Official Title: A Dose Finding Trial for Angiotensin II in Hypertensive Adults on Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with Anesthesia-Mediated Hypotension

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Wake Forest®
School of Medicine

DEPARTMENT OF ANESTHESIOLOGY

A DOSE FINDING TRIAL FOR ANGIOTENSIN II (GIAPREZA™) IN HYPERTENSIVE ADULTS ON ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS WITH ANESTHESIA-MEDIATED HYPOTENSION

INFORMED CONSENT FORM TO PARTICIPATE IN RESEARCH
ROHESH J. FERNANDO, MD, FASE, PRINCIPAL INVESTIGATOR

SUMMARY

You are invited to participate in a research study. The purpose of this research is to determine the dose of a particular drug called Angiotensin II (Giapreza™) that is needed to appropriately maintain blood pressure in patients who normally take medications to treat high blood pressure (hypertension) but experience low blood pressure while under general anesthesia for surgery. You are invited to be in this study because you have hypertension (high blood pressure), are taking medications for this reason, and are undergoing a planned surgery under general anesthesia.

Your participation in this research will involve zero additional visits, other than the usual visit for your planned surgery and the preoperative anesthesia visit that typically accompanies it.

Participation in this study will involve receiving Angiotensin II intravenously after you are asleep under general anesthesia for surgery. However, you will only be given this medication if your blood pressure decreases enough to require being treated with medications. In addition, you will have five blood samples drawn. Two will be at the time that your intravenous line is placed in the preoperative holding room and three will be after you are under anesthesia. All research studies involve some risk, however there are no significant risks expected in this study. If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: Angiotensin II (Giapreza™) could be more effective in treating low blood pressure than the medications currently used.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Rohesh J. Fernando, MD, FASE. If you have

questions, suggestions, or concerns regarding this study or you want to withdraw from the study, his contact information is: [redacted].

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have high blood pressure (hypertension), are taking medications for this reason, and are undergoing a planned surgery under general anesthesia. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research is to determine the dose of a particular drug called Angiotensin II (Giapreza™) that is needed to appropriately maintain blood pressure in patients who normally take medications to treat high blood pressure but experience low blood pressure while undergoing general anesthesia for surgery. This is important because the medications used to start and maintain anesthesia frequently cause a decrease in blood pressure.

Currently, Angiotensin II (Giapreza™) is approved by the US Food and Drug Administration (FDA) to treat low blood pressure associated with shock, but it has not been specifically approved for treating low blood pressure during anesthesia.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Ninety people will be recruited at Wake Forest Baptist Health in order to enroll sixty people in this study.

WHAT IS INVOLVED IN THE STUDY?

You will have five blood samples drawn. Two will be at the time that your intravenous line is placed in the preoperative holding room and three will be after you are under anesthesia. You will be seen in the holding area prior to your scheduled surgery. An intravenous line will then be placed, as is typical for patients having surgery, so that you can be given medications and fluids into your vein. At that time the first two blood will be taken so that we can measure the levels of various hormones in your blood stream that your body uses to control your blood pressure. You will have your blood pressure and heart rate checked and recorded at that time as well.

Once you are taken back to the operating room for surgery your blood pressure and heart rate will again be checked and your anesthesia team will give you medications to put you to sleep for surgery. After you are sleeping your blood pressure will be checked every minute, which is typical for patients who have just been put under anesthesia. If your blood pressure goes down below a certain point you will be started on a constant infusion of Angiotensin II (Giapreza) at a low dose. The dose will be increased slowly if needed until your blood pressure returns almost back to where it started. After your blood pressure remains stable on the infusion of medication for 5 minutes, the third and fourth blood samples will be drawn and the infusion of medication will be stopped. Your blood pressure will be supported with other medications as needed per your anesthesia team. Finally, a fifth blood sample will be drawn thirty minutes after the surgical procedure starts.

You will have approximately 1-1.5 tablespoons of blood taken for each of the blood sample tubes. There will be a total of 5 blood samples that will be withdrawn from a vein at three time points. The first two samples will be taken in the holding room, the third and fourth samples will be taken 5 minutes after Angiotensin II infusion stabilization, and the fifth and final sample will be taken 30 minutes after Angiotensin II infusion. The total amount of blood withdrawn during the study will be approximately 5 tablespoons.

If your blood pressure does not drop to a level that requires treatment, then the study drug will not be administered. However, we may still draw the blood samples mentioned above to test the levels of hormones. This will be done for up to 15 patients that did not receive the study drug.

The study team will call you seven days after your surgical procedure to ask how you have been feeling.

How Long Will I Be in the Study?

You will be in the study for only about one week. The study starts when we place your intravenous line in the holding room and ends after our follow up phone call, which will take place seven days after your surgical procedure. If you are not feeling well at the time of the first follow up phone call, you may receive additional phone calls to determine whether you are experiencing a side effect due to receiving angiotensin II.

You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the drug we are studying include: blood clots, low platelet count, fast heart rate, fungal infection, delirium, and increased blood sugars. These risks come from a study of Angiotensin II (Giapreza) that was performed on very sick

patients in the intensive care unit so it is unclear how likely these are to happen in a study on healthier patients.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

You may experience discomfort, bruising and/or bleeding where the needle is inserted for your blood draws. Occasionally some people become dizzy, lightheaded, or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm from Angiotensin II (Giapreza) to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, hysterectomy, vasectomy of the partner in a monogamous relationship (same partner), or if at least 2 years have passed since you experienced menopause. An acceptable, although less reliable, method includes "double barrier contraception." Examples include the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. If you are a sexually active woman of childbearing potential, we will perform a pregnancy test on the day of surgery to check for possible early pregnancy prior to starting treatment.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: Angiotensin II (Giapreza) could be more effective in treating low blood pressure than the medications currently used.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options:

You could elect to receive more traditionally used medications if support of your blood pressure is needed while you are under anesthesia. How Angiotensin II (Giapreza) compares to these

other medications is currently unknown.

WHAT ARE THE COSTS?

All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the FDA which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest University Health Sciences. La Jolla Pharmaceutical Company will be providing support to Wake Forest University Health Sciences to help conduct this study. The study is also partially funded by the National Institutes of Health. The researchers do not, however, hold a direct financial interest in La Jolla Pharmaceutical Company or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. Wake Forest University Baptist Hospital does not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the sponsor may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the sponsor is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Rohesh J. Fernando, MD, FASE at [redacted] or [redacted] after hours.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes: information about your medical conditions, medications, your age, gender, weight, and vital signs.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; La Jolla Pharmaceuticals, central laboratories, Attoquant Diagnostics GmbH, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS), the National Institutes of Health (NIH), and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Rohesh J. Fernando, MD, FASE that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Rohesh J. Fernando, MD, FASE
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form, you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

What Are My Rights as a Research Study Participant?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because they feel it is in your best interest, you have an unexpected reaction to the medication, or because they believe that an alternative medication to support your blood pressure would be better/safer.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

Whom Do I Call if I Have Questions or Problems?

For questions about the study or in the event of a research-related injury, contact the study investigator, Rohesh J. Fernando, MD, FASE at [redacted] or [redacted] after hours.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the

Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm