IRB Protocol Number: 7537
Version 07/22/2019

Informed Consent for Participation in Research
Anti-viral therapy in Alzheimer's disease

Purpose and Overview

There is a theory, supported by basic science and clinical information, suggesting that viruses, particularly herpes viruses, play a role in the development of brain disease including Alzheimer's disease. This has never been evaluated in a systematic (planned) clinical trial with anti-viral medications. This study is being conducted to evaluate if the generic anti-viral medication, valacyclovir, is helpful in treating Alzheimer's disease in patients who have tested positive for antibodies to herpes simplex virus-1 or herpes simplex virus-2 in their blood serum. The majority of people above 65 years of age have had herpes virus infection during their lifetimes with persisting serum antibodies (the body's response to a virus) to herpes simplex virus-1 or herpes simplex virus-2. This study will examine the effects of valacyclovir or placebo on everyday cognition (learning, memory, attention, language, and related mental abilities) and function over an 18-month period.

In this study individuals with both Alzheimer's disease and positive test results for serum antibodies for herpes virus are eligible to participate. If you agree to participate you will undergo PET scanning, MRI scanning, a herpes virus blood test and a genetics blood test. Some participants will be asked to undergo a lumbar puncture (LP) procedure which is used to look at the fluid surrounding the brain and spinal cord. The LP in this study will be used to look at the levels of valacyclovir in the central nervous system and to assess specific proteins that are indicators of Alzheimer's disease. If you do not consent to the LP procedure you may still participate in the study. In this study you will be randomly assigned (by chance) to receive the active medication (valacyclovir) or placebo (sugar pill). You will have a 50% (one in two) chance of being assigned to valacyclovir. The placebo pills (or "sugar pills") look identical to the valacyclovir pills, but do not contain active medicine. During the 18-month study, neither your treating psychiatrist nor you will know whether you are receiving active medication (valacyclovir) or placebo (sugar pill). This information will be available to a limited number of research staff during the study in case of emergency. When you complete the study, your doctor will tell you if you have been receiving the medication valacyclovir or placebo (sugar pill) and further treatment will be prescribed according to how you respond during the study. Valacyclovir is not an experimental drug. It has been approved by the U.S. Food and Drug Administration to treat patients with herpes simplex virus-1 and herpes simplex virus-2, but it is not approved to treat Alzheimer's disease. If you agree to participate, you will be treated with valacyclovir or placebo (sugar pill) for 18 months. If valacyclovir or placebo (sugar pill) is stopped for any reason during the initial 18 months, the scheduled study visits

will continue for the remaining period until the 18 months are completed, even if you are no longer taking valacyclovir or placebo.

This study is supported by a grant from the National Institute of Aging, a division of the National Institutes of Health.

Voluntary

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Irving Medical Center.

Alternatives to Participation

This study will involve research treatment with valacyclovir or placebo (sugar pill). You do not have to join this study to receive treatment for your symptoms. If you decide not to participate, you can review treatment options with your doctor. Other commonly used FDA-approved medications for patients with Alzheimer's disease include cholinesterase inhibitors and memantine which you may have received or are receiving, and these medications will be continued and/or adjusted by your study doctor as clinically indicated.

Procedures

If you agree to participate, the study will continue for up to 18 months, during which time you will be asked to come to the Memory Disorders Center at the New York State Psychiatric Institute (NYSPI). After the screening evaluation you will come for an initial baseline visit, followed by visits at Week 2, Week 12, Week 26, Week 52, and Week 78. During the screening visit, you will undergo a clinical evaluation to see if you qualify for the study. You will be asked about your medical and psychiatric history, have a physical exam, and brief tests of memory will be administered. If it is determined that you do not qualify for this study at the screening evaluation, your commitment ends. However, if you do qualify for the study, we will ask you to enroll and sign the informed consent. After signing the informed consent, a blood draw will be completed for routine laboratory tests, and to test for serum antibodies to herpes virus (10 cc or 2 teaspoons). You will be notified within 1 week of the results for serum antibodies to herpes simplex virus-1 and herpes simplex virus-2.

In order to join the study, you will also need to identify an informant who will be available either in person or by phone. An informant may be a family member or a friend who will be able to provide information about you and

willing to be interviewed and to answer questionnaires regarding your memory as well as your daily and social functioning. He/She will be asked to come with you during each of your visits to the clinic. If your informant is unable to come to the clinic, he/she will be contacted by phone by a qualified member of our team. Each interview for the informant may take approximately 30 minutes to complete, and these will be done at every visit.

At the initial study visit, detailed history-taking, neuropsychological evaluation, and several rating scales will be performed. A test of smell will be administered at this visit. In this test, you will be asked to identify different smells on cards that emit an odor when scratched. This test will take approximately 30 minutes. An MRI scan of the brain, PET scanning and lumbar puncture will be conducted as described below. These measures will occur over the course of three days. Each day, you will spend approximately 3 to 4 hours total completing study measures.

Upon completion of the initial study visit, you will be given valacyclovir or placebo at no cost. As mentioned above, you will be assigned by chance to receive either active medication (valacyclovir) or placebo (sugar pill) and have a 50% chance of being assigned to the placebo group. If you are prescribed 2g of valacyclovir/placebo per day you will take two 500mg pills in the morning and two 500mg pills in the evening. If prescribed 3g per day you will take three 500mg pills in the morning and three 500mg pills in the evening, and if prescribed 4g per day you will take four 500mg pills in the morning and four 500mg pills in the evening. You will return any remaining valacyclovir/placebo pills in the pill bottle at each visit to be counted by a research assistant. If you are consenting to have a lumbar puncture, the procedure will be done at weeks 0**,** 12 and 78.

Genetic Testing

Additionally, we want to study genetic factors which are inherited factors passed from parents to their children that may be associated with the risk of developing Alzheimer's disease or other related disorders. The cells of your body contain a molecule called deoxyribonucleic acid, or DNA for short. DNA is passed down from your parents and carries a code, in the form of genes, which determines your physical characteristics, such as the color of your hair and eyes; and risk for some diseases. At the baseline visit, a blood sample of approximately 2 teaspoons will be drawn to assess apolipoproteins that occur naturally in the blood stream and their function is to transport cholesterol and related substances. The presence of some types of apolipoprotein may be associated with an increased risk of developing memory disorders, though this remains to be established. Therefore, the results of the apolipoprotein E genotyping obtained from your blood sample will not be released to you. The blood sample from which the DNA

will be extracted for apolipoprotein E genotyping will be stored without any personal identifying information in the Human Genetic Resources Core (HGRC) at the Columbia University Irving Medical Center.

The HGRC then arranges to have the apolipoprotein E genotype determined from the sample. The HGRC then sends the results to the Principal Investigator in this study. Your blood sample from which the DNA will be extracted will be labeled with the same number used in the other parts of the trial (your study ID number). The sample will not have your name, initials, or address on it. No one at the HGRC will ever know your identity. If, in the future, you decide that you want your sample destroyed, you must notify Dr. Devanand. The sample will be stored without information linking it directly to you, but Dr. Devanand will have the key to identify your sample.

This research will not include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

MRI Brain Scan

The MRI will be performed at the New York State Psychiatric Institute or the Mortimer B. Zuckerman Mind Brain Behavior Institute (a Columbia University Irving Medical Center Facility). MRI involves lying on a table, which slides into a large cylindrical magnet. Radio waves are used to take pictures of the brain. Before beginning the MRI, you will be asked to remove any metal or magnetized objects (such as keys, chains, hairpins, or credit cards). While in the MRI device, you will lie flat on your back for approximately 30 to 40 minutes. In the scanner, your head will be held in position using foam padding and a coil. You will be asked to breathe quietly and to remain as still as possible. You will not feel anything but will hear a banging noise that is made by the MRI scanner.

Results from interpretation of your initial (Baseline) MRI scan will be shared with you in person, by your study physician. Any questions or concerns you may have will be addressed.

PET Scan

During the PET scan, you will need to lie still while the scanner takes pictures of your brain. Both the 18F-Florbetapir Amyloid and 18F-MK-6240 tau PET scans will be conducted at the Kreitchman PET Center at Columbia University Irving Medical Center. Each type of PET scan will take place on a separate day at the following timepoints: Baseline and Week 78.

The 18F-Florbetapir Amyloid PET scan uses a dye that has radioactive tracers that are highlighted under the PET scanner 50 minutes after being injected into a vein in your arm. The scanning will take about 20 minutes.

The 18F-MK-6240 tau PET scan will also use a dye that has radioactive tracers that are highlighted under the PET scanner 80 minutes after being injected into a vein in your arm. The scanning will take about 40 minutes.

Results from interpretation of your initial (Baseline) 18F-Florbetapir Amyloid PET scan will be shared with you in person, by your study physician. Amyloid PET imaging is a routine clinical procedure and results are clinically relevant to you. Any questions or concerns you may have will be addressed. The results from the 18F-MK-6240 tau PET will not be shared with you; tau PET imaging results are still in research development and there is no standardized method to generate a clinical read and provide a report.

Neuropsychological Testing

The results of the memory and intellectual tests, and the smell tests, will be shared with you. The physician working with you will discuss your results at the end of the study visit(s) and answer any questions you may have. After the initial (Baseline) visit, the study team will not share certain test results with you.

Neuropsychological testing involving paper and pencil tests of memory and other intellectual functions will be conducted at 5 of your clinic visits taking 40 minutes to 2 hours on each occasion. The test of smell will be given to you at two visits: Baseline and Week 78.

The total time for most study visits in this part of the study will be approximately 90 to 120 minutes. If you find any questions during the interviews upsetting, you do not have to answer them.

Lumbar Puncture (LP)

For patients consenting to the lumbar puncture, it will be conducted at Columbia University Irving Medical Center. Prior to the start of the Lumbar Puncture, the physician performing the procedure will talk you though each step. The physician will feel your lower back for the best location; your skin will then be sterilized with Betadine and the physician will inject Lidocaine 1% local anesthetic. During the lumbar puncture you will lie on your side with your knees drawn up toward your chest and a needle will be carefully inserted into the spinal canal (a canal in the spinal column through which the spinal cord passes) low in the back where the sample of cerebrospinal fluid (CSF) is collected from. The procedure takes about 20 to 30 minutes. You will have to lie still on your back for 30-40 minutes after completion of the Lumbar Puncture.

Your CSF will be analyzed, and the results from your initial (Baseline) CSF analysis will be shared with you in person, by your study physician. Any questions or concerns you may have will be addressed.

Blindness of Raters and Participants

The raters completing the outcome measures will remain blind to your randomized treatment condition (valacyclovir or placebo). The blind will not be broken during the entire trial. In case of clinical emergency, the blinded medication (valacyclovir or placebo) will be continued if possible; if not, the blinded treatment will be stopped. You will be not be told which treatment condition (valacyclovir or placebo) you are in until the conclusion of the study at Week 78.

Investigator Initiated Discontinuation of Study

There may be times when the investigator decides to stop the study even though you may wish to continue. An example is a medical condition that would interfere with your participation.

Risks and Inconveniences

Valacyclovir Treatment: Possible side effects of valacyclovir include headache and dizziness, both of which are marginally more common in patients receiving valacyclovir compared to placebo. Additional side effects may include nausea, vomiting, and abdominal pain. You will be permitted to continue treatment with cholinesterase inhibitors and memantine (provided the dose has been stable for at least 1 month prior to study entry), which are currently the only FDA- approved medications for patients with AD, i.e., you will not be deprived of an approved treatment for AD.

Lumbar Puncture: Lumbar puncture (LP) may be associated with pain during the performance of the procedure. This is usually temporary and confined to the lower back. Headache, or less commonly, a persistent low-pressure headache may develop. If a post-LP headache persists it may need additional treatment, e.g. with fluids and analgesics (pain relief medication). Uncommonly a blood patch (injection of some of the subject's blood to patch the CSF leak) may be needed.

Potential but rare risks of lumbar puncture include infection, damage to nerves in the back, bleeding into the CSF space, and death. The risk of these is much less than 1%. In over 200 subjects who had LP in our various studies to date, no unexpected or severe adverse events have been noted. Some subjects have reported occasional headache and local pain that disappeared over the expected time course.

MRI Scan: The Magnetic Resonance (MR) scanner uses strong magnetic fields and radio waves to take measurements in your brain. Some people have reported sensations during MRI scans, such as “tingling” or “twitching” (or, very rarely, a painful sensation), which are caused in the magnetic field that can stimulate nerves in your body. With any MRI, on occasion, some people experience nervousness or discomfort due to the scanner’s

small space and the need to lie still. Pacemakers, some types of metallic implants, and medication patches may create increased risk with MRI, and this information will be reviewed to ensure your safety before conducting the MRI scan. The MRI scanner produces a loud noise; earplugs will be provided to reduce this discomfort. If you experience any discomfort and wish to stop the scan, you can tell the MRI technologist and he or she will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

PET Scan: A millisievert (mSv) is a way of measuring radiation. On the average, each person in the United States receives about 3 mSv every year from natural radiation. This research study includes exposure to radiation.

You will undergo 2 types of PET scanning procedure as previously described, with radiation exposure from each of the tracers, and from the corresponding PET/CT scans. A CT scan will be taken of your head at the start of each scanning session and lasts about one minute. The CT scan takes a picture of different tissues (such as the brain and skull) in the head. After the CT scan, we will start the PET scan. The combined radiation exposure from the maximum doses used for 18F- Florbetapir and 18F-MK-6240 are within the FDA limits for yearly radiation exposure and the second scan will be done 18 months after the first PET scan (for both tracers).

The procedures involving radiation in this research study will expose you to a very small amount (32.88 mSv) of radiation in addition to the amount that you might receive from your normal medical care. There may be an increase in the chances of you developing cancer many years after this study. The additional risk from this research study is less than 0.1% which is less than 1 in 1,000. At this very low level, scientists are uncertain as to the actual risk from research and there may be no risk at all.

18F-MK-6240 is a Phase II investigational radioactive tracer being used in this study for research purposes. An investigational tracer is a tracer that has been developed and tested in humans and is approved for human investigational use by the FDA but is not yet approved by the FDA for commercial use. In human studies to date no serious adverse events related to 18F- MK-6240 have been reported. As 18F-MK-6240 will be administered in microgram amounts, no effect related to the action of the radiotracer is expected.

We have performed 31 18F-MK-6240 scans at CUMC to date. Over 16 additional human subjects have been injected with 18F-MK-6240 at other sites. No adverse events related to injection of 18F-MK-6240 have been reported to date.

Blood Draws: The risks associated with blood draws include local tenderness, redness, infection, and mild bruising at the puncture site. If this occurs, it will usually disappear in a few days. Also, a feeling of lightheadedness may occur.

Apolipoprotein Blood Test: Because we are collecting genetic material (DNA), there are some unique risks involved. These may be associated with unforeseeable risks related to breach of confidentiality and discrimination resulting from concerns about increased risk of a genetic disorder. Since this research is seeking to understand genetic associations, you should not report it as genetic testing if asked. This genetic test is strictly for research purposes; therefore, the results will not be provided to you. The risk of accidental identification is minimized because the blood sample will only be identified by the study ID and without any personal identifying information.

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UPSIT: This smell test involves mainly synthetic odors and a few natural odors. If you have allergies that you feel may affect your ability to take the smell test, please inform your study physician in order to reach a decision about whether it is appropriate for you to participate in this study.

Medical History, Physical, Neuropsychological Testing: There is minimal risk associated with these procedures. If you find any questions objectionable, you do not have to answer them.

Benefits

You may or may not benefit from treatment with valacyclovir or placebo. You will have a 50% chance of receiving valacyclovir which may improve cognitive performance and overall functioning. You will also be monitored by the study physician while receiving research treatment.

Confidentiality

Your participation in this study will be confidential, and if the results are published your name will not be identified. Your data and/or biospecimens will not be used for commercial profit. Your records will be kept in files in locked offices and access will be allowed only to members of the research team or institutional personnel as part of a

routine audit. Your name and other personal identifying information will be stored in an electronically secure database at the New York State Psychiatric Institute. Only essential staff will be allowed access to this information. The study could not be completed without this information. There are legal advocacy organizations that have the authority under State law to access otherwise confidential subject records, though they cannot re-disclose this information without your consent. Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits).

Research records will be stored in a confidential manner so as to protect the confidentiality of your information**.**

Participants whose history is obtained through the collection of family history information (from the interviewee) are also considered research participants. They are subjected to minimal risk because all information is confidential. There are procedures to safeguard confidentiality of the information gathered about them from other family members, including names or identifying information kept on the family history form or in the records.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate does not stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate cannot be used to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate does not stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also does not prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Your MRI will be interpreted, and the results will be shared with you or a physician who you may designate. Your MRI report will be maintained as part of the clinical database at the New York State Psychiatric Institute or the

Columbia University Irving Medical Center along with your name and will be accessible to clinicians at the Medical Center. Your psychiatric diagnosis will not be a part of the report.

A description of this clinical trial is 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.

In addition to the confidentiality protections described in this consent form, a Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance or by adoption agencies. GINA also does not protect you against discrimination based on an already diagnosed genetic condition or disease. If you would like to know more about it, you can discuss this with the principal investigator of this study or you can go to the following website: www.genome.gov/10002328

Use of DATA for Future Research

The investigator or study team may wish to use or share the data (Private information and/or biospecimens without identifying information) obtained in this study with other investigators both inside and outside of Columbia for additional research studies, now or in the future. All the data related to you will be de-identified, which means they will be labeled with a code and will not include your name or any other identifiable information. The list that links your code to your name will be secured in a locked file cabinet separate from the rest of the research data. The data about you may be shared with other researchers. If this information is shared, your name or any other identification will not be included. You have the right to have your unused information kept about you for research purposes destroyed at any time. You can request this at any time by contacting Dr. Devanand at 646-774-8658.

Study Compensation

You will receive $100 for each PET scan and $50 for each MRI scan; you will receive 4 PET scans and 2 MRI scans. You will receive $100 for each lumbar puncture procedure. In addition, informants will receive $10 per hour or $200 for the entire study that requires approximately 20 hours of informant time during the one-year study. Travel expenses to and from the clinic can also be reimbursed. Initial evaluation visits are the only visits where the cost of travel cannot be reimbursed. Patients or informants must produce a copy of the transportation receipt (if anything other than the standard MetroCard fare, i.e. cab fare) to the study coordinator, who will submit it for payment.

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In Case of Injury

In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances. New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

Please be aware that:

1. The New York State Psychiatric Institute, Columbia University Irving Medical Center and New York Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital
2. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.
3. No monetary compensation for wages lost as a result of injury will be paid to you by the New York State Psychiatric Institute, Columbia University Irving Medical Center or by New York Presbyterian Hospital.
4. By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

Questions

You are free to ask any questions to the Principal Investigator, Dr. D.P. Devanand (646-774- 8658) and Co-Investigator, Dr. Edward Huey (212-305-1134). Drs. Devanand and Huey also serve as the study physicians in this study. Dr. Devanand and Dr. Huey will answer any questions you may have about the procedures or their effect on you as best as they can. You have been informed that if you believe that you have sustained injury as a result of participating in a research study, you may contact the Principal Investigator, Dr. D.P. Devanand (646-774-8658) or Co-Investigator, Dr. Edward Huey (212-305-1134) so that you can review the matter and identify the medical resources that may be available to you.

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If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of participants in research studies). You may call the IRB Main Office at (646) 774-7155 during regular office hours.

I voluntarily agree to participate in the research study described above.

Print Patient name: _____

Patient Signature: _____

Date: _____

Study Physician

I have discussed the proposed research with the patient,_____, and, in my opinion, this patient understands the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print Study Physician Name: _____

Study Physician Signature: _____

Date: _____

You will be given a copy of this consent form to take with you.