to report by law.

In addition, the Certificate does not prevent government authorities who oversee research from reviewing this study. This Certificate does not mean that the government either approves or disapproves of this study. It just helps protect your privacy.

Please contact the Principal Investigator to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:

Rita Basu, MD
Department of Medicine-Division of Endocrinology
University of Virginia Health System
Fontaine Research Park
560 Ray C Hunt Drive, Room 3108
P.O. Box 800831
Charlottesville, VA 22908-0831 Telephone: 434-924-5183

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908 Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Would you like the study team to communicate with you by email or text message?
If you choose to communicate with the study team by unsecure email (email that is not encrypted) or text message to your personal phone, there is some risk that your health information could be read or accessed by someone else while the information is sent or saved by your email or phone provider.

Your personal email or phone provider may also share or release your information because they do not have to follow the privacy laws that UVA follows. Sometimes email and phone providers release information to marketing companies for use in direct advertising. If you choose to communicate by email or text messaging, UVA cannot control this potential loss of privacy but we want to tell you about this possible risk.

You do not have to agree to communicate with the study team by email or text message to be in this study. If you agree to texting or emailing, the study team will collect your phone and /or email address from you that you would like them to use to contact you. Please note, if you agree to text messaging, charges may apply depending on your data/text plan with your phone provider.

Signatures

What does your signature mean?
Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent
By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT(PRINT)	DATE

Notification of My Health Care Provider

Please indicate below whether you want us to notify your health care provider that you have agreed to take part in this study.

_____ Yes, I want the study doctor to notify my health care provider that I have agreed to take part in this study.

Health Care Provider Name:
Health Care Provider Address:
Study team will send a copy of the consent form to the health care provider.

_____ No, I do not want the study doctor to notify my health care provider that I have agreed to take part in this study or I do not have a health care provider.

Leaving the Study Early

Signatures should be obtained in this section if the subject decides to leave the study early.

If you leave the study early the study leader will keep the data collected about you up until the time you leave the study to help determine the results of the study.

____ I am withdrawing my consent for this study. No additional information may be collected about me including follow up information from my medical records.

Consent from Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained the implications of withdrawing from the study to the subject and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT(PRINT)	DATE