Cardiac and Metabolic Effects of Semaglutide in Heart Failure With Preserved Ejection Fraction

NCT05371496

2/12/2025

MAYO CLINIC

Name and Clinic Number

Approval Date: **February 12, 2025**
Not to be used after: **February 11, 2026**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: Evaluation of the Cardiac and Metabolic Effects of Semaglutide in Heart Failure with preserved Ejection Fraction (CAMEO-SEMA): A Phase II, Prospective, Double-Blind Randomized Trial

IRB#: 22-000522

Principal Investigator: Barry Borlaug, M.D. and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to find out if an aggressive intervention to lose weight, will improve symptoms in patients with obesity-related cardiomyopathy, which is also known as the obese phenotype of heart failure with preserved ejection fraction (HFpEF). You have been asked to take part in this research because you have obesity-related cardiomyopathy/HFpEF.
What's Involved	Study participation involves either undergoing a weight loss intervention, which will consist of lifestyle interventions (diet and increase activity levels) plus either active treatment with semaglutide once weekly, or placebo (no active ingredient) once weekly. There is a 33 percent chance that you will receive the placebo treatment and a 67 percent chance that you will receive the semaglutide treatment.

	The study will take up to 52 weeks to complete and will require multiple visits to Mayo Clinic. These visits may include a physical exam, taking blood samples, urine pregnancy test (if a woman of child-bearing potential), performing two Right Heart Catheterizations, (with echocardiograms during the procedures), cardiac and limited abdominal MRI (without contrast), DEXA scans, oral glucose tolerance tests, an optional urine sample (for future analysis), Saliva and Fecal sample, complete a blood volume test, complete a questionnaire (KCCQ), lifestyle counseling, and taking study medicines. You will take the study drugs once a week, even when not in the clinic. You will also have the option to have a fat biopsy when you have your oral glucose tolerance tests. Not all of these will occur at every visit. You will find detailed visits listed in this consent.
Key Information	The most important risks to be aware of if you participate in this study are as follows: risks of the heart catheterization which include bleeding, and/or damage to the blood vessels or heart. There are other side effects that may develop from the medicine used to help you lose weight such as nausea, constipation, diarrhea, or upset stomach. Generally, these symptoms resolve with time, but if you do not tolerate the medicine, a lower dosage can be administered. This study may not make your health better. However, it is hoped that weight loss will prevent worsening of your heart failure and improve survival. You won't need to pay for tests and procedures which are done just for this research study. However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care, including co-payments and deductibles. There are alternatives to taking part in this research. Your other choices may include participating in diet and lifestyle changes to reduce your weight on your own. The research team will discuss the other treatment options with you.
Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

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Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies Withdrawing from the research study	**Principal Investigator:** Dr. Barry Borlaug **Phone:** (507) 255-1051 **Study Team Contact:** Dr. Borlaug's Research Team **Phone:** (507) 255-2200 **Institution Name and Address:** Mayo Clinic 200 1st St SW Rochester, MN 55905
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Participant Advocate (RPA)** **(The RPA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchparticipantadvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:
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.

A description of this research study will be available on https://www.mayo.edu/research/clinical-trials. This Web site will not include information that can identify you. You can search this Web site at any time.

Why are you being asked to take part in this research study?

You are being asked to take part in this research study because your doctor has determined that you have obesity-related cardiomyopathy, which is also referred to as the obese phenotype (a phenotype is a trait that includes things like your height and weight, age or skin color), of Heart Failure with preserved Ejection Fraction (HFpEF).

The plan is to have about 81 patients take part and complete this study at Mayo Clinic Rochester.

Why is this research study being done?

This research is being done to find out if an intervention to achieve aggressive weight loss (with a medication, semaglutide, administered once weekly by injection at home) can improve the abnormalities in your heart that cause you to feel short of breath with activity.

The drugs and procedures that are being tested are already approved for the purposes of weight loss. The investigational component of this study is to see if using these approaches, we can help improve your heart function in order to help you and others with obesity-related cardiomyopathy/HFpEF to feel better.

Information you should know

Who is Funding the Study?
This study is funded by the United States Department of Defense (DOD). The DOD will pay Mayo Clinic to cover the costs related to running the study. Novo Nordisk will be supplying Mayo with the semaglutide medication and matching placebo at no cost.

Information Regarding Conflict of Interest:
Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

You will be in the study for about 12 months and will come to Mayo Clinic for research visits 6 times during the course of the study.

What will happen to you while you are in this research study?

During the study, you will either receive treatment with semaglutide or placebo, administered through a pen injector at home once weekly, in addition to healthy lifestyle counseling (diet and exercise recommendations). A placebo looks exactly like the study drug, but it contains no active ingredient. We use placebos in research studies to learn if the effects seen in research participants are truly from the study drug. You have a 67% chance of receiving the semaglutide treatment and a 33% chance of receiving the placebo treatment. Your study doctor will explain what you have to do and the tests that you will have during the study.

You will only be given study medication while the study is going on but not after it has ended.

If you decide to take part, your study doctor will first look at your records, ask you questions about your health and do tests to see if this research study is right for you.

If you choose to participate, you will be asked to sign this Consent Form and follow the study procedures described below.

During this study, we will ask you to fill out questionnaires about health and well-being. We hope that you will answer all of the questions, but you can skip any questions you don't want to answer. The questionnaire will take about 20 minutes to complete.

Baseline Visit Screening and Procedure	Prior to your Right Heart Catheterization (RHC) procedure: • You will review and sign this consent form. • You will have a history and physical exam, including reviewing your medical history and assessing your NYHA classification (a measurement of degree of heart failure according to symptoms at rest and with activity). • Your medications will be documented. • You will have your weight recorded

	• A routine blood sample will be collected (NT-proBNP, CBC with differential, creatinine, blood urea nitrogen, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, total, direct and indirect bilirubin, hsCRP, renin, aldosterone, and HgbA1c). Approximately 2 tablespoons of blood will be collected. • Urine pregnancy test, if you are a female of child-bearing potential • Optional Saliva sample will be collected • Optional Fecal sample will be collected at the visit, or you will be provided with the equipment to do it at home and mail your sample in. Based on the above results, the study doctor will let you know if the study is suitable for your continued participation. If you are able to continue, the following will occur: **<u>Procedure Visit</u>** • You will have your RHC procedure. Hemodynamic testing during the right heart catheterization measures the blood pressure inside the veins, heart, and arteries. It also measures blood flow and how much oxygen is in the blood. It is a way to see how well the heart is working during your procedure. Fluoroscopy will be used during this procedure. Fluoroscopy uses X-rays to create moving images of your bones and internal organs. • Echocardiogram during the procedure. An echocardiogram is an ultrasound evaluation of the structure and function of the heart. You will rest on an examination table and an ultrasound probe will be brought into contact with your chest facilitated by ultrasound gel. This test does not involve any radiation. It usually takes 1 hour. • Venous, arterial, and coronary sinus research blood samples will also be obtained during the procedure. The total amount of blood drawn will be approximately 54 mL (approximately 3.6 tablespoons) of blood. • Once your procedure is complete, you will be observed in the recovery area per standard clinical practice and then you will be dismissed.

3 Days prior-to 7 Days post Procedure visit	At this visit: • You will check into the CRTU on the 5th floor of the Domitilla Building at St. Mary's Hospital. • You will have a blood volume analysis (BVA) test. The BVA test (also called a plasma volume test or a red cell mass test) is a procedure used to measure the volume (amount) of blood in the body. The test also measures the volume of plasma and of red cells in the blood. See end of this section for further information regarding this test. • You will have oral glucose tolerance testing. This test is non-invasive test where your blood sugar and fat levels are measured after receiving a sugar drink. See end of this section for further information regarding this test. • You will have a Dual Energy X-ray Absorptiometry (DEXA scan). A DEXA scan measures the amount of fat in your body using an x-ray that measures bone, calcium and fat. For this, you will lie on a table and a scanner will pass over your body twice. • You will complete a quality-of life questionnaire (KCCQ). • You will have an MRI scan of your heart and abdomen. This will measure your heart function and the amount of body fat that is present in your heart and abdomen. The MRI machine is a large, tube-shaped magnet. When you lie inside an MRI machine, the magnetic field temporarily realigns water molecule in your body. Radio waves cause these aligned atoms to produce faint signals, which are used to create cross-sectional MRI images-like slices in a loaf of bread. • Based on results from the above testing you will be randomized to either the semaglutide or placebo-treated group. • A nurse coordinator will teach you how to self-inject the study medication once/week at home. Written instructions will be provided as well. • OPTIONAL: We will ask you for a urine sample to be stored for future testing. See end of this section for further information regarding this sample. • OPTIONAL: You will be asked to have an optional fat biopsy. See end of this section for further information regarding this test.

In person and Telephone/video visits Done throughout the course of the study	• Multiple visits will occur through videoconference (preferred) or telephone (Weeks 2, 4, 8, 12, 26, 36 and 44) and in person (Week 16,) to assess for adverse events, collect current weight, and ensure compliance with medication and lifestyle interventions. During the first few visits you will learn about meal replacements and how to track a food diary. At Week 16 you will return your remaining study drug (semaglutamide/placebo) up to that point, as well as give another Saliva sample if you opt into this sampling. • You will be asked to keep a medication log throughout the course of the study. Study staff will review this at follow up visits.
Week 52 Visit	At this visit: • You will have a history and physical exam • Your medications will be documented • You will have your weight recorded • Return your remaining study drug (semaglutamide/placebo). • You will have an assessment of adverse events • A routine blood sample will be collected (NT-proBNP, CBC with differential, creatinine, blood urea nitrogen, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, total, direct and indirect bilirubin, hsCRP, renin, aldosterone, NTproBNP, and HgbA1c). Approximately 2 tablespoons of blood will be collected. • Urine pregnancy test, if you are a female of child-bearing potential, • You will have your RHC procedure. Hemodynamic testing during the right heart catheterization measures the blood pressure inside the veins, heart, and arteries. It also measures blood flow and how much oxygen is in the blood. It is a way to see how well the heart is working during your procedure. • Echocardiogram during the procedure, • Venous, arterial, and coronary sinus blood samples will also be obtained in triplicate at rest and during exercise. The total amount of blood drawn will be 54 mL (approximately 3.6 tablespoons) of blood,

	• Once your procedure is complete, you will be observed in the recovery area per standard clinical practice and then you will be dismissed. • OPTIONAL: We will ask you for a urine sample to be stored for future testing. See end of this section for further information regarding this sample. • OPTIONAL: You will be asked to have an optional fat biopsy. See end of this section for further information regarding this test. • OPTIONAL: You will be asked to provide a saliva sample • OPTIONAL: You will be asked to provide a fecal sample, you can do this at your visit, if able, or equipment will be provided for you to complete this at home and mail it to the study team. • EXCEPTION: Study participants that permanently discontinue treatment prior to week 26 will complete noninvasive testing (DEXA, MRI, Echo, KCCQ Questionnaire, Optional Urine Sample, Optional Saliva and Stool Sample) at the week 52 visit, while also being offered the option to complete invasive testing (Right Heart Catheterization with Echocardiogram, Oral Glucose Tolerance Test, Blood Volume Test and a Fat Biopsy).
3 Days prior-to 3 Days post Week 52 visit	At this visit: • You will check into the CRTU on the 5th floor of the Domitilla Building at St. Mary's Hospital. • You will have your weight recorded • You will have a blood volume test • You will have an oral glucose tolerance test. • You will have a DEXA scan • You will complete a quality-of life questionnaire (KCCQ). • You will have a cardiac and limited abdominal MRI test. • You will have an assessment of adverse events

Blood Volume Analysis Test:
You will be asked to drink a solution 30 minutes prior to the test. You will need to lie still on a flat surface for 15 minutes. During the blood volume analysis portion of the test, a small amount of a radioactive isotope or tracer is injected. Blood samples are taken at 6 time points during the test (a total of about 50 mL or 3 tablespoons of blood will be drawn) and analyzed. The blood volume test is used to measure the amount of blood in your body.

You will be awake during the test. You will lie on your back on an exam table for the entire test. Minimal movement is allowed during the test, except for sitting up, to allow accurate recording of the test results. We will try to make you as comfortable as possible during the test.

Throughout the test, the nurse or technician will ask you how you feel. You may not have any symptoms, or you may experience symptoms such as light-headedness, nausea, and palpitations (fluttering in the chest).

It is important to tell the staff how you are feeling throughout the test. Adjustments can be made if necessary, to make you more comfortable.

Results from the BVA will be documented in the medical record.

Oral Glucose Tolerance Test
For this test you will have an IV line placed to measure blood samples at baseline. You will then receive a sugar drink, after which small blood samples will again be obtained every few minutes through the IV line for 3 hours. A total of about 42 mL or 2 ½ tablespoons of blood will be drawn. This test is used to measure how well your body manages blood sugar and fats.

Tests done only for research purposes are not meant to provide clinical information or help care for you. The results are only important for research. Therefore, the results of tests done with your information and samples will not be provided to you. In the rare event that a finding might affect the health of you or your family, we will contact you and you can choose whether to receive or refuse the information. If you decide to follow up and further medical testing or care is needed, the costs will be billed to you or your insurance.

Optional Urine Sample
You will be asked to provide a urine sample two times during the study, once at the beginning and once at the end of the study. Many patients with obesity develop kidney abnormalities, which are believed to be related to excess body fat. Urine samples are being collected to study how weight loss affects the kidneys. Samples will be collected and banked for future analysis to determine the effects of semaglutide-facilitated weight loss on measures of renal structure and function. Samples will include urine sodium, uric acid, endogenous lithium, renal tubular injury markers, renal RAAS components, urine diuretic levels, urine cyclic GMP, and or renal fibrosis markers. There may be additional testing done on this sample that is unknown at this time.

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Read the following statement and mark your choice:

I agree to provide a urine sample at my post procedure visit:

☐ Yes ☐ No Please initial here: _____Date: _____

I agree to provide a urine sample at my Week 52 visit:

☐ Yes ☐ No Please initial here: _____Date: _____

Optional Fat Biopsy
You will be asked to have a fat biopsy at two timepoints during the study. Those timepoints are just after your procedure and at week 52. Fat biopsy is being performed prior to treatment with study medicine and after, to learn how weight loss changes the structure and function of fat cells in the body. This is an optional additional procedure to learn more information and is not required.

A fat biopsy is collected from just under the skin of your abdomen. Your skin will be well cleaned and a medication to numb the skin (local anesthesia) will be given. After the skin is numb the fat samples will be collected using a sterile needle. This procedure is used to sample fat cells from the abdomen (belly). After cleaning the skin on the front of your abdomen with iodine, a local anesthetic will be injected under the skin. A trained/certified designee will make a small incision in the skin of your abdomen and inject additional lidocaine and some saline (saltwater solution) that allows for easier removal of the fat cells using a needle with a suction device. The needle may be inserted through the incision up to 3 times to obtain adequate/enough fat. Suction will continue for several minutes if necessary. About 3 grams (approximately 1 teaspoon size) of fat will be removed. After the fat sample is completed, the skin will be held closed with sterile adhesive strips and a bandage. Of note, you will not be allowed to swim or soak in a bathtub/whirlpool/hot tub for 72 hours after this procedure.

Read the following statement and mark your choice:

I agree to have a fat biopsy done at my post procedure visit:

☐ Yes ☐ No Please initial here: _____Date: _____

I agree to have a fat biopsy done at my Week 52 visit:

☐ Yes ☐ No Please initial here: _____Date: _____

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Optional Saliva sample

You will be asked to provide a saliva sample 3 times throughout this study. Once at baseline, your 16 week visit, and your 52 week visit. The study team will collect this at each visit.

There is evidence that there may be drug-microbiome interactions. Independent of targeted semaglutide effects, knowledge about microbiome mechanisms can inform the development of other therapeutics to modulate microbiome more robustly for favorable HFpEF outcomes. Also, there may be benefits to 'prehabilitation' with early microbiome altering therapies that enhance semaglutide response and vice versa.

Read the following statement and mark your choice:

I agree to have a Saliva sample collected at my post procedure visit:

☐ Yes ☐ No Please initial here: _____Date: _____

I agree to have a Saliva sample collected at my Week 16 visit:

☐ Yes ☐ No Please initial here: _____Date: _____

I agree to have a Saliva sample collected at my Week 52 visit:

☐ Yes ☐ No Please initial here: _____Date: _____

Optional Fecal sample

You will be asked to provide a fecal sample 2 times throughout this study. Once at baseline, and once at your 52 week visit. At both of these points you will be given the option to complete this collection at home. In which case, the study team will provide you with equipment and instructions on how to mail your sample to the study team.

There is evidence that there may be drug-microbiome interactions. Independent of targeted semaglutide effects, knowledge about microbiome mechanisms can inform the development of other therapeutics to modulate microbiome more robustly for favorable HFpEF outcomes. Also, there may be benefits to 'prehabilitation' with early microbiome altering therapies that enhance semaglutide response and vice versa.

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Read the following statement and mark your choice:

I agree to have a Fecal sample collected at my post procedure visit:

☐ Yes ☐ No Please initial here: _____Date: _____

I agree to have a Fecal sample collected at my Week 52 visit:

☐ Yes ☐ No Please initial here: _____Date: _____

What are the possible risks or discomforts from being in this research study?

As part of this study, you may be prescribed a medication called *semaglutide* in addition to undergoing healthy lifestyle interventions. This drug is approved for weight loss and has been shown to be safe and well tolerated. You may experience some or none of the adverse effects listed below.

The most frequently reported adverse effects are:

- Nausea
- Vomiting
- Upset stomach
- Constipation
- Diarrhea
- Headache
- Fatigue

Rare, serious adverse effects associated with use of semaglutide include increased risk of Medullary thyroid carcinoma, acute pancreatitis, anaphylaxis, hypersensitivity reactions, retinopathy (in patients with diabetes), and angioedema.

Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Fetal and newborn risk cannot be ruled out.

You should get medical help and contact the study doctor or staff right away if you have any of these or any other side effects during the study.

There are always risks with taking a research medication. In addition to the risks or discomforts listed here, there may be other risks that may be unknown. Also, the risks or discomforts described may occur more often or be more severe than has been seen before. Your study doctor will carefully check your health for your safety. It is important that you tell your study doctor if you have any symptoms or if your heart failure worsens. In an emergency, and if you cannot contact your study doctor, please contact your family doctor or go to a hospital emergency department. Side effects usually go away after the medication is stopped, but sometimes they may not go away or may even get worse. Your study doctor will carefully look after your health and may decide that you should stop taking the study medications if it is not safe for you.

Risks of Study Procedures:

Right Heart Catheterization
There is a risk of bleeding or bruising at the site where the doctor introduces the small tube (catheter) into a vein. Pressure will be applied to this area to prevent bleeding as much as possible.

There is a risk of partial collapse of your lung if your neck or chest veins are used to insert the catheter.

Other, rare complications may include:

- Abnormal heart rhythms, such as ventricular tachycardia (fast heart rate in your main heart chambers)
- Cardiac tamponade (fluid buildup around your heart that affects its ability to pump blood effectively), which can be life-threatening
- Low blood pressure
- Infection
- Air embolism (air leaking into your heart or chest area), which can be life-threatening
- Blood clots at the tip of the catheter that can block blood flow
- Pulmonary artery rupture. This is damage to the main artery in your lung. This can result in serious bleeding, making it hard to breathe.
- Fluoroscopy: The amount of radiation from fluoroscopy during RHC procedure has a low risk of harmful effects.

Your heart rate and blood pressure will be checked in the recovery period. The study doctor will advise you following the procedure about resuming normal activities and care after sedation.

Blood Volume Test and Oral Glucose Tolerance Test
The main risk of the procedure is an allergic reaction to the iodine used in the blood volume test although this is rare. If needed, Benadryl can be given in the lab. Local pain or irritation of the vein (phlebitis) may occur when the IV line is placed for either of these tests.

The amount of radiation you will receive during the I-131 albumin infusion has a low risk of harmful effects. The effect of the radioactive I-131 albumin on a fetus (developing baby still in the womb) or on a breastfeeding infant may be harmful. Because of these risks, women cannot take part in this study if they are pregnant or breastfeeding.

If you are a female, you must have a negative clinical pregnancy test in order to participate in this study unless you cannot become pregnant.

Optional Fat Biopsy
The most common risks of a fat biopsy include pain, a small scar, small dent or bump and bruising at the site of the biopsy. The bruising may last one to two weeks. Less common risks of fat biopsies include bleeding, infection, and numbness of the skin around the site of the biopsy. In very rare cases, people might have an allergic reaction to the numbing medicine. The allergic reaction could include rash/hive, flushing of the face, itching, wheezing, and tightness in the throat. There will be a small scar from the biopsy.

Cardiac and abdominal MRI scan
There is no radiation associated with MRI, but people who have metal devices like pacemakers cannot have an MRI. Some people with claustrophobia may feel too closed in and may not tolerate MRI scanning. If you feel too confined in the MRI scanner you can inform the technologist and the MRI scan will be stopped. The MRI machine makes loud knocking sounds when it is scanning. Because of this you will be asked to wear earplugs while getting your MRI scan. The earplugs minimize discomfort from noise and keep the MRI noise within the safety range.

Echocardiogram
This test uses sound waves to look at your heart. The person doing the test will press on your chest with a machine to obtain the pictures. The pressure may be uncomfortable.

DEXA Scan
You will receive radiation from the dual x-ray absorptiometry (DEXA scan). The total amount of radiation that you will receive has a low risk of any harmful effects.

Questionnaires
It may be uncomfortable for you to answer personal or difficult questions about your disease and how it affects your activities of daily living, but there is no pain expected with completing the forms.

Blood Draws
You may have pain, swelling, or bruising where the needle enters your vein. There may be risk of infection. You may feel dizzy or you may faint.

Pregnancy Risks
The effect of the medicine used in this study to help lose weight on a fetus, embryo, or on a breastfeeding infant, may be harmful. Because of these risks, women cannot take part in this study if they are pregnant or breastfeeding.

If you have not gone through menopause, you must have a negative pregnancy test in order to participate in this study unless you cannot become pregnant. If you become pregnant during the course of the study, study drug will be discontinued immediately.

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below for the entire study:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

Confidentiality Risk
As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best interest,
- If you don't follow the study procedures,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, we will contact you 2 weeks following the last dose of study drug taken to assess for adverse events and to assess if there is any clinical change following discontinuation of study treatment; additionally, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

What if you are injured from your participation in this research study?

Where to get help:
If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries?
Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

What are the possible benefits from being in this research study?

This study may not make your health better. However, it is hoped that weight loss will prevent worsening of your heart failure and improve survival. There are also other health benefits associated with weight loss including reduced risk for diabetes, improvement in sleep apnea and blood pressure, and other benefits. Information from this study may help doctors and researchers to treat and get a better understanding of heart failure and develop new tests or medications to help other patients with this condition.

What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your heart failure. Alternatives include participation in another research study, or diet and lifestyle changes on your own. There are no medications approved with a definite indication of benefit specifically for obesity-related cardiomyopathy. Talk to the Principal Investigator or your doctor to discuss other options and any questions you may have.

What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Physical Exams
- Research blood and urine labs at Procedure and Week 52
- Glycated hemoglobin (Hemoglobin A1C), Renin, Aldosterone, and pregnancy tests, if needed
- Right Heart Catheterizations
- MRIs of the heart and abdomen
- Echocardiograms
- DEXA Scans
- Video/phone visits
- Semaglutide/placebo (medication for this study)
- Optional fat biopsy at post procedure visit and Week 52
- Optional urine sample for future testing at post procedure visit and Week 52
- Optional saliva sample at post procedure visit, week 16 and week 52
- Optional fecal sample at post procedure visit and week 52

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care, including co-payments and deductibles.

- Routine labs at screening and Week 52

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

Will you be paid for taking part in this research study?

You will receive $250 after you complete the screening/procedure visit and another $250 after visits at 52 weeks. If you are able to complete the entire study, you will receive up to $500. In order to provide this compensation, the study team will need your Social Security number.

You may also be reimbursed for some of your travel expenses, up to a total of $500. Travel expenses can include: Mileage at current IRS business rate, hotel, parking, or meals for your visits. Itemized receipts are required. Your reimbursement for travel mileage is calculated based on the round trip number of miles you travel from your home address to the site address and back as determined by a web-based mileage calculator (e.g., MapQuest). This distance (miles) will be documented in your study file.

Payment for participation in research is considered taxable income and reportable to the Internal Revenue Service (IRS). Accounts Payable at Mayo Clinic will be given your name, address and Social Security number in order to issue a check for your study participation. If you receive research payments totaling $600 or more in a calendar year, a tax Form 1099 will be sent to you. For Mayo Clinic employees, research payments are included in your paycheck with applicable taxes withheld and reported on your Form W2 after calendar year-end.

Will your information or samples be used for future research?

Identifiable information such as your name, Mayo Clinic number, or date of birth will be removed from your information or samples collected in this study, allowing the information or samples to be used for future research or shared with other researchers without your additional informed consent. Blood samples may be used for non-DNA analyses such as biomarkers in cardiovascular diseases, such as heart failure.

How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. You will be assigned a unique study number. A list of identifiers will be maintained electronically on password protected Mayo servers and only the study team will have access to the link between your unique study number and your personal identifiers.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

Your health information may be collected from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Other Mayo Clinic staff involved in your clinical care.
- The sponsor(s) of this study and the people or groups hired by the sponsor(s) to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, the Department of Defense, and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research.

MAYO CLINIC

Name and Clinic Number

Approval Date: **February 12, 2025**
Not to be used after: **February 11, 2026**

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you, but does not include information that directly identifies you. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form.

If the results of this study are made public (for example, through scientific meetings, reports or media), information that identifies you will not be used.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic, or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private, and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

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You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
Plummer Building, PL 3-02
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Participant Advocate at: researchparticipantadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts forever, unless you cancel it.

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Enrollment and Permission Signatures

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature