Effect of Firdapse® in Patients Treated with Onabotulinumtoxin A

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A PROOF OF CONCEPT STUDY OF THE EFFECT OF AMIFAMPRIDINE (FIRDAPSE®) ON NEUROMUSCULAR TRANSMISSION IN PATIENTS TREATED WITH ONABOTULINUMTOXINA (BOTOX®, BTX-A)

Informed Consent Form to Participate in Research
James Caress, MD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to determine if a single dose of the FDA-approved medicine, amifampridine (Firdapse®), can temporarily reverse the effects of botulinum toxin. Amifampridine is a safe and effective medicine that treats a rare neuromuscular disease that is similar to an overdose of Botox. For this reason, amifampridine may be used in treating side effects of Botox injections. You are invited to be in this study because you have been treated with botulinum toxin type A (Botox®) for your headache. Your participation in this research will involve a single visit and lasts about 3 hours in total.

Participation in this study will involve taking a single, standard dose of amifampridine and undergoing a procedure known as single fiber electromyography (SFEMG) in a forehead muscle to see if the lingering effects of your Botox treatment can be temporarily improved with amifampridine. All research studies involve some risks. A risk to this study that you should be aware of is discomfort during SFEMG and a tingling sensation in your body which is a side effect of the medicine. You will not directly benefit from participation in this study but will be contributing to research that may play a role in your future treatment. You will be compensated for your time.

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. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study please contact the Principal Investigator at [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 Wake Forest University Health Sciences Research Subject Advocate at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies help scientists learn new information that may help other people in the future. You are being asked to be in this study because you are being treated for headache with botulinum toxin (Botox®). Your participation is voluntary. You do not have to be a part of this study if you do not want to. Please take your time in making your decision if you would like to join. 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 study is to determine if amifampridine can partially and temporarily reverse the effects of Botox. Currently, there is no approved treatment to reverse the effects of unintentional overdoses of Botox. About 5% of patients treated with Botox report mild side effects of facial weakness following Botox treatment and there is no treatment beyond waiting for Botox to wear off which takes several weeks to a few months. Amifampridine is used to treat a condition known as Lambert-Eaton Myasthenic Syndrome which is the result of a failure in signaling between the nerve and the muscle. Botox injections cause a similar failure in signaling between nerve and muscle which is why amifampridine might be helpful in patients who develop facial weakness after Botox treatment.

Following a Botox injection, nerve muscle signaling is impaired after a few days and remains impaired out to 6 months after treatment but usually there are no evident symptoms in patients. SFEMG is used to detect subtle impairment of this signaling and is expected to be abnormal in all patients treated with Botox 3 months after treatment even when there is no sign of facial weakness.

Amifampridine is a safe and well-tolerated drug approved to treat Lambert-Eaton Syndrome. It improves nerve muscle signaling within 30 minutes and its peak effect lasts about 2 hours.

All of this means that, although you have no signs of facial weakness, the effect of your previous Botox treatment can still be detected by SFEMG even a few months after your treatment and amifampridine could improve this signaling even after a single dose. This study is designed to explore whether amifampridine can improve signaling in preparation for later studies that will try show improved strength in the minority of patients who suffer clinically important facial weakness after Botox injections.

Amifampridine has been approved by the US Food and Drug Administration (FDA), but it has not been approved to treat side effects from botulinum toxin injections. In this study, the dose you will receive is a standard strength that is typically given several times a day but <u>you will only take a single dose.</u>

How Many People Will Take Part in the Study?

Twenty (20) people at this single research site will take part in this study. In order to identify the 20 subjects needed, we may need to screen as many as 30 because some people may be unable to complete the SFEMG procedure.

What Is Involved in the Study?

Prior to the study visit, a study coordinator will call you to verify some key points for eligibility including prior Botox exposure, past medical history, and allergies to medications. The coordinator can also answer questions you may have about the study.

At the study visit, you will meet the study doctor, who will verify the medical history and answer further questions before beginning the study. Following signing of this form, your vital signs will be measured and a urine pregnancy testing on pre-menopausal female participants will be performed. The doctor will perform the baseline single fiber electromyography (SFEMG). For this procedure, the doctor will clean the forehead with an alcohol swab and insert a thin needle electrode into the forehead muscle that elevated your eyebrows. This needle is similar in size to the needles used for Botox injections and will be similarly painful. The doctor will measure electrical impulses in the forehead muscle that is generated by you raising your eyebrows which reflects the nerve muscle signaling in 2-3 locations of your forehead. This will take about 15 minutes and the needle is removed.

Next, you will be given a single dose (two 10mg pills) of amifampridine to take orally. You will sit quietly for about 30 minutes while the medicine is absorbed and then will undergo another identical SFEMG which will also take about 15 minutes. Following completion of the testing, you will be monitored for approximately 90 minutes for any side effects of the treatment.

By 2 hours after dosing, the peak effect of the medicine is well past and it will be safe for you to return home or work. At this point, the study is over but you will be given a contact number to call in the event of any delayed concerns. The SFEMG results will not be analyzed during your visit so there will be no results to reveal.

The study team will be immediately available during the entire visit and you can call the study doctor with any questions following the study.

How Long Will I Be in the Study?

You will be in the study for about three hours. 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.

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. The single fiber EMG procedure causes mild to moderate discomfort for about 30 minutes and could cause bruising at insertion sites. In clinical practice, about 95% of patients tolerate this procedure.

The study medicine, amifampridine, at the dose you will take may cause a tingling sensation in your face or limbs because of its effect on nerves. About half of patients taking this dose experience tingling when taking amifampridine regularly but we believe that a single dose is unlikely to cause tingling. This side effect would resolve in less than 4 hours.

Neither the SFEMG nor the study medicine will have any effect on your future Botox dosing.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

There also may be other risks 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 to your health.

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm 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, OrthoEvra patch, NuvaRing, intrauterine devices (IUD), Nexplanon implant, DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a diaphragm with spermicide with Plan B used for any noticed condom or diaphragm failures. We encourage you to discuss this issue further with your physicians if you have any questions.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You are not expected to receive any direct benefit from taking part in this research study. We hope the information learned from this study will benefit future patients that experience side effects from Botox injections.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study. This is not a treatment study. Your alternative is to not participate in this study.

WHAT ARE THE COSTS?

All study costs, including any study products or 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 or permitted by law, or necessary to protect the safety of yourself or others.

Your 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.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $250 if you complete all the scheduled procedures. If you withdraw for any reason from the study before completion you will not be paid.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS FUNDING THIS STUDY?

Catalyst Pharmaceuticals Inc. is providing a grant along with study medicine to the researchers to support this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A

RESULT OF PARTICIPATING IN THIS STUDY?

Wake Forest University Baptist Medical Center maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of injuries or illnesses to some participants in certain research studies. 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. To the extent research coverage is not available, you or your insurance company may be charged for the costs of medical care. You may receive care at Wake Forest University Baptist Medical Center and/or Atrium Health.

If you are injured, the insurer 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 insurer 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 Dr. James Caress at [redacted] or after hours, [redacted] and ask for the neurologist on call.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you 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**:** basic demographic information and information about your previous Botulinum toxin treatments.

We will take steps 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; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and Atrium Health Facilities; 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) 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, videotapes, audiotapes or other recorded media which can identify you unless with your written authorization.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to your medical record for verification of clinical trial procedures or data to the extent permitted by other applicable laws. These monitors, auditors, and other individuals are also required to maintain the confidentiality of your protected health information.

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.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire.

You can tell Dr. Caress 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:

James Caress, MD

[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.

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 the SFEMG procedure cannot be reliably measured or you have an unexpected reaction to the study medicine. Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

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, Dr. James Caress at [redacted] or after hours, [redacted] and ask for the neurologist on call.

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