Brain Function and Connectivity in Methamphetamine Dependence: The Link to Neuroinflammation and the Effects of Ibudilast
(VA#4141)

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Subject Name: _____ Date: _____

Title of Study: Brain Function and Connectivity in Methamphetamine Dependence: The Link to Neuroinflammation and the Effects of Ibudilast

IRB Number: eIRB #18176

Principal Investigator: Milky Kohno, PhD ICF Version Date: 6/23/23

WHO SHOULD I CONTACT IF I HAVE QUESTIONS OR CONCERNS OR WISH TO OFFER INPUT?

About the research, call Dr. Kohno or the Hoffman Lab at (503) 721-7964.

If you become sick or injured or if you feel your privacy or confidentiality may have been violated, e.g., someone without authorization has received personal information about you, call Dr. Kohno at (503) 721-7964.

To speak with someone not connected with this research study about your rights, discuss problems, concerns and questions, obtain information and/or offer input, please call the VA Portland Health Care System (VAPORHCS) Research Office at (503) 273-5125, or the VAPORHCS Privacy Officer at (503) 273-5037.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. The purpose of this study is to learn about a new drug called ibudilast that may help treat methamphetamine addiction.

You have been invited to be in this research study because you are either trying to stop using methamphetamine or you have no history of drug or alcohol dependence or abuse. People who are in this research study because they have no history of drug or alcohol dependence are invited to be in this study as part of a control group so we can compare brain function and inflammation between people who have recently used methamphetamine and people who have never used methamphetamine.

Ibudilast is an anti-inflammatory drug that may reduce brain inflammation that occurs in methamphetamine users. We hope that ibudilast reduces brain inflammation and leads to better decision making. In order to see if ibudilast has any effect on brain function and inflammation, we will give the people who sign up for this study who are trying to stop using methamphetamine (the Ibudilast Group) a capsule of either ibudilast or placebo to take twice a day for 6 weeks. The people in this study who do not have a history of drug or alcohol dependence (the Control Group) will not receive ibudilast or placebo. This study uses computerized tests, which measure specific brain functions such as decision-making. A portion of the study involves using magnetic resonance imaging (MRI) and proton emission tomography (PET), two techniques that take pictures of the brain while a participant is lying in the scanner. We will also conduct laboratory blood draws to examine additional markers of inflammation. The objective of the study is to determine whether ibudilast might change brain function and, more specifically, how it affects brain inflammation. Prior to the PET scans, you would have a genetic test to make sure that this type of scan will work. Genes are the units of DNA, the chemical structure that carries your genetic information, which decides many human characteristics, such as the color of your eyes, your height and whether you are male or female.

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This is a Phase II clinical trial. In Phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

WHO IS PAYING FOR THIS STUDY?
VAPORHCS is paying for this study and MediciNova Inc is providing ibudilast and placebo at no cost.

HOW MANY PEOPLE WILL PARTICIPATE?
Approximately 200 people will participate in this research study at the VA Portland Health Care System.

HOW LONG WILL I BE IN THIS STUDY?
If you agree to join and do not withdraw from the study before all procedures are complete, your participation in this study will last for approximately 1 week (control group) or approximately 7 weeks (ibudilast group).

WHAT WILL HAPPEN DURING THIS STUDY?
The procedures, questionnaires, surveys, and blood draws will be done for research purposes and will not be completed if you decide not to take part in the study.

During your initial visit, a cheek swab will be taken from you and a genetic test will be performed to determine if you have a certain type of receptor molecule (genotyping) necessary for the type of PET scan we will do. If you do not have this type of receptor molecule, you will not be eligible to continue in the study and your participation will end after the first visit.

Ibudilast Group:
If you join this study and are in the ibudilast group, you will have a total of 7 visits. Two visits will take place at the VA only and 2 will take place at both Oregon Health & Science University (OHSU) and the VA. The remaining 3 visits will take place either at the VA, your treatment center, or over the phone. These will be brief weekly visits to ensure medication compliance and to discuss any new medications, study drug side effects or issues that may have come up. There will be one final telephone check-in approximately one to three weeks after your final visit.

Control Group:
If you join this study and are in the Control Group, you will have a total of 2 visits. One will take place at the VA only and 1 will take place at both Oregon Health & Science University (OHSU) and the VA.

You will undergo the following procedures at the VAPORHCS:

- Complete surveys with a research assistant
- Perform computerized tasks
- Give blood, urine, saliva and cheek swab samples

- Perform PET scan(s)

Ibudilast Group Only:

- Undergo a brief physical exam
- Be prescribed and given the study drug
- Safety check
- Return to complete a follow up set of imaging scans, surveys, urine sample, and computerized tasks.

A table of activities conducted during this study is below. Visits 2 and 7 may be broken up into multiple appointments depending on schedule:

	Visit 1 (Consent)	Visit 2 (Baseline)	Visit 3* (Safety Check)	Visit 4* (Check-in)	Visit 5* (Check-in)	Visit 6* (Check-in)	Visit 7* (Follow-up)
Visit	Day -7 to -1	Day 0	Day 7-10	Day 17-24	Day 27-34	Day 37-42	Day 42 - 49
Consent and Screening (VA)	X						
Surveys (VA)		X					X
Medical Evaluation (VA)		X					
Cheek Swab (VA)	X	X					
Blood Draw (VA)	X	X					X
Saliva Collection (VA)		X					X
Pregnancy, cotinine, and UDS test (VA)	X	X	X	X	X	X	X
MRI (OHSU)		X					X
PET Scan (VA)		X					X
Study Medication (VA)		X*	X				
Drug Compliance Assessments (VA)			X	X	X	X	X
Safety Assessment (VA)		X*	X	X	X	X	X
Substance Use Assessment (VA)	X	X	X	X	X	X	X
Total time	2-4 hours	8 hours	0.5 hours	0.5 hours	0.5 hours	0.5 hours	8 hours
Compensation	$50	Up to $200	$15	$15	$15	$15	Up to $300
*These visits/procedures will only occur for people who are in the Ibudilast Group.							

Journal Collection: We will ask you to keep a daily journal of alcohol, drug and nicotine usage and craving, which we will collect at each in-person visit.

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Study Medication: In this study, some people will receive study drug. Some of those people will receive the real study drug, and some will receive a fake drug called a placebo. A placebo is a pill or solution that tastes, looks and smells like the study drug but has no real medicine in it. A placebo is sometimes called a "sugar pill." The placebo being used contains mannitol, a sugar alcohol that naturally occurs in fruits and vegetables.

The study drug portion of this study is randomized. That means neither you nor your doctor can choose whether you will receive the study drug or the placebo. That will be decided by chance (like tossing a coin, heads could mean you get the study drug and tails that you get the placebo). If you are in the Ibudilast Group, you have a 50/50 chance of getting the study drug in this study. At Visit 2 you will receive two weeks (14 days) worth of either study drug or placebo and you will receive the remainder at Visit 3. Additional drug may be given at one of the follow up visits as needed to last until your final visit. The study doctors/nurses will not know which pill (or dose) you get. The study is done this way because sometimes knowing that you are getting the test drug can change the results of the study. Also, sometimes people get side effects from placebos. Even though no one will know which pill you will get in this study, if you start having serious side effects, for your safety, the study doctors can find out if you are getting the test drug or placebo. Please ask the study doctor for more information if you have any questions about this kind of study.

Blood Tests: About 2 tablespoons of blood will be drawn from a vein in your arm using a needle during Visit 1 These tests are performed to assess your general health and to ensure that you don't have any illnesses that might exclude your participation in this study. About 1 tablespoon of blood will be drawn at Visit 7 to repeat some of these same tests as well. All laboratory tests will be sent to the lab with a coded number. The blood tests performed will include CBC (complete blood count) and liver enzyme tests. If you are female, your hormone levels may also be tested during Visit 1, Visit 2, and Visit 7. Hormone testing will be done either with a blood test or we will collect a saliva sample. About 3 teaspoons of blood will be drawn during Visit 2 and 7 and stored in a blood bank. If Visit 2 and/or 7 are broken into multiple visits, saliva and blood samples may be collected on each day associated with this visit

As part of this study, blood samples will also be tested for hepatitis C (HCV) and for human immunodeficiency virus (HIV), unless you can provide documentation that these tests have been conducted within the last 2 months. If the results are positive, we will provide you with further information regarding HCV and HIV. Per VA requirements, you will be asked to provide a separate, verbal consent before an HIV blood test can be performed. If you provide this consent, it will be documented in your medical record, and your blood will be tested for HIV. If you refuse, your blood will not be tested for HIV, and you will not be eligible to participate in this study. If you are a VHA patient and have positive results, we will also offer to provide a referral for a further blood test to verify the HIV and/or HCV results. These additional tests are not part of this research study and would be paid for by you or your insurance company. Any VHA providers who access your medical record would be able to see such a referral, which will indicate the positive results from the study test.

MRI: You will complete up to 2 MRIs during this study at OHSU's Advanced Imaging Research Center. There will be several different scans during each MRI session and each session will last approximately 1 hour. Because the MRIs will take place at OHSU, the procedure and the possible risks and discomforts are addressed in a separate OHSU consent form.

PET-CT: You may also complete 2 PET scans at the VA Imaging Services. PET scanning uses small amounts of a radioactive material to look at inflammation in the tissues of your brain. Women must have a negative pregnancy test before PET scans are done. After receiving an injection with the material through an IV, you will lie on a narrow bed that is rolled into a tube where a machine will take pictures of your brain. In order to determine eligibility for this procedure, we will check to make sure you have the right kind of receptor molecule that will bind to the radioactive material (genotyping). Genotyping will be done using the cheek swab collected during Visit 1.

Blood samples for PET: An arterial catheter may be necessary. You should abstain from using aspirin and other anti-inflammatory drugs (such as ibuprofen [Motrin or Alleve]) for 7-10 days before and after arterial line insertion and avoid strenuous physical activity for 24-48 hrs after the scan.If you do get an arterial catheter, we will draw about 6 tablespoons of blood during each PET scan to ensure that there is enough radioactive material in your bloodstream for the scan and to check for markers of inflammation. For the blood draws during PET scans, an experienced physician will insert an arterial catheter in your wrist area. The arterial catheter, which looks like a regular IV tube is inserted into an artery, not a vein. This enables us to draw blood samples repeatedly. We will first clean the skin with an antiseptic to reduce the risk of an infection. The physician may use a suture to secure the arterial catheter to your wrist and may use lidocaine to numb the area since the insertion of an arterial catheter can cause pain. The catheter will be flushed regularly during your scan with saline (a salt solution), which prevents clogging of the catheter with a blood clot. After the catheter is removed, local pressure is applied for a minimum of 15 minutes to prevent bleeding under the skin. You will be asked to keep it clean and dry, avoid strenuous exercise, refrain from lifting heavy objects weighing more than 5 pounds, and to avoid repetitive movements for 48 hours. If an arterial catheter is not necessary, we may draw blood from an IV line instead.

Urine pregnancy test (HCG): Women will be asked to give a urine sample to screen for pregnancy. The test will not be conducted if you have been surgically sterilized.

Urine cotinine test: This test is used to determine the amount of cotinine in your urine. Cotinine is a chemical that your body produces when you are exposed to nicotine, for example when you smoke a cigarette, and it stays in your body for one day or more.

Urine Drug Screen (UDS): All participants will be required to provide a urine sample for a UDS at each visit. This test is performed to ensure that you have not taken illicit drugs before the MRI and PET scans, since this might interfere with the measurements. A positive test for drugs other than methamphetamine and marijuana

will exclude you from this study. The UDS results are used for the research study only and the urine samples will be destroyed immediately after processing.

Saliva samples: In addition to a UDS, saliva samples may be taken before MRI and PET scans to verify levels of methamphetamine in your system.

Questionnaires, Surveys and Computerized Tasks: At the first two visits you will complete several questionnaires that will ask about your substance abuse, as well as your physical and mental health. A research assistant will ask you the questions and write down your answers or you may be entering your answers onto a computer. At the second visit, we will teach you several computerized tasks that asks you to make decisions about money and several tests of your mental abilities and memory will be performed. This part of the visit will take about one hour and 25 minutes at the first visit, and about two hours at the second visit. For those in the Ibudilast Group, the questionnaires, surveys and computerized tasks will be repeated at your final visit.

X-ray: If there is a chance that you have metal fragments lodged in your eyes or face, you will have an x-ray prior to having the MRI, or you may provide records of a recent facial x-ray or MRI to show that you do not have metal fragments in your eyes or face. If it is found that you do have metal fragments in your eyes or head, **you must not participate in the study.**

As part of this study, blood and saliva samples, cheek swabs, coded imaging data, study data and coded demographic information will be stored (“banked”) in a repository maintained at the VAPORHCS. The repository may then release your samples and coded information for use in future research, which may include research about addiction and may include genetic research.

WHAT ARE THE RISKS and POSSIBLE DISCOMFORTS of PARTICIPATION?

The structured interview and the questionnaires will ask some questions that are personal and may cause you to become emotionally upset. You may refuse to answer any of the questions. If the questions make you very upset, we will help you to find a counselor.

You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, an infection, or fainting.

For those who are in the ibudilast group and take the study drug, you may have some side effects we do not expect because we are still learning about the study drug.

The most common side effects associated with the study drug are as follows:

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Ibudilast, 5 may have:

- Rash
- Dizziness
- Headache
- Lack of appetite
- Nausea
- Vomiting
- Abdominal pain
- Indigestion
- Yellowing of the skin or eye

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

There are several drugs (prescription and non-prescription) that may cause problems when taken with the study drug. The study doctor will carefully review all of the drugs you are taking before giving you the study drug. If any other health care provider prescribes any new drug(s) for you while you are in this study, please tell the study doctor before you take the new drug. You could also have your provider talk to the study doctor before prescribing the new drug. **Do not take any new over-the-counter drugs or herbal or dietary supplements** while you are in this study unless you first check with the study doctor.

For Women:
You should not become pregnant while participating. The study drug could affect a fetus in ways that we do not yet know about. If you are sexually active and at risk of getting pregnant, you and your male partner(s) must use one or two methods of birth control that work well, like birth control pills, a patch, long-acting progestins, an IUD, a diaphragm or condom with spermicide, or abstinence. You will have to maintain a form of contraception

for the duration of the study and for 30 days after the study. If you become pregnant during the research study, please tell the investigator and your doctor immediately.

For Men:
You should not cause a pregnancy while participating in this study. If you are a sexually active male and can cause a pregnancy you must be sure that you and your female sexual partner(s) use(s) a method of birth control that works well, like birth control pills, a patch, long acting progestins, an IUD, or a diaphragm with spermicide, or you must use a condom with spermicide during sexual intercourse. A vasectomy is an acceptable method of birth control. You must do this the whole time you are in this study. If a sexual partner becomes pregnant during the research study, please tell the investigator and your doctor as soon as you learn about the pregnancy

In this study you will be exposed to radiation during the PET-CT scan and if you have an x-ray prior to having the fMRI (because of possible metal in your body). Radiation is measured in units called millirems (mrems). All human beings are constantly being exposed to naturally occurring background radiation at a rate (depending on where you live) of about 300-360 mrem per year. During the time you are enrolled in this research study, each PET-CT scan will expose you to about 180 mrems, about the same as you would be exposed to in 6 months. If you have orbital x-rays to be sure you have no metal in your eyes, the x-ray machine will expose you to a total of about 40 mrems. No increased risk has been scientifically demonstrated from this level of exposure, though a very small increase in cancer risk may exist. For comparison, a routine chest x-ray is about 4 mrem and smoking 1.5 packs of cigarettes per day for a year amounts to 1300 mrem.

If you have a history of a bleeding disorder or are taking medication to thin your blood, you will not be allowed to participate in this study. On PET scan days, a radial arterial catheter may be inserted. Certain individuals may feel light-headed during arterial catheter placement or possibly faint. You could get an infection or may have significant local pain where the tube is placed. This would cause swelling, redness and pain. You may bleed or get a bruise. If any of these, or other, symptoms occur and do not diminish within 24 to 72 hours after the arterial line removal, or in the event that they worsen, you should call the study team immediately. In very rare instances (e.g., < 1/1000), blocking or tearing of the artery, arterial leakage, poor healing, or infection at the catheter insertion site may occur. There is a small chance your blood stream or heart valves might get a serious infection. You may get a blood clot that could go to your lungs. These problems are very rare. If you have these problems, you will need hospital care. If you experience any excessive pain, tenderness, swelling, redness, numbness, or decreased strength in the arm that had the catheter, you should immediately call your study team.

Placing an IV may cause some pain, and bleeding or bruising at the spot where the needle enters your body. Rarely, it may cause fainting or infection.

Information that identifies you will be used in this study. The research team will make every effort to protect your information. However, a breach in confidentiality and a resulting loss of privacy could result in monetary loss due to identity theft or carry other risks affecting ability to get insurance, current or future job status, parental rights or responsibilities, legal risk, or could result in embarrassment.

As a result of participation in this study, you may learn information that could be upsetting to you. If you are upset about the results learned during the course of the research study, Dr. Kohno or the study doctor may refer you to a counselor.

If you should ever express thoughts of wishing to harm yourself or considering suicide, we may call the National Suicide Prevention Hotline and/or the Veterans Crisis Line and transfer you to that call.

Some members of your family may not want research done on your tissues to understand the genetics or possible inherited disorders of you and your family. This may cause conflict with your family members and could affect your decision or the decisions of family members to have children. You may want to hold a discussion with your family members before deciding to participate in this study and signing this consent form.

The Genetic Information Nondiscrimination Act (GINA), a federal law, generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more employees to discriminate against you based on your genetic information.

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote or fire you or when setting the terms of your employment.
- However, there is a serious risk, if there is a loss of confidentiality and certain genetic information reaches your current or future life, disability, or long-term care insurance carrier, your employer (if s/he employs fewer than 15 employees), or others, that you or members of your family may experience some type of discrimination resulting in (1) **loss of life insurance, disability insurance, or long-term care insurance coverage and/or** (2) **loss of job**. All researchers associated with this study will make every reasonable effort not to disclose any of this information, but it is important for you to understand that the possibility of this information being disclosed exists, despite every reasonable effort. If you have any questions, please ask Dr. Kohno, who can be reached at 503-721-7964.
- The VAPORHCS also abides by the Oregon Genetic Privacy law (ORS 192.531 through ORS 192.549) and its requirements concerning confidentiality and the legal remedies provided by that law for breach of its

requirements. You have not waived your legal rights by signing this form. For clarification on this subject, or if you have further questions, please call the VA Regional Counsel office at (503) 412-4580.

Information that could be used to identify you will be banked for use in future research. The repository team will make every effort to protect your information, including by destroying the link to your personal information at the end of the study. However, a breach in confidentiality and a resulting loss of privacy could result in monetary loss due to identity theft. It could also carry other risks, such as embarrassment or affecting current or future job status, relations with your family, parental rights or responsibilities, or status in the community.

WILL I BENEFIT BY PARTICIPATING?

You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future

DO I HAVE TO PARTICIPATE IN THIS STUDY?

No. You may choose not to be in this study.

HOW WILL MY CONFIDENTIALITY BE PROTECTED?

Your information used for this study will be kept confidential as required by law. The results of your participation in this study may be used for publication or for scientific purposes, but the results will not include any information that could identify you. Your identity will not be disclosed unless you give specific, separate consent or if required by law. All VA research records will be held in accordance with the VA records control schedule.

Identifiers related to you (i.e. information that can identify you) will be used in this research study and will include: Name, home address, email, phone number, race, ethnicity, social security number, and birth date. These identifiers may be used to obtain information about you and/or your health from VA records and from the health information sources listed on the HIPAA authorization.

We may give your name, address, DOB and SSN to a third party, called Clincard (by greenphire), in order to issue a prepaid debit card. This information is used to register you for the prepaid debit card and so you can receive support, in case there is an issue with your card. You will be given an information page about the Clincard if that is the form of payment that you receive.

Rides to/from your appointments may be provided at no cost to you through a third party, called Circulation. If you choose this option, a profile will be generated on Circulation's website that includes your name, phone number, and preferred address for pickup/dropoff. Rider profiles are stored within Circulation until participation in the study is complete; afterwards, your information is erased from their web application.

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Your information and/or specimens may be shared with other researchers as part of this study. A code number will be assigned to your information and specimens. Only personnel for this study will be authorized to link the code number to you. You will sign a separate OHSU consent form that allows your name to be released to select OHSU research employees who are responsible for making the radioactive material that will be injected during your PET scan. Other researchers who may receive your information or specimens, as outlined in the VA and OHSU consent forms, will be given only the code number or only your full name but will never receive both your code number and name and will not be given any other information to link the code back to you.

By signing this informed consent, you give permission for the transfer of a copy of your coded data and specimens in the MARC biorepository and on the OHSU network drive and temporarily store data at the OHSU Advanced Imaging Research Center (AIRC). You also give permission for the transfer of a copy of your full name to OHSU personnel in order to make the radioactive material for your PET scan. OHSU, Dr. Kohno, and Dr. Loftis (the biorepository director) will be responsible for maintaining the security and confidentiality of the transferred data. VAPORHCS will continue to have ownership of your research data for this research study. All original research records, both hard copy and electronic, will be maintained at the VAPORHCS in accordance with current records retention requirements. Any information shared with OHSU may no longer be protected under federal law. Research records may be reviewed and/or copied by the sponsor.

All other parties, including employers, insurance companies, personal physicians and relatives, will be refused access to the information and specimens, unless you provide written permission or unless otherwise required by law.

Many study tests are completed in an encrypted database called REDCap. The REDCap database is password protected and maintained by the Oregon Clinical & Translational Research Institute (OCTRI) at OHSU. A user profile based on your study ID number will be created for you, which will not contain your name or other identifying information. The database will collect your responses to questions but will not contain any identifying information about you. By signing this informed consent, you give permission for this data to be maintained by OCTRI, which will be responsible for maintaining the security and confidentiality of the transferred data.

To help us further protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States

Government that is used for auditing or evaluation of federally funded projects 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 or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.
The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of child or elder abuse, or harm to self or others.

Mandatory reporting of suspected child or elder abuse. Under Oregon Law, suspected child or elder abuse must be reported to appropriate authorities.

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site does 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.

This study involves a drug regulated by the US Food and Drug Administration (FDA), the FDA may choose to inspect research records that include identifiable medical records, identifying you as a subject of this study.

Possibility of Disclosure and Notice of Privacy Practices.
The VHA complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and its privacy regulations and all other applicable laws that protect your privacy. We will protect your information according to these laws. Despite these protections, there is a possibility that your information could be used or disclosed in a way that it may no longer be protected. Our Notice of Privacy Practices provides more information on how we protect your information. If you do not have a copy of the notice, the research team will provide one to you. (Notice of Privacy Practices available online at http://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=3048).

If you are a non-Veteran, we will provide you with the VA Notice of Privacy Practices and ask you to sign the acknowledgment (VA Form 10-0483) you received the document. This acknowledgement may be scanned into your medical record.

WILL I BE ABLE TO SEE MY RESEARCH DATA?
During this research study, you will not be able to see the research data collected about you. After the study is complete and the study results are determined or published, you may request your health information.

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WILL I BE TOLD ABOUT THE STUDY RESULTS?
We will not contact you with results of this study after this study is completed.

If your blood samples, saliva samples, cheek swab, and/or data are used in future studies, the results of those studies involving the use of your data or specimens will not be made available to you because any information that would make those samples identifiable will not be made available to investigators who receive your sample.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
None of the participants will pay for any of the procedures or visits in this study because they are only for research study purposes. However, if you are hospitalized due to injury, you or your insurance company may be charged.

Some Veterans are also required to pay co-payments for medical care and services provided by VA ***that are not part of this study*** (e.g., normal hospital and prescription expenses that are not part of the research study, any treatment that is standard clinical treatment for your condition).

WILL I BE PAID FOR PARTICIPATING?
You will be paid in the form of prepaid debit cards (Clincards by Greenphire or VA Electronic Funds Transfer [EFT]), EFT bank transfer, voucher or gift cards. Clincards may incur fees (for example, if the card is inactive for more than six months), which will be deducted from the balance on your card. Details on how to use the card and any fees are included in the separate card member agreement and FAQ sheet.

If you drop out of the study before completing a visit, or one of your visits needs to occur over several visits, you will be paid for the activities that you completed that day. Not everyone will be asked to undergo a PET scan, however, if you do undergo a PET scan, you will be paid an additional amount for each visit. If you complete all of the study-related activities during the scheduled visits, including PET scans, you will have received a total of $250 if you are in the control group, and $610 if you are in the ibudilast group.

Control Group – total possible, up to $250:
• Visit 1: $50
• Visit 2: $200

Ibudilast Group – total possible, up to $610:
• Visit 1: $50
• Visit 2: $140 plus an additional $60 if you undergo a PET scan
• Visit 3: $15
• Visit 4: $15

- Visit 5: $15
- Visit 6: $15
- Visit 7: $240 plus an additional $60 if you undergo a PET scan

Individuals may be reimbursed for hardships, pending verification, up to $100 per visit.

You could be asked to repeat some study procedures. You would be paid at a pro-rate of $20/hr for any other repeated procedures or you may be paid for the entire visit.
We may double book certain appointments. If both subjects show up for the appointment, we may ask to reschedule your appointment. You would be compensated $50 for your time. Participation in double booked appointments is optional.

An Internal Revenue Service (IRS) Form 1099 may be generated, which will use your Social Security Number. This payment is considered taxable income. If you owe money to the government, this payment may be garnished to satisfy the debt.

WHAT WILL HAPPEN IF I AM HURT?

Every reasonable effort to prevent any possible injury from this study will be taken. In the event the study results in any physical, mental or emotional injuries to you, the VA will provide necessary medical treatment (not just emergency care) at no cost to you. This does not apply to treatment for injuries that result from if you do not follow the study procedures. Additional compensation, beyond paying for treatment, has not been set aside. The VA will also provide all necessary assistance in the event of any violation of confidentiality or privacy (for example, identity theft resulting from the loss of a social security number by anyone associated with this study). For eligible Veterans, compensation damages may be payable under 38 United States Code 1151. For all study participants, compensation damages resulting from the negligence of federal government employees may be available in accordance with the provisions of the Federal Tort Claims Act. For additional information concerning claims for damages, you may contact VA Regional Counsel at (503) 412-4580. You have not waived any legal rights or released the hospital or its agents from liability for negligence by signing this form.

WHO SHOULD I CONTACT IF I AM INJURED DUE TO THE RESEARCH?

If you believe that you may have suffered a research related injury (physical, mental or emotional injury or injury caused by loss of confidentiality or privacy), contact Dr. Milky Kohno at 503-721-7964.

In the event of a life-threatening emergency, call 911 or go to the Emergency Department (ED).

Subject Name: _____ Date: _____

Title of Study: Brain Function and Connectivity in Methamphetamine Dependence: The Link to Neuroinflammation and the Effects of Ibudilast

IRB Number: eIRB #18176
Principal Investigator (Researcher): Milky Kohno, PhD ICF Version Date: 6/23/23

WHAT ARE MY RIGHTS?

You may ask questions about research or about your rights as a subject. Dr. Kohno at 503-721-7964 will answer any questions you may have about this research study. If you have any questions regarding your rights as a research subject, you may contact the VA Portland Health Care System Research Office at (503) 273-5125, or VA Regional Counsel at (503) 412-4580.

Participation is voluntary. Your participation in this research study is voluntary. The VA Authorization for Use and Release of Individually Identifiable Health Information (Collected) for VHA Research to use your protected health information is also voluntary. You may refuse to sign this consent form and the authorization. However, in order to participate in this study, you must sign this consent form and the HIPAA authorization.

Dr. Hoffman and Dr. Cornejo are researchers on this study and may also be your health care provider. They are interested in both the clinical welfare of their patients who participate in this study and in the conduct of this study overall. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another provider who is in no way associated with this study. You are not under any obligation to participate in any research study offered by your health care provider.

What if I decide not to participate? You do not have to join this or any other research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join or if you drop out of the study at any time, there will be no penalty or loss of any benefits to which you are otherwise entitled. This will not affect your relationship with or treatment by the Veterans Health Administration (VHA) or your rights as a VHA patient. You will still receive all the medical care and benefits for which you are otherwise eligible.

CAN I DROP OUT (WITHDRAW) AFTER I SIGN THIS CONSENT FORM?

You may withdraw from this study at any time. This will not affect your rights as a VHA patient or your eligibility for medical care and benefits for which you are otherwise eligible with this institution or with the VHA.

To withdraw, you must write to Dr. Milky Kohno at VA Portland Health Care System, 3710 SW US Veterans Hospital Road, Mail code P35C, Portland, Oregon, 97239, or ask a member of the research team to give you a form to withdraw your consent and authorization. If you withdraw your consent and authorization, you may not be able to continue to participate in the study.

If in the future you decide you no longer want to participate in this research, you may request to have your blood, saliva and cheek swab samples destroyed by contacting Dr. Kohno at 503-721-7964. If your specimens are still identifiable, you may withdraw consent to use them at any time, and Dr. Kohno will assure that the specimens that you have given will be destroyed. If, however, the link between your identity and the samples has been destroyed, it will be impossible to remove your contribution from the repository.

Subject Name: _____ Date: _____

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By agreeing to be in this study, you agree that your blood and saliva samples, cheek swabs, and information may be used in future research about addiction and may include genetic research. A code number that doesn't contain any personal identifiers (such as your initials or date of birth) will be assigned to your samples and information. Only personnel working on this study will be authorized to link the code number to you. However, some of these personnel also work for the repository. Other researchers may receive your samples and information for future studies will be given only the code number and will not be given any other information allowing them to link back to you or your family.

If you do withdraw, we will not look at your medical record for purposes of the research anymore and will not collect any more information about you. However, we will keep and use the data that we already collected before you withdrew your consent.

If you withdraw before the end of the study, we will ask you to return any unused study medication to Dr. Hoffman's lab.

Can someone else stop me from being in the study?
The Principal Investigator would ask you to withdraw from the study if you were not able to complete the scientifically critical parts of the study, i.e., complete successful blood draws, perform computerized tasks or PET scan, or perform the MRI conducted at OHSU. You may also be removed if you do not take the study drug as directed or if you test positive on any urine drug screens or pregnancy tests.

WILL I BE TOLD IF THERE IS NEW INFORMATION THAT MIGHT CAUSE ME TO WANT TO QUIT THIS STUDY?
We will give you any new information during the course of this research study that might change the way you feel about being in the study.

Signature
Dr. Kohno or her study personnel has explained the study and the banking of my human biological specimens and coded information for future research to me and answered all of my questions. I have been told of the risks and/or discomforts and possible benefits of the study and of banking. I have been told of other choices of treatment available to me.

I have been told I do not have to take part in this study and refusal will involve no penalty or loss of VHA or other benefits to which I am entitled.

In case there are medical problems or questions, I have been told I can call Dr. Kohno at 503-721-7964 from 8 am to 4:30 pm, Monday through Friday, and the VA operator at 503-220-8262 to page Dr. William Hoffman or

Subject Name: _____ Date: _____

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Dr. Brandon Cornejo after 4:30 pm or on weekends. If any medical problems occur in connection with this study, the VA will provide emergency care.

By consenting to participate, I authorize the use of my bodily fluids, tissues, and health information.

My signature below indicates that I have read, or had read to me, all of the above information about the study and the banking of my human biological samples and coded information, and that my rights as a research subject have been explained to me. I voluntarily consent to allow the use of my coded information, blood samples, and cheek swabs from this study to be stored in a repository and used for future research, as described in this form. However, identifiers may be stored separately and held in accordance with the VA records control schedule. I have been told that I will receive a copy of this consent form.

_____
Printed Name of Subject

_____ _____ _____
Signature of Subject Date Time

_____ _____
Printed Name of Witness to participant's signature Relationship to Participant/Position Title

_____ _____ _____
Signature of Witness Date Time

_____
Printed Name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time

Do not change anything below this line, including bottom margin.
VAPORHCS Research Service Template Date: 3/1/2018

Subject Name: _____ Date: _____

Title of Study: Brain Function and Connectivity in Methamphetamine Dependence: The Link to Neuroinflammation and the Effects of Ibudilast

IRB Number: eIRB #18176
Principal Investigator (Researcher): Milky Kohno, PhD ICF Version Date: 6/23/23

Addendum: Banking your Contact Information for Future Research

WHAT IS THE PURPOSE AND WHAT WILL HAPPEN?
We are also asking you to allow your contact information (including name, phone number and address as well as demographic data including date of birth, gender, veteran status, smoking status, substance use information and mental health status) to be stored ("banked") in a repository located at VA Portland Health Care System (VAPORHCS). We will also be collecting a record of your participation in research studies run by the Hoffman/Kohno Lab or other approved contributing labs. By signing this form below, you agree to allow your contact information and data listed above to be made available to researchers at the VAPORHCS for the purpose of contacting you about future research studies.

WHAT ARE THE RISKS?
Information that identifies you will be banked. The repository team will make every effort to protect your information. However, a breach in confidentiality and a resulting loss of privacy could result in monetary loss due to identity theft. It could also carry other risks, such as embarrassment or affecting ability to get insurance, current or future job status, parental rights or responsibilities, or legal risk. The research team will make every effort to protect your private health information and guard against any loss of privacy.

HOW LONG WILL YOU KEEP MY INFORMATION?
Your research data will be stored indefinitely.

CAN I WITHDRAW MY PERMISSION TO USE MY CONTACT INFORMATION AND DATA?
To withdraw your consent for future use of your contact information, you must write to Dr. Kohno, at Mailstop P35C, 3710 SW US Veterans Hospital Road, Portland, OR 97239, or ask a member of the research team to give you a form to withdraw your consent and authorization. You will still receive all the medical care and benefits for which you are otherwise eligible. This will not affect your rights as a VHA patient.

HOW WILL MY CONTACT INFORMATION AND DATA BE USED FOR FUTURE RESEARCH?
If you agree, your name, phone number, address, date of birth, gender, Veteran status, smoking status, substance use information, mental health status and previous participation in a Hoffman lab research study may be used by VAPORHCS researchers to contact you regarding future research studies.

I agree to the following future uses of my contact information:

- Contacting me by letter and by phone
- Research about any type of health care issue, disease or disorder
- Any VA researchers

Subject Name: _____ Date: _____

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Signature

Dr. Kohno and any authorized member(s) of the study team has explained the banking of my contact information and date of birth, gender, veteran status, smoking status, substance use information, mental health status and previous participation in a Hoffman lab research study for future research to me and answered all of my questions. I have been told of the risks and/or discomforts and possible benefits of the banking.

I have been told that I may refuse permission for banking of my contact information and date of birth, gender, veteran status, smoking status, substance use information, mental health status and previous participation in a Hoffman lab research study for future research and that refusal will involve no penalty or loss of VHA or other benefits to which I am entitled.

In case there are problems or questions, I have been told I can call Dr. Kohno at (503) 721-7964.

My signature below indicates that I have read, or had read to me, all of the above information about the banking of contact information and date of birth, gender, Veteran status, smoking status, substance use information, mental health status and previous participation in a Hoffman/Kohno lab research study, and my rights as a research subject have been explained to me.

I voluntarily authorize my contact information and date of birth, gender, Veteran status, smoking status, substance use information, mental health status and previous participation in a Hoffman lab research study be stored in a repository and used for future research, as described in this form. I have been told that I will receive a copy of this consent form.

_____
Printed Name of Subject

_____ _____ _____
Signature of Subject Date Time

_____
Printed Name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time