

**CONSENT FORM****Subject Name** \_\_\_\_\_

**Title of Protocol** Effects of intervention with the GLP-1 analog liraglutide plus metformin versus metformin monotherapy in overweight/obese women with metabolic defects and recent history of gestational diabetes mellitus (GDM)

**Principal Investigators:** Renee Harris MD  
Karen Elkind-Hirsch, MS, Ph.D.

**Departments:** The Metabolic Health Clinic  
Woman's Health Research Department  
500 Rue de la Vie, Suite 513  
Baton Rouge, LA 70817  
(225) 231-5275

**Sponsoring Agency:** Novo Nordisk A/S

Please read this form carefully. This consent form contains important facts to help you decide if it is in your best interest to take part in this study. Take time to ask the study doctor or study staff as many questions about the study as you would like. If there are any words or information that you do not understand, please ask the doctor. The study doctor or study staff will explain them to you. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not. If you decide to take part in the research study, you must sign your name to the final page. Your taking part is entirely voluntary.

**Purpose of the Study:**

You are being asked to take part in a clinical research study because you had gestational diabetes mellitus (GDM) in your recent pregnancy. Women with prior GDM do not metabolize (digest) enough of the carbohydrates (simple and complex sugars) found in food. This study is being done to compare the ability of different medications to improve carbohydrate metabolism in women with prior GDM. One medicine is a pill that you take by mouth twice a day (metformin XR). The other medicine is a subcutaneous (under the skin) shot that you can give to yourself once a day. This medicine will be either liraglutide (Victoza) or placebo (a liquid that looks the same but has no drug in it). The effects of the liraglutide (Victoza), both good and bad, will be compared to the placebo. You will need to take both metformin and one of the

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injectable medicines for about 20 months. Liraglutide (Victoza) is approved by the U.S. Food and Drug Administration (FDA) for use in diabetic patients, but is considered an investigational drug in this study. This means it is not yet approved by the FDA for use in women with prediabetes (women who had gestational diabetes).

One hundred fifty women will take part in the study at The Woman's Hospital and The Metabolic Center of Louisiana in Baton Rouge, Louisiana. The length of time you will be in this study is about 84 weeks.

If you volunteer to take part in this research study, you will be asked to read and sign this consent form. You will then have a screening visit. Tests will be done during this visit to see if you meet all of the entry conditions to take part in this study. These will include:

- review of your reproductive history
- a medical history
- physical measurements of height, weight, and blood pressure
- a blood pregnancy test will be done to confirm that you are not pregnant

You will also provide information about the following:

- menstrual bleeding cycle length
- race
- current drug use
- cigarette smoking/tobacco use
- alcohol intake

If you agree to take part in this study, you will be chosen on a randomized basis. This is similar to flipping a coin. You will be placed into one of two groups. Both groups will take Metformin extended release pills. One group of women will also get the injectable study drug. A second group of women will get an injectable placebo (liquid with no drug in it). A computer will put you in a group by chance. If you are eligible to take part in the study and you meet the medical conditions, you will be randomized to one of two treatment groups:

- Metformin extended release plus liraglutide (Victoza)
- Metformin extended release plus placebo

A computer will choose which of the medicines you will get. Neither your doctor nor you will be able to choose which treatment you will be given. You have an equal chance of getting either the study drug or the placebo. The study staff and the women who take part **will not know** which group is getting the study drug or placebo.

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Once you have enrolled and been randomized to study drug, you will be taught how to take the medicine. All patients are on oral (by mouth) medicines. You will be instructed when to take the medicine and how many times a day. Before starting treatment with the injectable medicine, you will be trained how to use the pre-filled injection (shot) pen. All subjects (liraglutide or placebo group) will receive this training.

### Procedures during the Study

With each study visit, you will have the following clinical measures (vital signs) taken:

- height
- weight
- measurement of your waist and hips with a tape measure
- blood pressure
- pregnancy test

You will have clinical and laboratory testing over 80 weeks.

There will be a baseline visit and three testing visits. These testing visits will be scheduled at baseline and during study weeks 32-36, 56-60, and 80-84. During the testing visits, you will need to give blood (around 1 ½ teaspoons) for laboratory tests of your hormones and blood chemistries. This blood test is to find out if your thyroid, liver, and lipid levels are normal.

In addition, at the baseline visit and the three testing visits, you will take an oral glucose (sugar) tolerance test. For the sugar tolerance test to work, the night before the test you cannot eat anything after midnight and the only liquid you can drink after midnight is water. This test requires that blood samples be taken when you arrive, 30 minutes, 1 hour and 2 hours after drinking a sugar solution. In total, this test requires that you have your blood taken 4 times within 2 hours. The total amount of blood to be taken during each visit will be about 3 tablespoons. A total of 6 tablespoons of blood will be drawn during your taking part in this study, which will take about 6 months to complete.

In addition to these testing visits, we will also see you every 10 weeks. We will find out how you are tolerating the medicine, dispense new medicine, and get back unused medicine.

### 2. Risks/Side Effects

The treatments used in this study may cause some or none of the side effects listed. In addition, there is always the risk of some very uncommon or unknown side effects taking place.

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### **Risks Associated with Study Procedures**

In this study you will need to have blood drawn from your arm several times. You may have some tenderness from having blood taken from a vein in your arm. You may also have unpleasant effects from using either the pills or injection (shot) pen. Possible risks and side effects from each of these tests and drugs are listed below.

The risks of drawing blood include local pain, bruising and swelling, bleeding and infection at the site of the vein puncture. As well, an infrequent risk of lightheadedness, dizziness, and, rarely, fainting is possible. You will need to take subcutaneous shots of liraglutide (Victoza) or placebo. There may be a risk of infection, mild injection-site bruising related to the injection (shot) method, and local reaction at the injection sites. Women treated on this study will be encouraged to rotate shot sites to avoid local reaction.

### **Risks/Side Effects Associated with Study Medications**

Both liraglutide (Victoza) and extended-release metformin are medicines that have been approved by the U.S. Food and Drug Administration (FDA) for use in diabetic women. Neither drug has been approved for use by pregnant women.

You must not become pregnant while in this study. You can discuss birth control options with your doctor. A pregnancy test will be done before you start drug treatment, every ten weeks, at each testing visit, and at the end of the study.

Possible risks from these medicines are listed below:

Liraglutide (Victoza) is an injectable medicine used to improve blood glucose (sugar) control in adults with type 2 diabetes. It comes in a prefilled injection (shot) pen (pen-injector) with fixed doses and uses a very small needle. This drug is given by subcutaneous (under the skin) shot in the thigh, abdomen, or upper arm. The site of the shot should be rotated during therapy.

Liraglutide (Victoza) is a peptide (small protein) and therefore cannot be given by mouth. If it were taken in pill form, your stomach would break it down just like the protein in the foods you eat, and it wouldn't work. If you miss a dose, skip that dose and restart your therapy with the next scheduled dose. Liraglutide (Victoza) should be refrigerated (36-46 °F) until you use the first dose and protected from light. The product should not be used if it has been frozen. The pre-filled pen should be thrown away 30 days after first use.

Treatment will be started at a dose of 0.6 mg given the same time each day for 1 week. After 1 week, the dose of Victoza or placebo should be increased to 1.2 mg daily. At

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least one week after taking 1.2 mg a day, the dose may be increased to 1.8 mg daily. Liraglutide (Victoza) can be used with metformin or some other anti-diabetic medicines.

**The most common adverse side effects of Liraglutide (Victoza) include**

- nausea
- vomiting
- dizziness
- diarrhea
- headache
- feeling jittery
- acid stomach

Nausea is most common when first starting Liraglutide (Victoza), but lessens over time in most patients. **Less common side effects include:**

- tiredness
- decreased appetite
- indigestion
- excessive sweating

When taking any drug, there is a risk of an allergic reaction. Since this drug is a peptide, the potential to develop antibodies to liraglutide (Victoza) following treatment with liraglutide (Victoza) exists. **Some signs of allergic reactions are:**

- skin rash
- fever
- fast pulse
- sweating
- swelling around mouth, throat or eyes

If not treated quickly, more serious problems such as breathing difficulties or shock could occur. It is not possible to predict if any of these problems will develop. If you have a serious allergic reaction, you may be at risk of death if not treated. Please seek treatment and alert the study doctor and staff right away if you have any of these signs or any other side effects during the study.

Very low blood sugar (hypoglycemia) is an important side effect to consider when taking liraglutide (Victoza). **Liraglutide (Victoza) alone does not cause low blood sugar** but it has been shown to cause hypoglycemia when used with other anti-diabetes drugs. **The warning signs of low blood sugar may include:**

- headache
- drowsiness
- weakness
- dizziness
- confusion
- irritability
- hunger
- fast heartbeat
- sweating
- feeling jittery

You will be trained how to recognize the signs of low blood sugar, and what to do to treat it. It is a good habit to carry glucose (sugar) tablets or gel to treat low blood sugar. If you don't have these forms of glucose, eat a quick source of sugar such as table sugar, honey, or candy, or drink a glass of orange juice or non-diet soda to quickly raise your blood sugar level. Tell your doctor right away about the reaction.

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Liraglutide (Victoza) causes thyroid C-cell tumors in rodents (mice and rats). The human relevance is unknown. You should tell the study doctor if you experience any symptoms of a thyroid tumor (e.g. a mass in the neck, difficulty swallowing, shortness of breath or persistent hoarseness).

Liraglutide (Victoza) may reduce your appetite, the amount of food you eat, and your weight. Liraglutide (Victoza) should be used with care if you are taking oral medicines that require rapid absorption through your stomach. Liraglutide (Victoza) slows stomach emptying and can affect medicines that need to pass through the stomach quickly. Liraglutide (Victoza) can interact with other medicines. Drugs that depend on a threshold concentration to be effective, such as antibiotics, should be taken at least one hour before Liraglutide (Victoza) shot. If any new risks or side effects are found out that might change your decision to stay in this study, you will be told about it in a timely manner.

**Extended-release metformin** is an oral medicine that works by helping to return your body's correct response to the insulin you naturally make. It lowers the amount of sugar that your liver makes and that your stomach and intestines absorb. It is used along with a diet and exercise program to control high blood sugar in patients with type 2 diabetes. This medicine is taken by mouth with meals. Each tablet(s) must be swallowed whole, so do not crush or chew the pills. You should drink plenty of fluids while taking this medicine. Inactive parts of the drug may be passed in your stool as a harmless soft mass that may look like the original tablet. This is normal for this drug. Since this is an extended-release tablet, it lowers the number of times you have to take a pill each day. Extended-release metformin delivers the drug to your body in the same amounts as instant-release metformin over a longer period of time.

**The most common adverse side effects of metformin include:**

- nausea
- stomach upset
- diarrhea
- loss of appetite
- acid stomach
- a metallic taste
- increased abdominal gas
- vomiting

Side effects usually decrease over time. Taking metformin right before meals may lessen nausea and vomiting. Food decreases the rate the drug is absorbed, so taking the medicine with food can reduce the side effects of metformin. In this study, metformin will be started at a low dose and increased gradually as you are able to tolerate it.

A rare side effect of metformin use is a condition called lactic acidosis. If the liver is not able to change the lactic acid into sugar, the acid builds up in the blood. If not treated,

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this acid buildup can lead to coma and death. Lactic acidosis is more likely to occur in patients who:

- have kidney or liver failure
- have low levels of oxygen in their blood (hypoxia) or poor blood flow
- abuse (drink too much) alcohol
- have excess loss of body fluids (dehydration)
- are undergoing X-ray or scanning measures that require an injectable iodinated contrast drug, surgery, or have a serious infection

**Seek medical help right away** if you develop any of the following signs of lactic acidosis:

- unusual tiredness (fatigue) or severe drowsiness
- cold skin
- muscle pain
- breathing trouble or rapid breathing
- unusually slow or irregular heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital setting. If you have an illness that results in severe vomiting, diarrhea, and/or fever, or if drinking of fluids is really decreased, you need to call your physician. If stomach symptoms come back (after you are on the same dose for several days or weeks), tell your doctor right away. A late comeback of stomach signs may be due to lactic acidosis. Alcohol is known to intensify the effect of metformin and you should never drink excess amounts (greater than 2 glasses of wine, or beer, or 2 ounces of hard liquor a day) of alcohol (all the time or "short-term binge") while taking metformin. Taking metformin should be briefly stopped for all surgical procedures that include reducing fluids. You should not take metformin again until normal fluid intake is started again and renal (kidney) function is back to normal.

When taken alone, metformin will not cause low blood sugar (hypoglycemia), but it may happen if you do not eat enough calories (from food, juices, fruit, etc.). Some of the common signs include:

- |                   |                                 |
|-------------------|---------------------------------|
| • chills          | • weakness                      |
| • cold sweat      | • headache                      |
| • dizziness       | • fainting                      |
| • drowsiness      | • tingling of the hands or feet |
| • shaking         | • hunger                        |
| • rapid heartbeat |                                 |

Low blood sugar makes it hard to think clearly, drive a car, use heavy machinery, or do other unsafe activities where you could hurt yourself or others. Severe cases of low blood sugar could cause loss of awareness, and in extreme cases, death. Tell your

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doctor right away about the reaction. To help prevent low blood sugar, eat meals on a regular schedule and do not skip meals.

Serious allergic reactions to this drug are unlikely, but seek medical attention right away if it occurs. Some symptoms of allergic reactions are:

- rash
- itching
- swelling around the mouth, throat or eyes
- a fast pulse
- sudden drop in blood pressure
- sweating
- dizziness
- trouble breathing

A severe allergic reaction could be fatal. If you notice other effects not listed above, contact your doctor

There is very little data about using this medicine in combination with other anti-diabetic drugs. When liraglutide (Victoza) and metformin therapy were used together, there was no increase in the rate of low blood sugar. This suggests that it is unlikely that the dose of metformin will need adjustment due to low blood sugar.

Both liraglutide (Victoza) and metformin can interact with other medicines. Know the medicines you take including prescription and non-prescription drugs, vitamins, and herbal supplements. Keep a list of them to show the study doctor or study staff throughout the time you are taking part in this research study.

Because of possible or unknown side effects of the study drugs on a fetus, you must not be pregnant during the study. Tests to determine if you are pregnant will be done before starting the medicine and at 10 week intervals throughout the study. Pregnancy tests will also be done at each testing visit. Patients in all treatment groups will have the same tests done.

Any treatment can cause side effects. The drugs used in this study may cause some or none of the side effects listed. This study may also have risks not known at this time. There is always the risk of some very uncommon or unknown side effects occurring which have not been explained in this consent. Risks to subjects are minimized by using procedures consistent with sound research dosing. In addition, a listing of other known side effects of both drugs is on hand through the pharmacy, or from the drug company.

If you do not understand any of the above risks you may discuss them with Dr. Harris or Dr. Elkind-Hirsch. Although the risks of developing the above complications are small, they do exist. If they occur, Dr. Harris, Dr. Elkind-Hirsch and their team will

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watch you closely and take appropriate medical action. This may include stopping the use of the drug. Your primary care physician is still responsible for your medical care.

### 3. Benefits

As a result of taking part in the study, you will receive medical care. You will be checked throughout the study. Both medicines have been used in diabetic patients and have shown to improve sugar tolerance. However, this benefit cannot be certain in women with prior GDM. It is possible that you may not receive any benefit from this study. The risks associated with using the drugs are slight but they do happen. Society will gain from learning if the use of certain "anti-diabetic drugs" has a positive influence on sugar metabolism in women with prediabetes.

### 4. Alternative Treatment

Caloric restriction, weight loss, and exercise are alternative methods which are used to reduce insulin levels. A number of other anti-diabetic medicines, like the ones described in this consent but made by the same or other drug companies, are another choice that may be right for you. You may talk over the use of these with your primary health care professional or the health care professionals in this study. You do not need to take part in this study to receive treatment for your condition.

### 5. Costs

There will be no charge for any of the study measurements or blood tests. All study medications and exams will be provided free of charge throughout the time you are in this trial. Test results will be offered to you as well as your private doctor(s) if you give separate written consent for information to be sent to your doctor(s). You will get \$50 after study screening and after each testing visit (in which you have a 2-hour lab test at the hospital) to pay for local travel, meals and other costs from your study visit. Your health insurance company or you will pay for all other costs associated with your medical care. Woman's Hospital will be given payment from the study sponsor to cover some of the costs for carrying out the study and data collection.

### 6. Confidentiality

The results of this study may be published. Your name and identity will be kept private. Absolute confidentiality cannot be guaranteed. Your study records will be part of your medical chart. An agent from Novo Nordisk A/S, the company supplying the medicine, may look at your records. The data will not be shared with other researchers. The Woman's Hospital Foundation Institutional Review Board, Woman's Hospital Research and Development Committee, research and clinical study staff, as well as, Woman's Health Research Department, and the Food and Drug Administration may also check your study records.

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## 7. Contacts for Extended Medical Care

If an injury happens while you are taking part in this study, medical care will be given to you. No funds have been set aside to pay your costs in the event of an injury as a result of this study. If an injury does occur, medical care can be gotten easily. The cost of this medical care will be the responsibility of you and/or your insurance company.

If you are hurt while taking part in this study, you should contact the Woman's Metabolic Health Clinic at (225) 924-8550 (24 hr). For more information about this research or patients' rights in research, you may also contact Ericka Seidemann, Human Protections Administrator, at (225) 231-5296.

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.

## 8. Termination of Participation

At any time, you may ask that your test results not be used for research. Your decision to not take part will not have a penalty. You can leave the study at any time without changing your further care. Please call Dr. Elkind-Hirsch at (225) 231-5278 if you no longer wish to take part in the study. The researchers may need to stop your taking part in the study for any of the following reasons:

- you become pregnant
- an adverse event that leads to stopping of treatment by your physician
- you develop a related sickness, which increases the risk to you or halts the analysis of the study facts
- you have to take an unacceptable medicine at the same time
- not following study instructions
- finding out that you are not eligible
- new information about the study drug is discovered that may affect your wish to continue taking part
- the study doctor feels it is in your best interest

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## Acknowledgement Of Receipt Of Information And Consent To Participate

I HAVE HAD AMPLE OPPORTUNITY TO ASK ANY QUESTIONS CONCERNING THE STUDY AND MY PARTICIPATION IS VOLUNTARY AS REFLECTED BY THE SIGNED STATEMENT BELOW.

I have read the preceding description and have heard the verbal explanation of these procedures from my doctor. I freely give my consent to participate in this

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research. I have the right to ask questions and may refuse to continue in the study any time that I so desire. If I refuse to participate or if I withdraw from the study, the doctors will continue to care for me and treat me as necessary for my condition

During the course of the research study, I will be informed of any new significant findings that may relate to my willingness to continue to participate.

At any time during treatment I am free to discuss with my doctor or his/her designee or the WHF Human Protections Administrator my rights as a participant and any side effects that might occur.

I AM MAKING A DECISION WHETHER OR NOT TO PARTICIPATE IN THIS STUDY. MY SIGNATURE INDICATES THAT I HAVE DECIDED TO PARTICIPATE, HAVE READ (OR BEEN READ) THE INFORMATION PROVIDED HEREIN, AND THAT I HAVE RECEIVED A COPY OF THIS INFORMED CONSENT.

\_\_\_\_\_  
Patient Name Date

\_\_\_\_\_  
Witness Name Date

\_\_\_\_\_  
Patient Signature Date

\_\_\_\_\_  
Witness Signature Date

\_\_\_\_\_  
Investigator Signature Date

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