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Title of Study: The relationship among changes in Brain Network Activation, changes in core depressive and cognitive symptoms and safety and tolerability in adult outpatients with major depressive disorder treated with open-label, flexible-dose vortioxetine: A proof of concept study

Sponsor: John Zajecka, M.D.

RUSH

Subject Information Sheet and Consent Form

Introduction

You are being invited to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the information in this form carefully, as it may contain words you do not understand. You may wish to discuss it with your doctor, family, and/or friends. If there is anything that you do not understand or you would like more information, please ask questions and the study doctor or study staff will try their best to answer them. Once the study has been explained and you have had all your questions answered to your satisfaction, you will be asked to sign this form if you wish to participate. Before anything is done for this study, you must sign this form. A copy of this signed form will be given to you.

You do not have to take part in this study. You are free to withdraw from this study at any time you choose without giving a reason. This will not affect any future care you will receive. No promises can be made about the outcome of this as far as your current condition, either positive or negative. People who take part in research are called "subjects" instead of "patients".

Why are you being invited to participate in this study?

You are being asked to take part in this study because you are between the ages of 18-65 years and have major depressive disorder (MDD).

What is the purpose of this study?

This is a preliminary (or "pilot") study to evaluate whether brain network activation technology can predict the effects of vortioxetine on major depressive disorder and cognitive function, and whether further studies are justified.

Recent studies have shown that brain network activation analysis may be used as a tool to improve diagnosis and monitor treatment response in major depressive disorder. Brain

network activation is a method of analyzing brain activity. In order to collect the data needed for the brain network activation analysis, you will undergo a series of EEG (electroencephalogram) recording sessions.

Description of EEG procedure
An EEG is a test performed by placing a cap on your head which contains EEG sensors. The cap will fit snugly over your head and a small part of your face. (If you would like to see the cap before signing this consent document, please ask the study staff.) During the EEG, a machine records your brain waves as you perform mental tasks. The mental tasks involve having you respond to things you hear or see on a computer screen. The EEG procedure will last approximately 1½ to 2 hours and is performed 4 times during the study.

Vortioxetine is classified as an atypical antidepressant. It is currently sold under the brand name Trintellix. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of Major Depressive Disorder (MDD) in adults.

Because this is a research study, the vortioxetine will be given to you only during this study and not after the study is over, though it is available by prescription. The study staff will provide referrals to physicians for follow up care at the end of your study participation.
The Brain Network Activation™ technology was developed and is utilized by ElMindA Ltd.

How many study subjects are expected to take part in the study?

Up to 40 subjects are expected to enroll in this study. This is the only site participating in this study.

What will you be asked to do?

Screening/Visit 1:

Before any study-related tests and procedures are performed, you will be asked to read and sign this consent document. The study staff will ask you to give your consent for our clinic to request and receive your prior medical records that may help document your medical and psychiatric history for purposes of participating in this study.

Washout

If you are taking a medication that is not allowed on the study, you will be asked to stop taking it. This will likely include any medications you are taking to treat your depression, if any. This is called a washout period, during which the effects of these medications leave your body.

The following tests and procedures will be performed to determine if you qualify to take part in this study:

Visit 1 - Screen visit (week -1 to -2)

Following the informed consent process, subjects will begin the Screening Visit (Visit 1). The screening visit will include a psychiatric/medical history, vital signs, urinalysis, urine drug screen, urine pregnancy test (women), EEG, blood drawn for laboratory tests (CMP, CBC w/differential, TSH), ECG, and clinician and patient-rated scales.

Visit 2 – 10 (weeks 0 to 8)

- Subjects who meet all inclusion criteria and no exclusion criteria following the

screening visit will enter the study. Weekly study visits will be conducted for efficacy, safety, and tolerability.

- Study medication will be dispensed at Visits 2-9. The dose will follow FDA-approved package insert recommendations for vortioxetine. The dose for all subjects will start at 10 mg/day and increased to 20 mg/day at Visit 4. The dose will remain at 20 mg/day if tolerated, but can be reduced if you are unable to tolerate this dose. Dose changes are allowed based on how well you respond to and tolerate vortioxetine. The maximum dose is 20 mg/day and the minimum dose is 5 mg/day. No dose changes will be allowed after Visit 8 (if a dose adjustment is required after Visit 8, you may need to be withdrawn from the study).
- You will be asked to bring all unused medication and/or containers (even if empty) to each study visit.
- A baseline EEG will be taken before the subject begins taking vortioxetine and follow-up EEG readings will be taken at Visit 4, and Visit 10 (or last study visit if a subject is withdrawn early).
- Vital signs, review of adverse events, study drug accountability and clinician and patient-rated scales will be conducted at specific study visits.

If you participate in this study, you will be expected to complete all study-related procedures, arrive at the study center on time for all scheduled visits and comply with the following testing requirements for visits 1, 2, 4, 10 when an EEG is to be done:

- You should wash your hair the night before the visit, avoid leave-in conditioners and arrive with dry hair.
- You should arrive without make-up or hair products such as creams, gels, mousse etc.
- You should arrive after a full night's sleep.
- You should not consume caffeinated beverages 2 hours prior to testing.
- It is recommended to wear light and comfortable clothing.
- In case you require vision aids, you should arrive with glasses and not with contact lenses.

How long will you be in the study?

Your participation in this study will last approximately 10 weeks and include 10 study visits to the study center. The visits will occur on a weekly basis.

Most study visits will be completed in about 1 hour, except for visits 1, 2, 4 and 10, when an EEG is required (these visits will last approximately 3 hours each).

You may stop your participation at any time without affecting your ongoing medical care. However, if you decide to withdraw, it is recommended that you contact the study staff so that appropriate guidance can be provided for stopping the study medication.

You may be removed from this study without your consent. Possible reasons may be that the study doctor decides that continued participation in the study will be harmful to you, you are unable to keep your scheduled appointments or comply with study expectations, you will need a treatment not allowed on the study, your disease becomes worse or you develop a side effect or condition that may place you at risk by continuing to participate in the study, you are unable to take the treatment as directed, or the study is canceled.

What are the possible risks of the study?

Side Effects of Vortioxetine

All drugs have the possibility of complications and undesirable side effects. Side effects do not happen to everybody who takes vortioxetine. Side effects usually occur during the first or second week of taking the drug and seem to disappear or decrease in intensity and frequency with continued dosing.

Individuals receiving vortioxetine commonly reported the following adverse reactions or side effects (1%- 5%):

- nausea, dry mouth
- diarrhea
- constipation
- vomiting
- dizziness
- somnolence (sleepiness)
- upper respiratory infections
- nasopharyngitis (common cold)

Subjects with major depressive disorders may experience worsening of their depression and/or emergence of suicide thoughts and behavior, whether or not they are taking antidepressant medications. This risk may persist until your depression significantly lessens. There is a concern that antidepressants for certain people may have a role in making depression worse and causing suicidal thoughts. Both you and your family should be alert to your depression worsening and the occurrence of suicidal thoughts, especially at the beginning of dosing or at the time of dose changes. You must report such symptoms to your study doctor immediately, and the study doctor may recommend that you be evaluated in the emergency room, and possibly removed from the study.

Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think they are related to the study drug.

It is possible that you could have problems and side effects of vortioxetine that nobody knows about yet, which include your depression getting worse or even death.

It is possible that taking vortioxetine with your regular medications or supplements may change how vortioxetine, your regular medications, or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study.

Risks of EEG procedure

The EEG procedure is non-invasive and is not associated with health risks. Some subjects may experience mild discomfort while the EEG sensors are placed or removed.

Memory and thinking tests can sometimes make you tired or uncomfortable. The study staff will try to make you as comfortable as possible. You have the choice not to answer a question at any time during the study.

Similarly, answering interview questions and filling out questionnaires may cause you some discomfort, as some of the questions are very personal. We hope you will answer all the questions, but you can skip any questions you do not want to answer.

While the EEG test can detect seizures, we will not be analyzing your data for seizures. If we find an unexpected abnormality on your EEG, you will be contacted with a referral for a standard clinical EEG and interpretation.

Other Risks

You may feel discomfort during some of the tests and may also have risks, such as:

- Blood samples: possible side effects from blood drawing include faintness, swelling of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- ECG: Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.

During the washout period (if applicable), you will not be receiving active drug and your depression may become worse, stay the same or improve.

UNFORESEEN RISKS

All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction are:

- a rash
- having a hard time breathing
- wheezing when you breathe
- sudden drop in blood pressure
- swelling around the mouth, throat, or eyes
- fast pulse
- sweating

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

NEW FINDINGS

Any new information that is discovered during the study and which may affect your willingness to continue in the study will be made available to you.

Are there any anticipated pregnancy risks?

Women

Taking the study drug may involve unknown risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. Therefore, if you are pregnant, planning to become pregnant or are breastfeeding a child, you cannot participate in this study.

If you are a woman able to have children, you must use an effective method of birth control while you are participating in this study and for 30 days after your last dose of study drug. You

are considered able to have children if you have started your period AND have not completed menopause AND have not had a hysterectomy.

Acceptable methods of birth control for this study include:

- Barrier methods (male condom PLUS spermicide; cap (plus spermicidal cream or jelly) PLUS male condom and spermicide; diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide
- Intrauterine devices (IUDs) (copper T PLUS condom or spermicide; progesterone T PLUS condom or spermicide
- Hormonal contraceptives (implants; hormone shot/injection; combined pill; minipill; patch; vaginal ring PLUS male condom and spermicide)

If you become pregnant during this study, you should notify the study staff as soon as possible. The study drug will be stopped and your participation in this study will be ended. In addition, if you become pregnant during the study or within 30 days after your last dose of study drug, we will keep in touch with you until the end of the pregnancy. We will ask you to provide information about the outcome of the pregnancy. If you have a baby, we will ask about the health of the baby.

Are there benefits to taking part in the study?

There may be no direct benefit to you for participating in this study**.** You may see an improvement in your MDD symptoms. Also, others may benefit as a result of our gaining a better understanding of how the brain responds to depression treatment through BNA imaging.

What other options are there?

You do not have to take part in this study to receive treatment for your MDD. This study uses just one of the FDA-approved classes of antidepressants. There are other approved treatments for treating MDD, such as:

- psychotherapy (where you talk to a doctor or a health care professional about your MDD)
- other classes of antidepressants
- electroconvulsive therapy (ECT)
- vagus nerve stimulation (VNS)

Each type of treatment works well for some people and all may cause side effects. The study doctor can discuss the risks and benefits of alternative treatments with you. You may choose to stop taking part in the study at any time.

What about confidentiality of your information?

Records of participation in this research study will be maintained and kept confidential as required by law.

All data from this study will be tracked by a research sequence number, so you can be assured of confidentiality. Contact information is stored separately from the information collected during the experiment, and all contact information is stored with password protection. The results of the drug screening will be coded and have all identifying information removed. This data will not be available to anyone but the researchers. All screening information and questionnaires will be confidential and coded using a research sequence as well.

By signing this consent document, you give your permission for your unidentified data will be included in the ElMindA international database, and may be made available for scientific, clinical, and commercial proposes.

If you withdraw from this study, the data already collected from may not be removed from the study records. The study doctor and/or study team may ask you whether they can continue to collect follow-up data on you. If follow-up information will be requested, you will be asked to sign a separate consent form before this information can be collected.

Your identity will not be revealed on any report, publication, or at scientific meetings. In order to conduct the study, the study doctor, Dr, Zajecka will use and share personal health information about you. This includes information already in your medical record, as well as information created or collected during the study. Examples of the information that may be shared include your medical history, physical exam and laboratory test results. The study doctor will use this information about you to complete this research.

Confidentiality and disclosure of your personal information is further described in the attachment to this form. The attachment is titled HIPAA Authorization to Share Personal Health Information in Research (2 pages).

The Rush Institutional Review Board (IRB) will have access to your files as they pertain to this research study. The IRB is a special committee that reviews new and ongoing human research studies to check that the rules and regulations are followed regarding the protection of the rights and welfare of human subjects.

A description of this study 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 website at any time.

What are the costs of your participation in this study?

There is no charge for participating in this research study. The study sponsor pays for the study procedures, study visits and study medication.

What financial disclosure(s) apply to this study?

Rush University Medical Center is being paid by Takeda Pharmaceuticals to conduct this research. A portion of this money may go to the study doctor to compensate for other institutional research related costs.

Will you be compensated or paid?

You will be paid $25 for each study visit that does not involve an EEG and $75 for each visit that does involve an EEG. If you complete all study visits, you will be paid up to a total of $450. If you do not complete the study, you will be paid for each of the visits you have completed.

Payment will be made by check approximately 2-4 weeks following the end of your participation in the study. The purpose of this payment is to reimburse you for your time and travel expenses.

If you have any questions regarding your compensation for participation, please contact the study doctor at the telephone number listed on page one of this consent document.

You will be required to provide your Social Security Number to be paid. If you receive payments of $600 or more from Rush in a calendar year, this information must be reported to the Internal Revenue Service (IRS).

Your participation in this research study may contribute to the development of commercial products from which the Sponsor company or others may derive economic benefit. You will have no rights to any products, patents or discoveries arising from this research, and you will receive no economic benefit.

What happens if you experience a research related injury?

If you experience any injury or illness as a direct result of your participation in this research study, you will be referred for medical care in the same way as you would normally, aside from this study. The cost of that treatment will be billed to you or your insurance company. Please check with your insurance company regarding coverage.

If you have any medical problems during the study, please contact the study doctor. He or she will explain your treatment options to you and/or help you find a place to get treatment.

Rush University Medical Center has no program for financial compensation or other forms of compensation for injuries which you may incur as a result of participation in this study.

What happens if you need emergency care?

If you need emergency care while you are participating in this study, it is important that you tell emergency personnel of your participation in this study and notify the study doctor as soon as possible.

Whom do you call if you have questions or problems?

Questions are encouraged. If there are any questions about this research study or if you experience a research related injury, please contact: Dr. John Zajecka at 312-942-5592 or 312-980-0585 (24-hour answering service). Questions about the rights of research subjects may be addressed to the Rush Research & Clinical Trials Administration Office at 1-800-876-0772.

By signing below, you are consenting to participate in this research study. You have read the information given or someone has read it to you. You have had the opportunity to ask questions, which have been answered satisfactorily to you by the study staff. You do not waive any of your legal rights by signing this consent form.

SIGNATURE BY THE SUBJECT:

_____	_____	_____
Name of Subject	Signature of Subject	Date of Signature

SIGNATURE BY THE INVESTIGATOR/INDIVIDUAL OBTAINING CONSENT:

I attest that all the elements of informed consent described in this consent document have been discussed fully in non-technical terms with the subject. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Signature of Individual Obtaining Consent Date of Signature

❑ *Check here if the Individual Obtaining Consent observed the signing of this consent document and can attest, to the best of their knowledge, the person signing the consent form is the subject or the subject's legally authorized representative and the person signing the form has done so voluntarily. By checking this box, the Individual Obtaining Consent does not need to sign on the Witness signature line (below).*

SIGNATURE BY WITNESS/TRANSLATOR
(for use if this consent is being used as a written summary of the research along with a short form consent OR when the person obtaining consent is not the witness):

I observed the signing of this consent document and attest that, to the best of my knowledge, the person signing the consent form is the subject or the subject's legally authorized representative and the person signing the form has done so voluntarily.

Signature of Witness/Translator Date of Signature

❑ Check here if a separate witness signature is not necessary.

SIGNATURE OF THE PRINCIPAL INVESTIGATOR

I attest that I am aware of the enrollment of this subject in the study discussed in this consent document.

Signature of the Principal Investigator Date of Signature

❑ Check here if Principal Investigator obtained consent and a separate signature is not required.