A Proof of Concept Randomized Controlled Trial of XEN1101 for the Treatment of Major Depressive Disorder

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NCT04827901
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STUDY INFORMATION:

Study Title: A Proof of Concept Randomized Controlled Trial of XEN1101 for the Treatment of Major Depressive Disorder

SITE **Study site(s):** ***SITE***

SITE **Principal Investigator (Lead Researcher): [First Name Last Name, Degree(s)]**

SITE **Physical Address: [Hospital/clinic name; Annenberg 22nd Floor, Room XXX; This will usually be the location where the subject should go for study visits; otherwise it can be the PI's office address]**

SITE Mailing Address: [e.g. One Gustave L Levy Place Box XXXX, NY, NY 10029]

SITE **Phone: [e.g. 212-XXX-XXXX; this number should reach the research team directly, not be just a general clinic or department number]**

SUMMARY OF THIS RESEARCH STUDY:

This document explains a research study you might be interested in joining. Participation in the study is voluntary. You can agree to join or not. Your decision will not limit your ability to get medical care at **[SITE]**. You should only agree to take part if you understand the study and if all of your questions about the research study are answered. If you do join the study, the research team must share any new information with you that may change your mind.

The purpose of this research study is to investigate a medication called XEN1101 for the treatment of Major Depressive Disorder (MDD, a.k.a. depression). XEN1101 is an investigational drug, meaning that it has not been approved for use by the United States Food and Drug Administration (FDA), the branch of the federal government that approves new drugs. Part of the study's purpose is to investigate any changes in brain activity that may be related to changes in depression symptoms.

If you choose to take part, you will be asked to:

- Attend 8 study visits over 18 weeks,
- Complete brain scans, blood draws, and take the prescribed medication or a placebo, and
- Agree to have private information and study data stored indefinitely.

If you choose to take part, the main risks to you are (1) feeling worse if any treatment is stopped while waiting for the investigational drug to possibly be effective, (2) a worsening of symptoms if assigned to placebo, (3) side effects of XEN1101 (e.g., dizziness, drowsiness [please see page 13 for a full list of side effects]); (4) discomfort or pain during or after the blood draw, including bruising, infection, and dizziness or feeling faint after your blood has been taken; (5) having claustrophobic reactions in the

MRI scanner. If you have metal objects of any kind in your body, you will not be able to participate for matters of your own safety.

You may benefit from taking part in this research. One potential benefit is experiencing a temporary improvement in your symptoms of depression.

Instead of taking part in this research, you may consider treatments such as medications (approved medications include fluoxetine, sertraline, etc.) or cognitive behavioral therapy that have been shown to be effective as treatment for MDD.

If you are interested in learning more about this study, please continue to read below.

STUDY PARTICIPATION:

You may qualify to take part in this research study because you are between the ages of 18 to 65, have been diagnosed with Major Depressive Disorder (MDD), and are medically healthy.

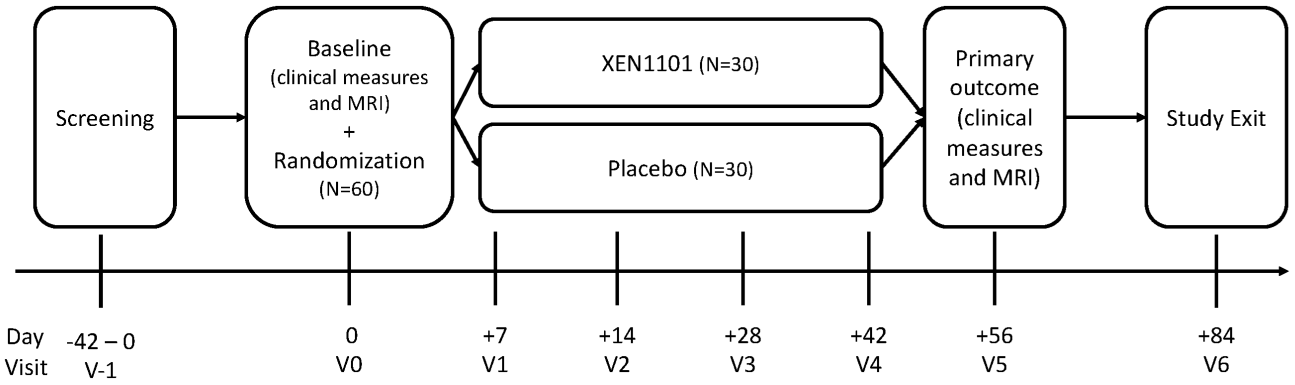
Your participation in this research study is expected to last 18 weeks.

Funds for conducting this research are provided by the National Institute of Mental Health (NIMH).

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

DESCRIPTION OF WHAT IS INVOLVED:

If you agree to participate in this research study, here is what may be involved. Please see below for a diagram explaining the study flow:



Screening (1-3 visits, 3-5 hours long)
First, research personnel will ask questions about your health and do tests to see if you are eligible for this study. This is called the "screening visit." The following examinations will be done during 1-3 visits, which are expected to take approximately 3-5 hours total.

- *Medical, Psychiatric, and Personal History*: Research personnel will ask you questions about your medical and psychiatric history, including history of depression and medications you have taken. Severity of your depression including suicidal thoughts will be assessed. You will also be asked if you have any planned surgeries or other medical procedures. You will be asked to identify if you have a current treating mental health provider and provide the contact information for this provider.
- *Urine sample*: You will be asked to pee into a cup. This urine sample will be used for routine analysis, to test if you are pregnant, and to test for illegal drugs. If you test positive for pregnancy or illegal drugs, you will be unable to participate. If you are pregnant or plan on becoming pregnant, please inform research personnel immediately. You will be unable to participate. Tell us all drugs you are taking currently or may have taken in the past including legal or illegal, prescribed or over the counter, and any herbs or supplements. In particular, you will be asked for a list of medications that you are taking or may have taken during the current or past depressive episodes.
- *Physical exam*: A study doctor will check you for general signs of disease.
- *Eye exam*: You will need to undergo an eye exam prior to starting the study medication and again at the end of the study. This eye examination will last up to 2 hours and include dilation of your pupil. If you are found to have problems with your eyes, you will not be eligible to participate in the study.
- *Blood sample* (approximately 3 teaspoonfuls or 14.79 milliliters) will be drawn from a vein in your arm. This blood sample will be used for routine laboratory tests: blood count, glucose levels, chemistry panel, thyroid function, and liver function.
- *Baseline ECG:* Your heart function will be assessed using a test called an Electrocardiogram (ECG), which consists of putting stickers on your chest that detect details of your heartbeat.
- *Height, weight and vitals:* Your height, weight, blood pressure and heart rate will be recorded.
- *Baseline Rating Scales:* Research personnel will conduct pencil and paper assessment of the severity of your depression including suicidal thoughts.
- *Questionnaires:* Research personnel will ask you to complete questionnaires, which include questions about your severity of symptoms of depression including suicidal thoughts, and any antidepressant medications you have taken. This will take approximately 50-60 minutes each time to complete the questionnaires.

If you are already participating in and/or have already completed screening assessments under the screening protocol "A Screening Protocol for Adult Patients with Mood and Anxiety Disorders, Chronic Medical Conditions, and Healthy Volunteers" (RUTH STUDY ID: STUDY-10-00606; GCO: 06-0945; PI Dr. Murrough), and these assessments have been completed within 1 month of signing the consent for this protocol, you do not need to repeat these assessments.

WHAT HAPPENS TO THE MEDICATION I AM CURRENTLY TAKING FOR MY DEPRESSION?
If you are currently taking any medications that are not allowed when you are on the study, including antidepressants, you will not be withdrawn from the medication for the sole purpose of study participation and the decision to discontinue any medication is not made by the Lead Researcher. If you are taking a medication not allowed in this study, you may stop the medication under the supervision of your treating physician. If you are taking an antidepressant or other medications for depression at the time of signing this consent, you will need to stop them with your treating physician at least 2 weeks before the start of the study drug (4 weeks in the case of fluoxetine). Any medication taper that takes place must be initiated and overseen by your treating physician. Research personnel will tell you if this is applicable for you. The study psychiatrist will be available to discuss this process with you and with your treating physician.

Visit 0 (Week 0)
At this visit, baseline procedures are completed before the study drug or placebo is dispensed. The procedures may be completed at two visits within one week of each other and are expected to take 5 hours total.

- *Questionnaires*
- *Rating Scales*
- *Vital signs*
- *Blood sample:* (approximately 1 teaspoonfuls or 5 milliliters) will be drawn from a vein in your arm. This blood sample will be used for routine laboratory tests: blood count.
- *Physical exam*
- *Urine collection:* This urine will be used to conduct a urine drug screen and pregnancy test. If you test positive for pregnancy or illegal drugs, you may be exited from the study at this time.
- *Clinician visit:* You will meet with a qualified healthcare professional to review any change in your medical history or current medications since the prior appointment.
- *Cognitive tasks:* You will also complete computerized cognitive tasks. These tasks will be done inside or outside the MRI scanner. These tasks ask you to participate in a game, which will be explained to you beforehand.
- *MRI:* The MRI uses strong magnetic fields and radio waves to take pictures of your brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the imaging procedure, the team will determine that you do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and you will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). You will be asked to lie flat on your back in the MRI scanner for approximately 60 minutes and to remain as still as possible. You will not feel anything, but you will hear a knocking noise. This is a normal sound produced by the MRI scanner and does not indicate that anything is wrong. You will be provided the ability to notify the staff at any time during the duration of the scan if you would like to be taken out. The results from you MRI exam will be reviewed by a neuroradiologist, a doctor trained in MRI interpretations. Although these scans are conducted for research purposes only and the settings are not adjusted to find medically important findings, if an incidental finding of importance to your

health is discovered on screening lab tests, you will be notified along with your treating physician. These findings will only be shared with your treating physician if you give us permission to contact them.

- *Medication dispensation:* After this visit, you will begin taking the study drug (XEN1101 or placebo). You will receive a labeled bottle containing a week's supply of medication and will be instructed to take 2 capsules once each day at bedtime for a total dosage of 20mg.

RANDOMIZATION:

At this visit, you will be assigned either the study drug (XEN1101) or a placebo. No one, not you, or anyone from your medical team or from the research team will be able to choose what group you are assigned to or what study drug you get. It will be by chance, like flipping a coin. You will have an equal chance of being given each study drug. Neither you nor the Lead Researcher or your own doctor will know which study drug you are getting. If there is an emergency, they can get this information.

Because this research study involves the use of an investigational medication, a note must be included in your electronic medical record that you are taking part in the research. This way, anyone involved in your medical care at Mount Sinai will know that you are a study participant, and they can work to avoid any problems or negative outcomes that could arise if they do not know.

Visit 1 (Week 1)
At this appointment the study team will be checking how you are feeling since starting the study drug or placebo. You will complete the following assessments, which are expected to take 2 hours.

- *Questionnaires*
- *Rating Scales*
- *Vital signs*
- *Urine pregnancy test, if applicable*
- *Physical exam*
- *Blood draw:* approximately 1 teaspoonfuls or 5 milliliters will be drawn from a vein in your arm. This blood sample will be used to analyze the amount of study medication within your body.
- *Clinician visit:* You will meet with a qualified healthcare professional to review any changes to your medical history or current medications and review any side effects that you may be experiencing due to the study medication or placebo. If you have trouble tolerating the medication, you may be changed to a lower dose to decrease side-effects.
- *Medication dispensation:* At this visit, you will be given a two-week supply of the study drug (XEN1101) or Placebo.

Visit 2-4 (Weeks 2-6)
These visits will occur every other week over the course of 6 weeks, a total of three appointments. At this visits the study team will review how you have been feeling since the prior appointment. The procedures are anticipated to take roughly 2 hours.

- *Questionnaires*
- *Rating Scales*

- *Vital signs*
- *Urine pregnancy test, if applicable*
- At visits 2 and 3, a physical exam will be performed.
- At visit 2, an additional ECG will be performed.
- At visit 3, a blood sample (approximately 1 teaspoonfuls or 5 milliliters) will be drawn from a vein in your arm. This blood sample will be used for routine laboratory tests: blood count.
- *Clinician visit:* A qualified healthcare professional will review any changes to your medical history or medications since the prior appointment and will ask if you have experienced any side effects since the last visit.
- *Medication dispensation:* At each visit, you will be provided a two-week supply of the study medication (XEN1101) or Placebo.
- In between these visits, a study team member will call you to see how you are doing on the medication.

If a portion of this exam is conducted remotely, you will complete all questionnaires via an email link and will be asked to meet with a study rater and/or a qualified healthcare professional via a HIPAA compliant video platform.

Visit 5 (Week 8)

- *Questionnaires*
- *Rating Scales*
- *Vital signs*
- *ECG*
- *Physical exam*
- *Urine collection:* This urine will be used to conduct a urine drug screen, routine safety analysis and a pregnancy test (if applicable).
- *Blood draw:* approximately 4 teaspoonfuls (19 milliliters) will be drawn from a vein in your arm. This blood sample will be used for routine laboratory tests: blood count, glucose levels, chemistry panel, thyroid function, and liver function as well as to analyze the amount of study medication in your body.
- *Clinician visit:* A qualified healthcare professional will review any changes to your medical history or medications since the prior appointment and will ask if you have experienced any side effects since the last visit.
- *Cognitive tasks*
- *Post-treatment brain scan:* A second MRI scan, similar to the first, will take place.

Study Exit Visit (Week 12)

At this final visit, the study team will be asking you questions and checking for any change in your medical history. These procedures can be completed on up to three separate visits and are expected to take 4 hours.

- *Questionnaires*
- *Rating Scales*

- *Eye exam*
- *Physical exam*
- *Vital signs*
- *ECG*
- A study team member will ask how you have been feeling while no longer taking the study medication and a qualified healthcare professional will review any changes to your medical history or medications since the prior appointment.
- *End of study plan*: A clinician will discuss your post-study participation treatment options with you. If applicable, the study team will ask if they can reach out to your mental health provider to aid in the transition of care. In the event that you don't have a current mental health provider, a clinical referral can be provided.

If any abnormal values are found on during the safety procedures at visit 5 (week 8), vital signs, ECG, blood draws, or urine collection may be repeated at the study exit visit. Once these procedures are completed, you will be considered exited from the study.

Early Study Exit (Week 0-Week 12)
If for any reason, after completing visit 0 but before completing the scheduled exit visit, you need to end your participation, the study team will ask you to return to complete the following procedures. They can be completed on up to three separate visits and are expected to take 5 hours.

- *Questionnaires*
- *Rating Scales*
- *Vital signs*
- *ECG*
- *Physical exam*
- *Eye exam*
- *Urine sample:* This urine sample will be used for routine analysis and to test if you are pregnant.
- *Blood sample* (approximately 4 teaspoonfuls or 19 milliliters) will be drawn for routine laboratory tests: blood count, glucose levels, chemistry panel, thyroid function, and liver function as well as to analyze the amount of study medication in your body.
- *Post-treatment brain scan*
- *Cognitive tasks*

Unscheduled Visit
If the study doctor thinks that you should have additional visit(s) for your safety (e.g. if you experience a new symptom or side effect), you may be asked to come to the study center for an additional visit. If necessary, additional tests related to such a safety concern may be ordered at no additional cost to you. During these visits your vital signs will be checked, your overall mental status, whether you have any thoughts or feelings of depression or suicidality, your medications and how you have been feeling since the last visit.

PREGNANCY:

If you can possibly get pregnant, a urine pregnancy test will be done before you begin the study and will be repeated at each study visit.

You cannot be included in the study if you are or become pregnant, as the study drug could harm your fetus. You should also not be in the study if you are producing milk to feed a child because the study drug could harm your baby.

Unless you are at least one year past menopause or have had a successful operation to make pregnancy impossible, you should use effective birth control. Unless you are sexually abstinent, (not having genital sex), the recommended methods of birth control are:

- An intrauterine device (IUD),
- Contraceptive injection (Depo-Provera),
- Double barrier methods (condoms with contraceptive foam or diaphragm with spermicidal gel),
- Sexual abstinence (no sexual activity), or
- Sterilization (a vasectomy, getting tubes tied, or a hysterectomy).
- The efficacy of hormonal contraceptives can be compromised by the co-administration of the study drug, therefore if combined or progesterone-only hormonal contraceptives are used, you must agree to use an additional barrier method of contraception.

All birth control methods (other than abstinence and sterilization) are only effective if you use them properly, start them at least one month before you begin the research study, and continue using them throughout the research study and for six months after the research study ends. If you are unsure whether the method of birth control you use is approved to use while you are in this study, you should ask the Lead Researcher before you begin the study. If you are less than one year post-menopausal, you could still become pregnant. If you or your partner becomes pregnant, or may be pregnant, at any time, or in the month following your exit from the research study, you must tell a person from the research team immediately. The team may stop the study drug and refer you/your partner to an obstetrician/gynecologist for follow-up.

Should you/your partner become pregnant, whether or not you/your partner have the baby, the people funding and overseeing the research may ask for information on the pregnancy, even if you are no longer part of the study. You/your partner will be asked for additional written consent to share this information if that happens.

SEMEN/SPERM:

Drugs can be found in semen and alter sperm. Since you are taking part in a study using experimental drugs treatments, it is recommended that 1) You use a condom, 2) You do not get a partner pregnant or expose them to semen, and 3) You do not donate semen. These recommendations apply both while you are taking the study drug, and for 3 months after you stop taking the study drug. This is because levels of the study drug may be present in the sperm and/or semen even after you stop taking the study drug. You are encouraged to tell your female partner(s) and/or their doctor(s) that you are participating in this clinical trial.

FUTURE CONTACT:

The researchers may wish to use your personal information to contact you in the future. Do you give the researchers permission to **contact you** in the future to request the collection of additional information about you, discuss how your private information, study data and/or samples might be used, or discuss possible participation in another research study?

Please initial your choice: Yes_____ No_____

If "Yes", please indicate your preferred method of contact: (check all that apply)

[ ] Email [ ] Phone [ ] Letter [ ] Text

USE OF YOUR DATA AND/OR SAMPLES:

The researchers would like your permission to keep your personal information (such as, name, address, date of birth, social security number) and study data and/or samples (blood, tissue, urine, saliva, or any other body matter) to use or share in future studies. Please select Yes or No to each of the questions below.

(1) Will you allow the researchers to store your data and/or samples to use in future research studies?

Please initial your choice: Yes_____ No_____

If you select 'No", please stop here. If 'Yes", please continue to the next question and tell us how your personal information and study data and/or samples may be used in future research.

(2) Do you give the researchers permission to keep the data and/or samples indefinitely, so they could use them in future studies that are **directly related** to the purpose of the current study?

Please initial your choice: Yes_____ No_____

(3) Do you give the researchers permission to keep the data and/or samples indefinitely, so they could use them for future studies that are **not related** to the purpose of the current study (for example, a different area of research)?

Please initial your choice: Yes_____ No_____

(3.1) From time to time, researchers outside of medicine and related sciences would like to use data and/or samples. This might be in fields such as anthropology, human origins, or mapping human migration patterns. Do you give permission for researchers **outside the field of medicine** to use your data and/or samples?

Please initial your choice: Yes_____ No_____

a. If the future research in a different area can be done without having to know that the data and/or samples came from you personally, that will be done.
b. If the future research in a different area requires that it is known specifically who the data and/or samples came from, then one of the following will be done:
    i. If you allowed the researchers to contact you in the future, they may be able to contact you to explain why your data and/ or samples are needed and what will be done with it. Your permission will be asked to use your data and/or samples in that research project.
    ii. If you do not give permission to be contacted in the future, or if it is found that contacting you is not practical (for example, because you have moved), your data and/or samples may still be used. The Institutional Review Board (IRB) will be asked for permission to use the data and/or samples linked to your identity. The IRB can give permission for researchers to use and share identifiable health information without contacting you, but only if it determines that sharing the data and/or samples will not be more than a minimal risk to you or your privacy. The IRB is a committee of doctors and scientists and nonscientists, including people not associated with this hospital or medical school, whose job it is to protect people who participate in research.

(4) Do you give permission to have your data and/or samples given **to other researchers,** including those at **[SITE]**, other medical or scientific institutions and for-profit companies, for use in research within the limits you have chosen above?

Please initial your choice: Yes_____ No_____

(5) Do you give permission to have portions of data and/or samples deposited in large public databases (repositories), for research with the limits you may have chosen above? Please read the paragraphs below which explains repositories, then initial your choice:

To do more powerful research, it is helpful for researchers to share the data and/or samples from samples they study. They do this by putting data and/or samples into a repository. A repository is

where something is stored safely for a specified period of time. Data and/or samples from one study may be stored in a repository along with data and/or samples from other studies. Researchers can then use the data and/or samples from multiple studies to learn even more about health and disease. If you agree to take part in this study, some of your genetic and health information might be placed into one or more scientific databases, but they will not share your direct identifiers (for example, name, address, date of birth). These databases are maintained by **[SITE]**, another institution, the federal government, or private companies. Any researcher who wants to do a study using data and/or samples from the repository must apply for permission. There are different ways of reviewing such requests. Researchers with an approved study may be able to see and use your data, along with that from many other people. Researchers may use your samples for genetic sequencing and other experimental testing. Researchers will always have a duty to protect your privacy and to keep your information confidential, but there are always risks associated with data and/or sample collection and sharing. They are described in more detail in the Risks section.

Please initial your choice: Yes_____ No_____

Whether or not you have allowed us to share your data and/or samples with repositories, the researchers at **[SITE]** will keep data and/or samples collected about you during this research study to use in future research studies consistent with the wishes you expressed above.

(6) With your permission, data from this study will be submitted to the National Institute of Mental Health Database (NDA) at the National Institutes of Health (NIH). NDA is a large database where deidentified study data from many National Institute of Mental Health (NIMH) studies is stored and managed. Deidentified study data means that all personal information about you (such as name, address, birthdate and phone number) is removed and replaced with a code number. Sharing your deidentified study data helps researchers learn new and important things about mental health and substance use more quickly than before.

During and after the study, the study researchers will send deidentified study data about your health and behavior to the NDA. Other researchers across the world can then request your deidentified study data for other research. Every researcher (and institutions to which they belong) who requests your deidentified study data must promise to keep your data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

You may not benefit directly from allowing your study data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about mental health and substance use and how to help others who have problems with mental health and substance use. NIMH will also

report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about the study data you contributed to NDA.

You may decide now or later that you do not want your study data to be added to the NDA. You can still participate in this research study even if you decide that you do not want your data to be added to the NDA. If you know now that you do not want your data in the NDA, please tell the study researcher before leaving the clinic today. If you decide any time after today that you do not want your data to be added to the NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of the NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, this is available on-line at http://nda.nih.gov.

Do you give permission to share your information with NDA for research purposes? This data will be limited to use for mental health research and all your data will be de-identified (your name will not be used) and a code will be used so the data cannot be linked directly to you.

Please initial your choice: Yes_____ No_____

YOUR RESPONSIBILITIES IF YOU TAKE PART IN THIS RESEARCH:

If you decide to take part in this research study, you will be responsible for the following things:

- Tell the study doctor if you notice any sudden changes in your mood, behavior, thoughts, or feelings.
- Take the study medication at the prescribed dose and time. Tell the study doctor about any health problems you have during the study.
- Tell the study doctor about any new medicine you take during the study.
- Do not take any other drugs or remedies unless the study doctor has approved them beforehand. This includes prescription drugs and over the counter medicine (including vitamins and herbal remedies) that you buy without a prescription.
- Complete questionnaires yourself and participate in interviews several times.
- Come to all study visit appointments and be available for the telephone appointments.
- Do not participate in other medical research studies.
- Use effective birth control; examples of effective birth control include barrier contraception (for example condoms), oral contraceptive pills or intrauterine devices for six months after the study.
- Do not breastfeed.
- Do not get pregnant or cause your partner to become pregnant.
- Do not take recreational or illegal drugs; examples of include marijuana, cocaine, heroin, or other narcotic substances. Marijuana or cannabis that is prescribed for a medical need is also not allowed.

COSTS OR PAYMENTS THAT MAY RESULT FROM PARTICIPATION:

Being in this study will not cost you anything extra. If you agree to take part in this study, you will be paid up to $825 for your time and effort. You will receive a check for $65 upon completing the screening. In addition, you will receive checks for $50 for each treatment visit (6 visits), $180 for each scanning visit (2 visits), and $65 for completing the study exit visit. In addition, you may receive up to $35 based on your performance on computer tasks during the study. Please note, that this additional $35 is not guaranteed, and you may not receive any additional payment as part of the MRI task.

If you are unable to complete the entire study, the payment will be prorated for the part you have completed. You will be paid based on the completion of the following visits:

Study Visit	***Compensation***
Screening	*$65*
Treatment Phase Visits (x6)	*$50*
MRI Scanning Visits (x2)	*$180*
Task Performance	*$0-35*
Study Exit	*$65*
Total	***$790-825***

It can take up to 6 weeks to prepare and give you a check for study participation. If you do not get a check by then, you can first contact the research team. If further assistance is needed, please contact Mount Sinai's Program for the Protection of Human Subjects at (212) 824-8200.

Tax law may require the Mount Sinai Finance Department to report the amount of payment you receive from Mount Sinai to the Internal Revenue Service (IRS) or other agencies, as applicable. Generally, this happens if you receive payments that equal $600 or more from Mount Sinai in a calendar year. You would be responsible for the payment of any tax that may be due.

You will receive up to $250 in transportation reimbursement throughout the course of the study. To be reimbursed for travel a receipt must be provided to the study team.

It is possible that products may someday be developed with the help of your data and/or samples, and there are no plans to share any profits from such products with you.

POSSIBLE BENEFITS:

There is a chance this study may benefit you, but this is not guaranteed. Others may benefit from what researchers learn from the study. Possible benefits to you include:

- Temporary improvement in your depressive symptoms.
- Your participation in this study may yield useful information that will be helpful to the development of a new treatment for treatment-resistant depression.

POSSIBLE RISKS AND DISCOMFORTS:

Risks of XEN1101: Based on previous studies, the most common side effects of the study medication are dizziness, drowsiness, difficulty with memory, headache, difficulties paying attention, lightheadedness/fainting, and blurry vision. These side effects may be mild, moderate, or severe. In addition to the common side effects described above, the following side effects are possible and may be either mild, moderate or severe. In some cases, side effects can be life-threatening.

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- Disturbances in thinking and perception. These side effects can include confusion, hearing or seeing things that are not real, being suspicious or distrustful, believing things that are not true, or other unusual or extreme changes in behavior or mood.
- Problems urinating or retaining urine. These side effects can include having difficulty or being unable to urinate or experiencing a painful or weak urination.
- Problems related to your heart or vascular system. These side effects can include changes to your heart rate, heart palpitations or heart “skipping a beat.”
- Problems related to your vision or eye. These side effects can include retinal changes or discoloration. Vision problems have not been observed with the study drug. However, a drug that is related to the study drug was found to cause retinal changes that can progress to vision loss.
- Suicidal thinking or behavior. Drugs related to the study drug may cause suicidal thoughts or actions in a small number of people. These include thoughts about suicide or dying; attempt to commit suicide; new or worse depression; new or worse anxiety; feeling agitated or restless; panic attacks; trouble sleeping (insomnia); new or worse irritability; acting aggressive, being angry, or violent; acting on dangerous impulses; an extreme increase in activity and talking (mania); or other unusual changes in behavior or mood.

In the event that these side effects are not tolerable or cause concern, the study team can discuss reducing your study medication dose or exit you from the study.

Participants should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with the study medication.

General MRI Risks and Discomforts:
MRI scanning involves the use of a magnet and radio frequency energy. Therefore, patients who have implanted metal devices, such as pacemakers, certain aneurysm clips, or shrapnel or metal in the eye

are at risk. You will complete a screening form to identify metals, but if you have any question of metal in the body, you should inform the technologist or investigators before entering the magnet room. If you have metal in your body that you are unable to remove, the safety team will determine whether you will be able to undergo MRI scanning safely. Because of the strong magnetic field associated with the scanner, it is rare, but possible, that a metallic object could fly through the air toward the scanner and hit you. To reduce this risk, everyone in the vicinity of the magnet will remove all metal from their clothing or pockets when in the scanning environment.
To create images, MRI employs radio waves. These waves are not harmful, however, MRI scanners do produce loud noises when these waves are generated. To minimize discomfort, you will be provided with disposable earplugs or headphones that help suppress external noise levels but do not eliminate the noise so that you can have voice communication with the scanner operator. Some individuals may experience a feeling of claustrophobia (fear of being trapped in a narrow place) during scanning, but the machine may be stopped at any time during the scan upon your request. Please note that if you are unable or choose not to complete the MRI portion of the study, you will not be able to participate in the remainder of the study.

Other risks of MRI that rarely occur include neurostimulation effects, such as muscle twitches and tingling sensations, due to the rapid switching of magnetic fields, and a slight increase in body temperature that may occur in the presence of radio frequency energy. These are very unlikely under current operational guidelines. In the very remote event that the magnet loses its magnetism, helium gas in the magnet will escape. The room is designed with ventilation systems to prevent accumulation of these gases. Should this occur, you will immediately be brought out of the magnet room.

Other risks:

- Risk of loss of private information; this risk always exists, but there are procedures in place to minimize the risk.
- Privacy Risks: Your name and other information that could directly identify you (such as address, date of birth or social security number) will never be placed into a scientific database.
- Blood Draw: The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw.
- Psychological risks: During the psychiatric interviews, participants will possibly be exposed to the discomfort of being asked personal questions they may find distressing. You may choose to not answer any questions that make you uncomfortable. The risks and discomforts associated with answering questionnaires are minimal.
- Group Risks: Although your name will not be given to the researchers, they will receive basic information such as your race, ethnic group, and sex. If your private information was misused, it is possible you would experience other harms, such as stress, anxiety, stigmatization, or embarrassment from revealing information about your family relationships, ethnic heritage, or health conditions.
- If you are pregnant or become pregnant, this research may hurt your baby or your pregnancy in ways that are unknown. The unknown risks might be minor or might be major (death) for

the pregnancy. You should not become pregnant or impregnate a woman while in this research study. Please read the acceptable methods of birth control found under the Description of What Is Involved section of this document.

- Not being on a standard or approved treatment for your depression, or stopping one that you were previously on, may lead to a worsening of your condition.
- Incidental Findings: This MRI scan is not being done for your regular medical care. The machine settings used for this special MRI are not chosen to pick up structural changes in the brain, for example: masses or bleeds. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the Lead Researcher will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician and may result in additional cost to you.
- In addition to these risks, this research may hurt you in ways that are not known. The unknown risks might be minor or might be major (death).

OTHER OPTIONS TO CONSIDER:

You may decide not to take part in this research study. If you decide not to take part, this will not affect the clinical care you receive at **[SITE]**. The choice is totally up to you.

Instead of being in this research study, your choices may include:

- Treatments such as medications or cognitive behavioral therapy that have been shown to be effective as treatment for MDD. These alternatives are available to you at Mount Sinai and elsewhere and will be described to you fully prior to agreeing to participation in this study.
- The benefits from these treatments could be alleviation of your depressive symptoms, however, the risks could be side effects, or the treatment may not help relieve your depressive symptoms. You will be reminded that these alternative treatments for major depressive disorder are available in clinical practice before being considered for this study.

IN CASE OF INJURY DURING THIS RESEARCH STUDY:

If you are injured or made sick from taking part in this study, you will get medical care. Generally, it will be billed to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, copayments, and coinsurance. This does not prevent you from seeking payment for injury related to malpractice or negligence. Contact the Lead Researcher for more information.

ENDING PARTICIPATION IN THE RESEARCH STUDY:

You may stop taking part in this research study at any time. No matter what you choose, your care and benefits through **[SITE]** will not be negatively impacted.

If you decide to stop being in the study, please contact the Lead Researcher or the research staff. If you choose to stop participating in the study before you have completed it, you may be asked to return to the study doctor to have final tests done. The study team will also provide you with referrals where you can continue to receive treatment for depression.

You may also withdraw your permission for the researchers to use and share any of your protected information for research, but you must do so in writing to the Lead Researcher at the address on the first page. Even if you withdraw your permission, the Lead Researcher may still use the information that was already collected if that information is necessary to complete the research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from taking part in the research study.

If you stop being in the research study, the research team may not remove information they have already placed in the study database and may continue to use that data as part of this study. The research team may ask you whether they can continue to collect information from your medical record.

Withdrawal without your consent: The Lead Researcher, the funder, or Mount Sinai may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the study team have not been followed, the Lead Researcher believes it is in your best interest, or for any other reason. If data and/or samples have been stored as part of the research study, they too can be destroyed without your consent.

More possible reasons for removal from the study include:

- Medically important results of blood tests, physical examination, or ECG.
- Participants judged to be at serious suicidal risk by the PI.
- Any unstable medical illnesses.
- Development of pregnancy during the study.

CONTACT INFORMATION:

If you have any questions, concerns, or complaints at any time about this research, or you think the research has harmed you, please contact the office of the research team and/or the Lead Researcher at phone number **[SITE contact e.g. 212-659-xxxx; this number should reach the research team directly, not be a general clinic or department number]**.

If there is an emergency, please call 911 or go to the emergency room. Let the emergency room staff know you are in a research study so they can contact the Lead Researcher if needed.



DISCLOSURE OF FINANCIAL INTERESTS:

Researchers sometimes get paid for consulting or doing work for companies that produce drugs, biologics, or medical devices. If you have questions regarding industry relationships, you are encouraged to talk to the Lead Researcher or visit our website at http://icahn.mssm.edu/ where Mount Sinai publicly discloses the industry relationships of our faculty.

Dr. James Murrough (the Lead Researcher in this study) receives financial compensation as a consultant from Xenon Pharmaceuticals, the manufacturer of the KCNQ channel opener (XEN1101) that is the focus of this study.

Dr. Murrough is a named inventor of a pending patent application related to the use of KCNQ channel modulators for depression. This is filed through the Icahn School of Medicine at Mount Sinai and is currently unlicensed.

If you have questions regarding paid relationships that your physician/researcher may have with industry, we encourage you to talk with them, or check for industry relationships posted on individual faculty pages on our website at http://icahn.mssm.edu/.

MAINTAINING CONFIDENTIALITY – HIPAA AUTHORIZATION:

As part of this study, some of your private and/or protected health information (PHI) will be obtained, used, and shared with your permission. There is a federal Health Insurance Portability and Accountability Act (HIPAA) that makes sure this is done correctly and safely.

What is protected health information (PHI)? PHI is the combination of two things:

1. PHI contains information that identifies you. It will be used to contact you and link you to your health information, like name, date of birth, medical record number, and address.
2. PHI also contains health information, including information about your mental and physical health from your visits to doctors or hospitals, or from study visits.

Every time you visit a hospital or your doctor, PHI is created and recorded in your medical record by your healthcare providers. In the same way, the PHI created as part of this study will be linked to who you are and your medical information.

What PHI is collected and used in this research study, and might also be shared with others?
As part of this research project, the research team at the hospital(s) involved in the research will collect your name, address, telephone/fax numbers, dates directly related to the individual (birth, admission, discharge, date of death, etc.), e-mail addresses, social security number, medical records number, or

health plan numbers. The researchers will also get information from your medical record or will obtain your consent for release of medical information from your private doctor.

During the study the researchers will gather information by:

- Reviewing and/or taking your medical history (includes current and past medications or therapies, illnesses, conditions or symptoms, family medical history, allergies, etc.).
- Doing a physical examination that generally also includes blood pressure reading, heart rate, breathing rate, and temperature.
- Completing the tests, procedures, questionnaires, and interviews explained in the description section of this consent.
- Reviewing mental health records.

Why is your PHI being used?

Researchers need the information that identifies you so they can contact you during the study. They need your health information and the results of any tests and procedures being collected as part of this study to answer the questions posed in the study. The purpose of this study is discussed earlier in this consent form. Before researchers analyze the data, they remove any information that would let others know who you are or that you took part in the study. If researchers publish or present study results at scientific meetings, lectures, or other events, their presentations would not include any information that would let others know who you are, unless you give separate permission to do so.

The Lead Researcher may also use and share the results of these tests and procedures with other healthcare providers at **[SITE]** who are involved in your care or treatment. The research team and other authorized members of **[SITE]** workforce may use and share your information to ensure that the



research meets legal, institutional or accreditation requirements. For example:

STUDY INFORMATION:

Study Title: A Proof of Concept Randomized Controlled Trial of XEN1101 for the Treatment of Major Depressive Disorder

SITE **Study site(s):** ***SITE***

SITE **Principal Investigator (Lead Researcher): [First Name Last Name, Degree(s)]**

SITE **Physical Address: [Hospital/clinic name; Annenberg 22nd Floor, Room XXX; This will usually be the location where the subject should go for study visits; otherwise it can be the PI's office address]**

SITE Mailing Address: [e.g. One Gustave L Levy Place Box XXXX, NY, NY 10029]

SITE **Phone: [e.g. 212-XXX-XXXX; this number should reach the research team directly, not be just a general clinic or department number]**

SUMMARY OF THIS RESEARCH STUDY:

This document explains a research study you might be interested in joining. Participation in the study is voluntary. You can agree to join or not. Your decision will not limit your ability to get medical care at **[SITE]**. You should only agree to take part if you understand the study and if all of your questions about the research study are answered. If you do join the study, the research team must share any new information with you that may change your mind.

The purpose of this research study is to investigate a medication called XEN1101 for the treatment of Major Depressive Disorder (MDD, a.k.a. depression). XEN1101 is an investigational drug, meaning that it has not been approved for use by the United States Food and Drug Administration (FDA), the branch of the federal government that approves new drugs. Part of the study's purpose is to investigate any changes in brain activity that may be related to changes in depression symptoms.

If you choose to take part, you will be asked to:

- Attend 8 study visits over 18 weeks,
- Complete brain scans, blood draws, and take the prescribed medication or a placebo, and
- Agree to have private information and study data stored indefinitely.

If you choose to take part, the main risks to you are (1) feeling worse if any treatment is stopped while waiting for the investigational drug to possibly be effective, (2) a worsening of symptoms if assigned to placebo, (3) side effects of XEN1101 (e.g., dizziness, drowsiness [please see page 13 for a full list of side effects]); (4) discomfort or pain during or after the blood draw, including bruising, infection, and dizziness or feeling faint after your blood has been taken; (5) having claustrophobic reactions in the MRI scanner. If you have metal objects of any kind in your body, you will not be able to participate for matters of your own safety.

- The Mount Sinai Program for the Protection of Human Subjects is responsible for overseeing research on human subjects and may need to see your information.
- If you receive any payments for taking part in this study, the **[SITE]** Finance Department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- If the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities.

Who, outside **[SITE]**, might receive your PHI?

As part of the study, the Lead Researcher, research team and others in the **[SITE]** workforce may disclose your PHI, including the results of the research study tests and procedures, to the following people or organizations: (It is possible that there may be changes to the list during this research study; you may request an up-to-date list at any time by contacting the Lead Researcher.)

- The United States Department of Health and Human Services (DHHS) and the Office of Human Research Protection (OHRP) (the government organization that is responsible for protecting human research participants).
- Other collaborating research center(s) and their associated research/clinical staff who are working with the investigators on this project: Icahn School of Medicine at Mount Sinai Hospital and Baylor College of Medicine.
- Outside laboratory who will be performing laboratory analysis for all the research centers involved in this project: York Bioanalytical Solutions Limited.
- The sponsoring government agency and/or their representative who need to confirm the accuracy of the results submitted to the government or the use of government funds: National Institute of Mental Health.
- A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety.
- The United States Food and Drug Administration.
- Others: Xenon Pharmaceuticals.

In almost all disclosures outside of **[SITE]**, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Some records and information disclosed may be identified with a unique code number. The Lead Researcher will ensure that the key to the code will be kept in a locked file or will be securely stored electronically. The code will not be used to link the information back to you without your permission, unless the Institutional Review Board (IRB) allows it after determining that there would be minimal risk to your privacy. The Certificate of Confidentiality obtained from the Department of Health and Human Services will not be used to prevent disclosure to local authorities of child abuse and neglect, or harm to self or others. It is possible that a sponsor or their representatives, a data coordinating office, or a contract research organization, will come to inspect your records. Even if those records are identifiable when inspected, the information leaving the institution will be stripped of direct identifiers. Additionally, *the OHRP as well as the FDA will be granted direct access to your medical records for verification of the research procedures and data. OHRP and FDA are authorized to remove information with identifiers if necessary to complete*

their task. By signing this document, you are authorizing this access. The results of this research may be published. However, your name and other identifying information will be kept confidential.

For how long will [SITE] be able to use or disclose your PHI?
Your authorization for use of your PHI for this specific study does not expire.

Will you be able to access your records?
During your participation in this study, you will have access to your medical record and any study information that is part of that record. The research team is not required to release research information to you that is not part of your medical record.

Do you need to give us permission to obtain, use, or share your PHI?
NO! If you decide not to let us obtain, use, or share your PHI, you should not sign this form, and you will not be allowed to volunteer in the research study. If you do not sign, it will not affect your treatment, payment or enrollment in any health plans or affect your eligibility for benefits.

Can you change your mind?
If you decide to stop being in the study, please contact the Lead Researcher or the research staff. The research team may ask you whether they can continue to collect information from your medical record. You will also have to decide if you wish to limit the continued use of the information collected during the study. Under US privacy laws you may also withdraw your permission for the researchers to use and share any of your protected information for research, but you must do so in writing to the Lead Researcher at the address on the first page.

If you have not already received it, you will also be given The Hospital's Notice of Privacy Practices that contains more information about how The Hospital uses and discloses your protected PHI.

It is important for you to understand that once information is disclosed to others outside [SITE], the information may be re-disclosed and will no longer be covered by the federal privacy protection regulations. However, where possible, [SITE] has entered into agreements with those who will receive your information to continue to protect your confidentiality.

If researchers are reviewing your medical records or asking questions about your medical history or conditions, it is possible that they may learn information related to your HIV status. If that is the case, the following information concerns you. If researchers are not reviewing your medical records or asking questions about your medical history or conditions, then you may ignore the following section.

Notice Concerning HIV-Related Information
If you are authorizing the release of HIV-related information, you should be aware that the recipient(s) is (are) prohibited from re-disclosing any HIV-related information without your authorization unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at

(888) 392-3644 or the New York City Commission on Human Rights at (212) 306-5070. These agencies are responsible for protecting your rights.

Certificate of Confidentiality

To further protect your privacy, the researchers have obtained a Certificate of Confidentiality from the DHHS. This is intended to ensure that your identity as a participant in this research study will not have to be disclosed as a result from a subpoena, for the purpose of identifying you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings other than to the FDA or OHRP as identified above.

The research staff will not share any of your personal information, study data, and/or samples with anyone who is not a member of the research team, including any family members or friends, other than to those identified above. However, you should know that if it is learned that you or someone else is threatened with serious harm, such as a child or an elderly person being abused, the research team may notify the appropriate authorities if necessary to protect you or others. 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. This means that you and your family must also actively protect your own privacy. If an insurer or employer learns about your research participation, and you agree that they can have your research information, then the researchers may not use the Certificate of Confidentiality to keep this information from them.

HOW THE INSTITUTIONAL REVIEW BOARD (IRB) CAN HELP YOU:

This research has been reviewed and approved by an Institutional Review Board (IRB). You may reach a representative of the Mount Sinai Program for Protection of Human Subjects at telephone number (212) 824-8200 during standard work hours (Monday-Friday, 9am-5pm, excluding holidays) for any of the reasons listed below. This office will direct your call to the right person within the Mount Sinai Health System:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You are not comfortable talking to the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

ADULT PARTICIPANT:

Your signature below documents your permission to take part in this research study and to the use and disclosure of your protected health information. A signed and dated copy will be given to you.



_____	_____	_____	_____
Signature of Participant	Printed Name of Participant	Date	Time

PERSON EXPLAINING STUDY AND OBTAINING CONSENT:

_____	_____	_____	_____
Signature of Consent Delegate	Printed Name of Consent Delegate	Date	Time

WITNESS SECTION:
When a witness is required to observe the consent process, it should be documented below (for example, when participant is illiterate, visually impaired, or this document accompanies a short form consent).

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant, and that consent was freely given by the participant.

_____	_____	_____	_____
Signature of Witness	Printed Name of Witness	Date	Time