CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

INVESTIGATOR'S NAME: LUIS A. MARTINEZ-LEMUS, DVM, PHD; JAUME PADILLA, PHD; CAMILA MANRIQUE, MD

PROJECT #: 2025921

STUDY TITLE: TARGETING ADAM17 ACTIVITY FOR CORRECTION OF VASCULAR INSULIN RESISTANCE IN TYPE 2 DIABETES

INTRODUCTION

This consent is designed to give you a brief overview of the projects that are being conducted in this research study. The form may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand. The Principal Investigator is Dr. Luis Martinez-Lemus. The people working with Dr. Martinez-Lemus on this study are called the study team. Research studies include only people who choose to participate. As a study participant you have the right to know about the procedures that will be used in this research so that you can make the decision whether to participate. The information presented here is simply an effort to make you better informed so that you may give or withhold your consent to participate in this research study. Please take your time to make your decision.

Today, you are deciding if you are interested in participating in the study. This study is being sponsored by the National Institutes of Health. To participate in this study, you will need to provide your written consent.

WHAT SHOULD I KNOW BEFORE I DECIDE WHETHER TO TAKE PART IN THIS STUDY?

- Taking part in a research study is voluntary. You decide if you want to take part, and you can stop taking part at any time. Your regular medical care at the University of Missouri Hospitals and Clinics will not be affected now or in the future if you decide not to participate in this study.
- We are doing this study because we want to learn the extent to which administration of the dietary supplement phosphatidylserine (PS) effects vascular function and blood flow responses to insulin in individuals with type 2 diabetes.
- Thirty-four people with type 2 diabetes between the ages of 45-64 will take part in this study at the University of Missouri.
- If you take part in this study, you will come to the Clinical Translational Research Unit (CTSU) or a different University of Missouri research location for 5 scheduled visits. The CTSU has clinic rooms specially designed for research. You will have blood tests, DEXA scans, Glycocheck, brachial artery FMDs, Oral glucose tolerance tests (OGTT), Passive Leg Movement (PLM) blood flow with heart rate and blood pressure monitoring, ambulatory blood pressure monitoring (ABPM), questionnaires and physical exams completed during this study. We will explain these procedures in this form.

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- The use of the drugs: Glucose beverage (Dextrose) are being used in an off-label application for this study.
- This study includes taking the dietary supplement phosphatidylserine (PS) or a placebo for 4 weeks.
- The total amount of time you could be in this study is about 12 weeks.
- If you join this study, you will not have to stop your diabetes treatment for as long as you are in the study.
- Taking part in this study may or may not make your health better. We hope that the information we learn from this study will help identify new strategies to improve vascular function in people with type 2 diabetes.
- We will share any clinically relevant information obtained from study procedures with you after the completion of the study intervention. This could include results from 24-hour ambulatory blood pressure monitoring, body composition analysis via DEXA, etc.
- As with any research study, there are risks that we know about and there may be some we don't know about. We will explain these risks in this form.
- We will only include you in this study if you give us your permission first by signing this consent form.

WHY IS THIS STUDY BEING DONE?

Phosphatidylserine (PS) is a phospholipid (fat substance) that is found in the membranes of your cells. PS plays a role in helping cells message each other. We are investigating the role of PS supplementation in preventing the cell pathway that breaks down insulin receptors which increases insulin resistance in people with type 2 diabetes. The goal of this study is to determine if/how much the dietary supplement PS improves blood vessel function and blood flow responses to insulin in individuals with type 2 diabetes. Our plan is to provide you with 900 mg of a PS supplement or a placebo for 4 weeks and perform measurements on your blood vessels. Thirty-four people will be selected to complete this study.

WHAT IS INVOLVED IN THE STUDY?

Overall, the research project will last about 8 weeks and will consist of a 4-week period of PS or placebo supplementation as outlined below (**Figure 1**). If you are eligible and wish to continue, you will be provided with supplement or placebo pills at the time of pre-assessment to take at designated times during 4-week dosing period. Overall, this research includes one consenting visit, two equipment fitting visits, and two assessment visits.

Figure 1. Overview of study design

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Consenting visit
Today's visit will take up to 1 hour. We will describe the study in general. We will answer any questions you may have. If you are interested in proceeding with the study, you will sign this consent form. After consenting, the study team will collect medical information, including DOB, gender, ethnic/racial category, height, body weight (history of body weight gain or loss), waist circumference, vitals, and a medical history questionnaire. You will be scheduled for equipment fitting #1 and the pre-assessment visit.

	Screening Visit	AMBP Fitting (Day -7 to -2)	Pre-Assessment (Day 0)	Dosing Window (Days 1-28)	AMBP Fitting (Day 21-26)	Post-Assessment (Day 28)
Informed consent form signing	X					
Medical history	X					
Concomitant medication assessment	X		X	X	X	X
Height assessment	X		X			X
Weight assessment	X		X			X
Waist circumference assessment	X		X			X
Vitals signs (blood pressure, heart rate and respiratory rate, temperature)	X		X			X
24-hour ABPM		X			X	
24-hour ABPM activity log		X			X	
AM **T2D** medication hold			X			X
24-hour exercise hold		X	X		X	X
Overnight fasting			X			X
Fasted blood draw			X			X
Glycocheck			X			X
PWV			X			X
Brachial FMD			X			X
PLM Blood Flow with BP and HR			X			X
OGTT with Blood Flow, BP, HR			X			X
DEXA			X			X
Supplement/placebo dispensing			X			
Daily Supplement/Placebo dosing				X	X	X
Compensation	$0		$200			$400

Table 1. Overview of study activities.

Equipment Fitting Visits
At each of the equipment fitting visits, you will meet with the study team for about one-half hour at the CTSU. The study team will have you wear the ambulatory blood pressure cuff for the 24-hours after the visit and record all your activities in a log. Both the cuff and the log will need to be returned at the time of the following assessment visit. At the time of your initial equipment fitting visit, the study team will also orient you to the use of the Glycocheck equipment that will be used at the time of assessment.

Assessment visits
You will have 2 assessment visits, one before starting the study supplement/placebo and one after 4 weeks of taking the supplement/placebo. We anticipate that each assessment visit will last about 8 hours. You will come to the CTSU after a nocturnal sleep period (sleeping overnight), fasting overnight for 8+ hours (no food or drink, except water), and holding any glucose lowering AM medications (you can resume regular medications after the visit). You will also be

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asked to avoid caffeine and alcohol for 12 hours prior to the visit and to avoid exercise for 24 hours prior to the scheduled appointment. During this visit (**Error! Reference source not found.**) you will have vitals and a fasting blood draw completed, and you will complete procedures, including DEXA, carotid-femoral pulse wave velocity (cfPWV), brachial artery flow-mediated dilation (FMD), Passive Leg Movement (PLM) with measures of leg blood flow,

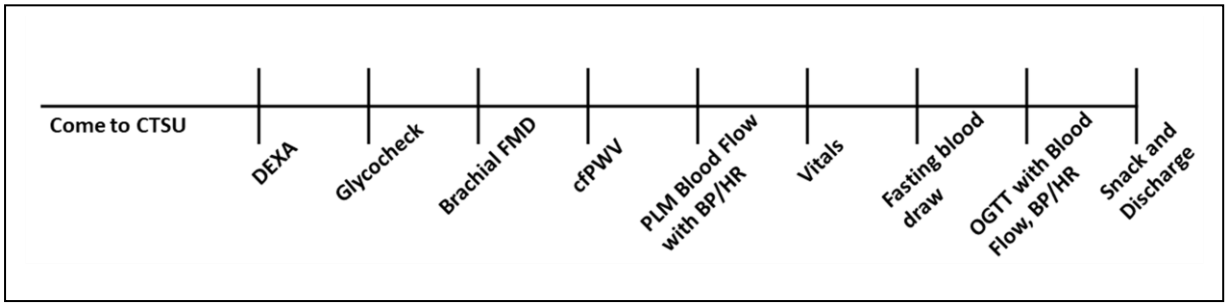

Figure 2. Order of procedures at assessment visits.

heart rate and blood pressure, Glycocheck, and oral glucose tolerance test (OGTT) with measures of leg blood flow, heart rate and blood pressure. You will be supplied with four weeks of supplement (or placebo) and a pill box and instructed on the dosing regimen. The study team will also contact you during the 4-week period to ask about your dosing compliance. You will be scheduled for equipment fitting #2 and post-assessment, which will occur at the end of week 4. All the study procedures will be repeated at post-assessment and the duration of the visit will be up to 8 hours.

WHAT ARE THE PROCEDURES AND RISKS OF BEING IN THIS STUDY?

Insertion of venous catheters and blood drawing

An IV used for blood draws will be placed by a nurse. The potential risks of venous catheterization include infection, swelling and discomfort at the catheter insertion sites. Some bleeding may occur during the insertion of the catheters as well after the catheters have been removed. There is also the possibility of fainting, dizziness, and possible pain and bruising because of catheter insertion. These risks will be greatly minimized by using sterile procedures and having an experienced registered nurse placing the venous catheters. Risk of bleeding is reduced by applying pressure at the site of puncture. Bruising is treated with ice. Fainting is prevented by drawing blood in the semi-recumbent position. If you wish to perform other research studies after you finish this project, you should let the investigator of the other study know that you have donated up to 110 mL (or about 1/2 cup) of blood.

Carotid-femoral Pulse wave velocity

This is a non-invasive assessment of arterial stiffness. A blood pressure cuff will be wrapped around your upper leg. The cuff will periodically inflate to squeeze tightly for less than 2-minutes. A pressure sensor, the size of a pencil will be placed over the skin of your neck region to obtain the pressure wave form in the neck vessel (i.e., carotid artery). This procedure takes about 15 minutes and requires an upper arm blood pressure to be taken beforehand. There are no risks associated with this procedure.

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When assessing PWV, the blood pressure cuff will squeeze the leg; however, any discomfort will be alleviated as soon as the pressure in the cuff is released. This procedure is not standard of care.

Oral glucose tolerance test
This procedure could cause possible nausea from the sugary glucose beverage. It may also cause your blood glucose level to be elevated. We will test your fasting blood sugar levels with a glucometer prior to starting this test. If your fasting blood sugar is more than 200mg/dL, we will not perform this test. This procedure is not standard of care.

Passive leg movement (PLM)
This procedure poses no risks. Guided movement at the knee joint may cause minor discomfort. This procedure is not standard of care.

Participant Monitoring (heart rate, blood pressure)
Patches will be placed on your chest to measure your heart's electric activity. A finger blood pressure cuff will be placed on your finger to monitor pressure. This procedure poses no risks. Some people may have a skin irritation from the patches that connect the wires on your chest to the computer. Skin and hair are pulled slightly when the patches are removed after the test. Research personnel will attach and remove the patches as carefully as possible. Some minor discomfort may occur with finger blood pressure cuff inflation. These procedures are not standard of care.

Glycocheck
A small, light-emitting probe will be placed under your tongue. The probe allows researchers to see your blood vessels and assess the integrity of the glycocalyx on the inner surface of the blood vessels. There are no risks associated with this test. This procedure is not standard of care.

Brachial artery FMD
A blood pressure cuff will be inflated on your forearm for up to 5 minutes. During this time, your arm may get numb due to decreased blood flow. An ultrasound image/video of your upper arm will be taken before, during, and after the inflation of the blood pressure cuff. This is a measurement of endothelial function. There are no risks associated with this procedure. When assessing FMD, the blood pressure cuff will squeeze your arm tightly; however, any discomfort will be alleviated as soon as the pressure in the cuff is released. This procedure will be performed in duplicate. This procedure is not standard of care.

Measurement of body composition by DEXA
You will have a DEXA (Dual Energy X-ray Absorptiometry), which is a procedure to measure your body composition - how much fat and muscle your body has. It is a type of x-ray machine with a moving arm. This procedure involves lying on a table for 15 minutes while the DEXA machine passes over your body. Although you will need to remain very still and quiet, you will feel nothing and should have no discomfort. You will be exposed to a small radiation dose which is about 2% of the average radiation dose from all sources (natural background radiation, consumer appliances, radon gas, medical tests, etc.) that a person receives in the United States each year. However, radiation effects are cumulative. You should always inform future doctors of your participation in this study. For female participant, a urine pregnancy test will be performed before the scan. This procedure is not standard of care.

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Phosphatidylserine Supplement (PS)
The proposed dose of the PS supplement (900mg/day) is well-tolerated and posed no risks. No side effects have been reported. Administration of this supplement is not standard of care.

Randomization
You will either take a placebo or a supplement as part of this study. There is random chance of you being assigned to either the placebo or supplement treatment. This is referred to as randomization. Neither you or the study team will know whether you are taking the placebo or supplement. This is called blinding.

One out of every two participants will be randomized to receive PS, and one out of every two participants will be randomized to receive placebo. There are no risks associated with randomization or blinding in this study

Results of Study Evaluations
Results of the 24-hour blood pressure evaluation will be reviewed by Dr. Camila Manrique, MD If the average blood pressure reading from the 24-hour ambulatory blood pressure monitoring evaluation is >180/110, results of the evaluation will be shared with you within 5 days of result availability. You will be advised to follow up with your primary care provider regarding hypertensive management. If the average blood pressure reading from the 24-hour ambulatory blood pressure monitoring evaluation does not exceed 180/110, results will not be shared with you until the completion of all study activities.

All study results are considered as strictly informational and are not diagnostic. You will be encouraged to discuss those results with their healthcare providers to determine if any changes in your treatment regimen are needed.

WHAT WILL BE MY RESPONSIBILITIES DURING THE STUDY AND ARE THERE BENEFITS?

While you are part of this study, the researchers will follow you closely to determine whether there are problems. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, prescribed, or purchased over the counter.
- Report to the researchers any injuries or illnesses while you are on the study, even if you do not think they are related.

If you agree to take part in this study, there may not be direct medical benefit to you. Your participation will contribute to new knowledge. We hope the information learned will help identify novel strategies to improve vascular function in diabetes.

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WHAT ARE THE COSTS?

You will not be charged for any procedures that are part of this research study. Parking will be provided but there is no childcare during this study.

WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

As shown in **Table 1**, you will be compensated a total of $600 for completing this study. Study compensation is pro-rated with the completion of study visits: you will be compensated $200 after the completion of the first assessment and $400 after the completion of the second assessment. Checks are sent to you through the mail and usually take 1-2 weeks to arrive. We will need your social security number to pay you. Any payment may need to be reported as income on your tax return. If you are not a resident/citizen (non-resident alien) of the United States, you will need to work with the MU nonresident Tax Specialist at 573-882-5509.

WHAT OTHER OPTIONS ARE THERE?

You do not have to participate in this study. Standard of care, i.e., meeting with a medical provider for the evaluation and treatment of type 2 diabetes with pharmacotherapy and diet/lifestyle intervention will not be withheld during this study. The research team will ask you to update them with any changes to medication regimens that may occur between the time of your screening and post-assessment visits.

WHAT ABOUT CONFIDENTIALITY?

Information produced by this study will be stored in the investigator's files. Files are kept in a locked office or locked file cabinet that is only accessible to the investigator and the study coordinator. Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law. It is possible that your research record, including identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), federal or state government agencies (including the FDA), MU IRB, or hospital accrediting agencies, in the course of carrying out their duties. The Food and Drug Administration (FDA) may access your records for auditing purposes. If your record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, the University of Missouri will use reasonable efforts to protect your privacy and the confidentiality of your medical information. The results of this study may be published in a scientific journal or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

We will keep the information and/or samples we collect from you for this study to use in experiments related to this project without asking for your consent again. Information that could identify you will be removed from your research data/samples so no one will know that it/they belong to you.

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WHAT IF I AM INJURED?

It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional, and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff.

The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?

Taking part in this study is voluntary. You do not have to take part. Your present or future medical care will not be affected if you decide not to take part.

If you do decide to take part, you can change your mind and drop out of the study at any time. This will not affect your current or future care at the University of Missouri Hospitals and Clinics. There is no penalty for leaving the study and you will not lose any benefits that you are entitled to receive.

If the study investigator decides to take you off the study, he will explain the reasons and help arrange for your continued care by your own doctor, if needed.

We will tell you about any new information discovered during this study that might affect your health, welfare, or change your mind about taking part.

A Data Safety and Monitoring Board, an independent group of experts, will review the data collected during this study. We will tell you about any new information discovered during this study that might affect your health, welfare, or change your mind about taking part.

WHERE CAN I GET MORE INFORMATION ABOUT THIS STUDY?

A description of this clinical trial will be available on 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.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

If you have more questions about this study at any time, you can call Dr. Luis Martinez-Lemus at (573) 884-3729.
You may also contact the University of Missouri Institutional Review Board (IRB) if you:

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- Have any questions about your rights as a study participant;
- Want to report any problems or complaints; or
- Feel under any pressure to take part or stay in this study.

The IRB is a group of people who review research studies to make sure the rights of participants are protected. Their phone number is 573-882-3181. There email is muresearchirb@missouri.edu.

If you want to talk privately about your rights or any issues related to your participation in this study, you can contact University of Missouri Research Participant Advocacy by calling 888-280-5002 (a free call), or emailing MUResearchRPA@missouri.edu.

We will give you a copy of this consent form. Please keep it where you can find it easily. It will help you to remember what we discussed today.

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SIGNATURE OF STUDY PARTICIPANT

Consent to Participate in Research

By signing my name below, I confirm the following:

- I have read/had read to me this entire consent form.
- All my questions were answered to my satisfaction.
- The study's purpose, procedures, risks, and possible benefits were explained to me.
- I voluntarily agree to take part in this research study. I have been told that I can stop at any time.

Subject's Signature	**Date**

Signature of Witness (if applicable) *	**Date**

** A witness is required when a participant is competent to provide consent but is blind or cannot read or write.*

SIGNATURE OF PERSON AUTHORIZED TO OBTAIN CONSENT*

I have explained the purpose of the research, the study procedures (identifying those that are investigational), the possible risks and discomforts and potential benefits of the study and have answered questions regarding the study to the best of my ability.

Signature of Person Authorized to Obtain Consent	**Date**

**This signature is required for FDA regulated research and/or research that involves any medical procedure or surgical treatment.*

General Consent Version 8.0 - 07/17/2024 Reconsent? Yes No

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