"Tocilizumab, An Il-6 Receptor Antibody, As Add-On Treatment For Residual Positive, Negative, And Cognitive Symptoms Of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial"
Consent summary form

Below is a summary of the study you are being asked to participate in. This outline is meant to be a guide for you to use while considering the study and reading the consent form. It is not meant to replace the consent form you will need to sign if you decide to participate in the study. The consent form contains much more detailed information about the study and the risks you will need to consider in order to make your decision.

- You are asked to participate in research study that looks at how a drug, tocilizumab, affects the symptoms of schizophrenia.
- It is important that you understand that you will receive no personal benefit from your involvement in the research itself.
- You will participate in several psychological tests that examine your symptoms of schizophrenia.
- This research study may be completed as an inpatient or an outpatient and will take approximately 16 weeks
- Tocilizumab is given as an intravenous (IV) medication, which means that you will need an IV each time you get it, up to three times.
- You will have the option of doing up to two magnetic resonance imaging (MRI) brain scans with dye. You do not need to do any MRI scans to participate in the research study of tocilizumab-the MRI part is optional. Each scan takes about one hour to complete. One scan is done at the beginning of the study and one at the end of the study.

Risks of tocilizumab drug:

- Tocilizumab is an FDA-approved medication for rheumatoid arthritis and juvenile idiopathic arthritis.
- Some possible side effects include chills, nausea, vomiting, a severe allergic reaction, nasopharyngitis, high blood pressure, rash, abdominal pain, diarrhea, mildly elevated liver blood tests, headache, dizziness, elevated cholesterol levels, or worsening of symptoms. You will be constantly watched during the drug administration to ensure your health and safety. We will stop giving the drug if there are any safety concerns.
- You will be given an 8mg/kg dose of tocilizumab, or a placebo.
- If you decided to do the MRI part of the study, there are additional possible side effects and potential risks you should know about, and these are detailed in the consent form. For example, there is a dye used in the MRI, gadolinium, which may have side effects, including nausea, dry mouth, dizziness, headache, hives, and a rare kidney condition called nephrogenic systemic fibrosis. The details of the common and rare side effects of this dye are listed in the consent form and you can discuss these with the study doctor.

As in all research, it is your choice to participate in this study and you do not have to participate if you do not want to. Also, you may stop participating at any time. This research study is not meant to benefit you directly. Please read the Consent Form carefully and ask the study physician any questions or concerns you might have.

NEW YORK STATE PSYCHIATRIC INSTUTUTE
COLUMBIA UNIVERSITY DEPARTMENT OF PSYCHIATRY
CLINICAL INVESTIGATION CONSENT FORM

(For patients participating in "**Tocilizumab, An Il-6 Receptor Antibody, As Add-On Treatment For Residual Positive, Negative, And Cognitive Symptoms Of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial**")

Purpose of Study

You are being asked to participate in a research study of tocilizumab. You qualify to participate in this study because you are between 18 and 59 years old and have a diagnosis of schizophrenia or schizoaffective disorder. This study is paid for by the Stanley Medical Research Institute. The study drug, tocilizumab, is being provided by the makers of tocilizumab, Genentech.

For this study you will receive a drug called tocilizumab, or placebo, which is saline water and does not have any tocilizumab in it. The drug or placebo will be given into a vein in your arm over 60 minutes. You will not know whether you will receive tocilizumab or placebo. Tocilizumab is drug that is FDA-approved for rheumatoid arthritis and juvenile idiopathic arthritis. The main purpose of this study is to see if it affects your symptoms of schizophrenia. It has never been studied in a clinical trial of people with schizophrenia. In order to examine your symptoms of schizophrenia, you will take several psychological tests. If you have already participated in the general schizophrenia research study at the New York State Psychiatric Institute, you may have already finished some of this testing. If so, we will use the results of those tests for this study. If you have not taken these psychological tests before, you will take them as part of your participation in this study.

You will also have the option of doing an MRI scan at the beginning and end of the study. The MRI scans are optional-you do not need to do the MRI scans to do the study of tocilizumab.

Alternatives to study participation

This is not a treatment study: data are being collected for research purposes only. The alternative would be to not participate in this research study and to continue with your treatment as usual, which may include medications, therapy, and other interventions. Medications such as tocilizumab are available for use but have not yet been studied in individuals with schizophrenia. It is also not necessary to participate in this research study to have an MRI, and the MRI done as part of this study is not the same as one done for medical purposes.

Study Procedures

Participation in the general schizophrenia research study and evaluation

If you are interested in participating in this study, we will review your medical records to decide if you are eligible for the study. We may also have to ask you

additional questions to determine your eligibility. All subjects will also receive blood and urine testing, as well as medical and psychiatric examinations, at the beginning of the study to make sure that you can participate in this study. These blood tests may be done fasting. This testing may take more than one day. As part of your blood tests you will be tested for hepatitis B and hepatitis C. The doctor will inform you that, if your hepatitis test is positive, your result must be reported to the New York State Department of Health. Female subjects will receive regular pregnancy tests, including a blood pregnancy test at the beginning of the study. We will also test you for tuberculosis with a "ppd" skin test. If that is positive, or if you have a history of positive ppd skin tests, we may ask you to have a chest x ray to decide whether or not you can participate in this study.

We will also ask you whether you would be interested in having some of your rating sessions audio or video taped. These procedure would be fully optional and would not affect your participation in this study. They are described in more detail below.

Overview of the study

If you qualify for the study you will be asked to participate in:

- 3 days of treatment with the research drug (tocilizumab or placebo). The drug is infused through a catheter (a small plastic tube) that is placed in a vein in your arm using a needle. The infusion is done over 60 minutes. The catheter will be placed right before the drug is given to you, and then removed right afterwards.
- You may participate in this study as an inpatient or outpatient and, overall, will take approximately 16 weeks.
- 4 Clinical, psychological, and medical testing sessions. Some of this testing may already have been done as part of the general schizophrenia research study at the New York State Psychiatric Institute. If so, those tests will not be repeated and we will use the results of those tests for this study. If you have not taken these tests before, you will take them as part of your participation in this study.
- One follow-up visit 2 weeks after you are given tociliuzmab.
- You will have the option of doing two MRI scans, one at the beginning and one at the end of the study.

Drug administration. A study physician will inject the study drug (tocilizumab or placebo) into a vein in your arm very slowly over 60 minutes. You will be watched closely during and after the drug administration. If you have any serious side effects to the drug, the injection will be stopped. A doctor or nurse will be present with you at all times during the drug administration to monitor your health.

They study drug (tocilizumab or placebo) will be administered into a vein in your arm through a catheter (a small plastic tube). The catheter will be placed right before the drug is given to you, and then removed right afterwards. This catheter will be used to take blood samples so that we can measure the blood levels of certain chemicals in the blood to see if tocilizumab has any effect on these chemicals. We will also check for blood levels of your schizophrenia medication. This catheter will be removed immediately after you have finished receiving tocilizumab or placebo on that day.

Clinical and Follow-up visits: While you are in this study you will be asked to do clinical testing a total of 5 times. These visits will include a medical and psychiatric interview, a medical examination, blood samples, urine samples and an EKG. The goal of these follow-up visits is to confirm that the study has not affected your health. You may be asked to participate in more than these follow-up visits if the study physician feels it is needed based on the results from your exams.

Psychological and Cognitive testing: You will participate in several psychological tests as part of this study at the beginning of the study and at weeks 2, 4, 8, and 12. If you have already participated in the general schizophrenia research study at the New York State Psychiatric Institute, you may have already finished some of this testing. If so, we will use the results of those tests for this study. If you have not taken these psychological tests before, you will take them as part of your participation in this study. In addition, we will ask you to take a computerized test of your short-term memory. All together, these questionnaires and tests should take about 2-3 hours. We will be unable to tell you how well you do on these tests while you are participating in the study. However, after the study is completed, we can discuss the results of the study with you if you wish.

If you decide to leave the study early, we will ask you to do the follow-up safety testing and memory and concentration tests. We will also ask you if you would be willing to have your last infusion of the study drug (tocilizumab or placebo) if you have not already had it.

We will obtain urine tests for drugs of abuse and pregnancy (if you are a female) at every visit.

MRI (Magnetic Resonance Imaging). You may also do MRI scans at the beginning and end of the study if you would like to. The MRI uses strong magnetic fields and radio waves to pictures of your brain. MRI involved lying on a table that slides into a large magnet shaped like a cylinder. Before Beginning the imaging procedure, we will ascertain that you do not have a pacemaker or any metallic implants (other than tooth fillings, or braces), and you will be asked to remove any metal or magnetized objects (such as keys, chins, hairpins, or credit cards). You will be asked to lie flat on your back in the MRI scanner for 45-60 minutes. Your will be asked to remain as still as possible. You will not feel anything, but will hear a knocking noise. This is a normal sound produced by the MRI scanner and does not indicate that anything is wrong. This testing will take a total of 1 hour.

During the MRI scan, you will receive an intravenous injection of a Gadolinium compound. Gadolinium compounds are dyes that dissolve in blood and are eliminated by the kidneys. Gadolinium compounds do have rare side effects. There are different forms of compounds, and we purposefully use the form (MultiHance) that has a low number of side effects. One side effect is nausea, observed in 1.8% of people injected with MultiHance. A second side effect is hives, observed in 0.7% or people injected with MultiHance. Both of these side effects resolve within a few hours.

End of the Study Clinical Treatment

You will be able to receive treatment from a psychiatrist and a psychotherapist in our outpatient clinic (Lieber Schizophrenia Research Clinic) for at least 4 months after your participation in the study, or you may return to your previous treatment provider. The treatment in the Lieber Schizophrenia Research Clinic is free except for the cost of medications.

Risks

1. Tocilizumab is FDA approved for individuals with rheumatoid arthritis or juvenile idiopathic arthritis. Possible effects of tocilizumab include mild infection including nasopharyngitis, high blood pressure, rash, abdominal pain, diarrhea, mildly elevated liver blood tests, headache, dizziness, and elevated blood cholesterol levels. More serious and uncommon side effects including injection site reaction, low blood platelet levels, low white blood cell levels, and tuberculosis if you have already been exposed to this infection. Rare side effects that have been observed in individuals who take tocilizumab, but may be due to other medications or causes, include gastrointestinal perforation, cancer, inflammation of the lining of the lungs, demyelinating disease, and heart failure. About 2 in 1000 people who receive tocilizumab may have a severe allergic reaction to getting tocilizumab including chills, fever, nausea, and vomiting. Worsening of symptoms of schizophrenia is also a possible side effect. Some people develop antibodies to tocilizumab. In order to decrease the chance that an adverse event occurs, we will do a complete medical test before you receive tocilizumab. We will also monitor you closely while you receive the study drug, as well as afterwards. You will not be allowed to participate in this study if you have a medical condition that would put you at risk of a severe side effect.

2. *Intravenous Catheter:* Mild discomfort can be expected from placement of a catheter (which is like a small plastic tube) into a vein with a needle. It may be uncomfortable to have an intravenous catheter in your arm. Intra-venous lines can also cause bleeding, blockage of the vein, infection or clotting, although these are unlikely since the IV will be in your arm for only approximately an hour. These risks are decreased by using proper techniques. In addition, injecting the drug into your vein may cause pain or skin irritation at the sites where the drug is injected.

3. *Blood samples:* A total of about 8 ounces (approximately 17 tablespoons or 245mL) of blood will be drawn over the study period. This is less than a typical donation to a blood bank, and should not cause any problems.

4. *Interviews*: Sometimes people can feel boredom or frustration while taking computer tests or pen and paper tests. You should feel free to tell the research staff whenever you feel this way so that they can help you take a break. Research staff will

also ask you whether or not you are bored or frustrated and will give you many breaks to try to avoid boredom and frustration as much as possible.

5. Gadolinium risks: Gadolinium compounds do have side effects. There are different forms of compounds; we use (MultiHance). Common side effects of gadolinium: One side effect is nausea and vomiting, observed in less than 2% of people injected with MultiHance. If you feel nauseous, please alert staff immediately. Dry mouth (less than 2%), dizziness (less than 3.6%), and headache (less than 5%) are possible side effects. An additional side effect is hives, observed in less than 1% of people injected with MultiHance. All of these side effects resolve within 20 minutes to several hours. People with asthma, allergies, or known sensitivities to dyes are at increased risk for more serious side effects (less than 1 in 10,000 injections estimate), such as severe allergic reaction that may result in sudden difficulty breathing, and therefore will not be injected with Gadolinium. Rare side effects of gadolinium: Some patients with bad kidney problems have developed a condition known as nephrogenic systemic fibrosis (NSF), a serious condition that may be fatal, after receiving gadolinium compounds. You will be screened for renal impairment through medical history interview and laboratory blood tests. There have been no reported cases of NSF in people who do not have a history of kidney failure.

The Food and Drug Administration (FDA) has issued an announcement stating they are investigating a possible risk of adverse health effects from repeated use of gadolinium for MRI. Though the FDA has not reached a conclusion at this time, you should not participate in this study if you have previously had more than 1 or 2 MRI scans with gadolinium.

6. MRI risks: While there have been no reports of any harmful long-term effects caused by 3T magnets or magnets of even higher strength, the long-term effects of being placed in a magnet of this strength are unknown. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. If you are a female in your childbearing years, you will be asked to take a pregnancy test to ensure that you are not pregnant. Some people have reported sensations during MRI scans with the 3T magnet, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in your body. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. Except for pacemakers, some types of metallic implants, and medication patches, we are not aware of any other potentially dangerous interactions or hazards associated with the MRI scan. The MRI scanner also produces a loud noise; earplugs will be provided to reduce this discomfort. If you experience any discomfort and wish to stop the scan, you can tell the MRI technologist, and he or she will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

Summary of key safety recommendations

- You should refrain from using alcohol, drugs or other medications the evening before the study.
- You should tell us about any past or present medical problems, and about use of medications, drugs and alcohol.
- You should tell us of any history of blood or liver problems, or a history of tuberculosis or a positive ppd skin test.

For females of child-bearing age: You cannot participate in this study if you are pregnant. A negative pregnancy test is required to enter the study. However, since this test might not detect the very early phase of pregnancy, you should refrain from sexual contact for 15 days before the trial if you are not using a reliable method of birth control. Reliable birth control includes oral contraceptive pills or condoms. You should inform us immediately if there is any chance that you may have become pregnant during this time, because of the possibility of tocilizumab exposure causing harm to the fetus. A pregnancy test will be performed on the drug administration days.

Results of your MRI While MRI scans are sometimes done for clinical purposes, the kind of MRI scan you will have as part of this study is for research purposes only. This means that the scans are not designed to provide clinical information that might be helpful to you or your doctor and they may not show problems that would normally be found in an MRI ordered to evaluate a specific medical problem. It is likely that the MRI scan will not have the quality of those done for clinical purposes. However, within a month of the MRI, the scan will be read by a neuroradiologist for evidence of any obvious irregularities requiring your follow-up. You, or a physician whom you may designate, will be informed only when significant abnormalities are detected. If you wish, we can also inform you if there were no obvious findings. Given the nature of the scan, the absence of a finding does not mean that one is not present.

Benefits

It is important that you understand that you will receive no personal benefit from your involvement in the research itself. The benefits of this research relate primarily to understanding the effects of the drug on symptoms of schizophrenia. This may also help to understand the effects of the drug on the brain. You will not have access to this drug after you have completed this study.

Costs and Compensation

For this study, you will receive compensation based on the time that you spend during each visit:

-$50 for each visit when you do not receive study drug (baseline [up to two baseline sessions], week 2, 12, 14) and take assessments

-$100 for each week 0, 4, 8 visit which will involve both assessments and study drug

-$100 for each MRI scan, if you choose to do MRI scans as part of this study.

-Reimbursement for local transportation

In total, you will receive up to $550, or $700 if you do the MRI scans. You will be paid by cash or check, which will be mailed to your address 4-6 weeks after the study

procedure. If you do not participate in all the study procedures, your payment will be pro-rated based on your participation.

If you earn more than $600, we are required by law to report your earnings to the IRS. Therefore, your Social Security Number and amount earned will be reported and you will receive the appropriate IRS form at the end of the year in which you have been paid. No information about which study you have participated in or anything else about this study will be provided to the IRS. Please note that payment for this study may affect entitlements/benefits that you receive, such as Medicaid, Social Security, and other city and state support services.

Confidentiality

Research records will be available to research staff, state, federal, and institutional personnel, and to the Food and Drug Administration. Records, including signed consent forms, will be kept in locked files, and your name will never be used in publications or presentations. Electronic data from the study will be stored in a password-protected database in the Division of Translational Imaging at New York State Psychiatric Institute. Access to this database is limited to investigators and research staff within the Division. Additionally, your name and other personal identifying information will be stored in an electronically secure database at the New York State Psychiatric Institute. There are legal advocacy groups that have authority under State law to access otherwise confidential subject records, although they cannot re-disclose this information without your consent. The results of your MRI scan will be maintained in an electronically secure database at NYSPI and be accessible only to the members of the research team. The coded brain imaging data will be shared amongst investigators at NYSPI, CUMC, and Cornell medical centers for purposes of brain imaging data analysis.

We will also share only the safety information with Genentech, the makers of tocilizumab. Any information that we share with them will only include an identification number that does not include any of your personal information and cannot identify you in any way.

<u>Research Standards and Participants' Rights</u>

Voluntary participation

Participation in this project is voluntary, and you may refuse to participate or discontinue participation at any time without loss of benefits to which you are otherwise entitled. A decision not to participate in this study, or to withdraw at any time, will not affect your present or future medical care or employment at either the New York State Psychiatric Institute or New York Presbyterian Hospital. On the other hand, it is possible that your participation in the study would be terminated without your consent, for example if you had a positive pregnancy test. You will be notified of significant new findings that may relate to your willingness to continue to participate.

Compensation for Research Related Injuries

Federal regulations require that we inform you about our institution's policy with regard to compensation and payment for treatment of research-related injuries. Short

term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute will be provided. In addition, we will provide assistance in arranging follow up care in such instances.

New York State Psychiatric Institute and the Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that participation in this research does not waive any of your legal rights to seek such compensation through the courts.

If you believe that you have sustained injury as a result of participating in a research study, you may contact the principal investigator, Dr. Ragy Girgis at 646-774-5553 so that you can review the matter.

Please be aware that:

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

Questions

The investigators will answer, to the best of their ability, any questions you may have now or in the future regarding study procedures or your response to them. You can call the principal investigator, Dr. Ragy Girgis, at 646-774-5553.

You will be notified of significant new findings that may relate to your willingness to continue to participate in this study.

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of human subjects in research studies). You may call the IRB Executive Director at 646-774-7161 during regular office hours.

Please check below to indicate whether or not you want to participate in the MRI part of this study.

____ I am interested in participating in the MRI part of this study.

____ I am not interested in participating in the MRI part of this study.

Statement of Consent

I have discussed this study with the study physician to my satisfaction. To the best of my knowledge, I am not pregnant. I have been informed that my participation is voluntary, and that I can withdraw from the study at any time without prejudice.

I have read the above and I voluntarily agree to enter this research study.

_____
Signature of Subject

_____ _____
Printed Name of Subject Date

Statement of Investigator

I have discussed the proposed research with this subject and, in my opinion, this subject understands the benefits, risks and alternatives (including non participation) and is capable of freely consenting to participate in this research.

_____ _____
Signature of Study Physician obtaining consent Date

_____
Printed Name of Study Physician

OPTIONAL:
Patient Audiotape Consent Form: IRB #

As part of your participation in this protocol, you are being asked to be audiotaped during interviews by a member of the research team at the New York State Psychiatric Institute. You may be asked to be audiotaped for some or all of these interviews.

The audiotape will be used for educational and research purposes only. These tapes are used to teach professionals how to conduct the interviews and to ensure that different members of the research team are conducting the same type of interviews similarly. These tapes may be listened to by the researchers and clinicians involved with this clinic. We will keep and use these tapes for up to 10 years

Audiotaping is entirely optional. If you consent to the audiotape, you can withdraw your consent at any time and tapes can be erased during or after the interview. If you do not consent, or later decide to withdraw your consent, it will not affect your participation in this research protocol or in treatment at the New York State Psychiatric Institute in any way.

We will do our utmost to ensure the confidentiality of the audiotape. However, there is a slight risk that someone will learn about your personal information after listening to this audiotape. To minimize the chances of this happening, the audiotape and written material presented with it will not include your name. All audiotapes will be strictly confidential and will be kept in locked files. Only the research staff will have access to them, and they will listen to them only for research purposes.

Statement of Consent:

I reserve the right to withdraw this consent at any time.

_____
Patient's Name (print)

_____ _____
Patient's Signature **Date**

I have discussed the proposed audiotaping procedures with this subject and, in my

opinion, this subject understands the benefit, risks and alternatives (including non-participation) and is freely capable of consenting to participate in the audiotaping component of this study.

_____ _____

Signature of person obtaining consent **Print Name** **Date**

OPTIONAL:
Patient Videotape Consent Form: IRB #

As part of your participation in this protocol, you are being asked to be videotaped during interviews by a member of the research team at New York State Psychiatric Institute. You maybe asked to be videotaped for some or all of these interviews.

The videotape will be used for educational and research purposes only. These tapes are used to teach professionals how to conduct the interviews and to ensure that different members of the research team are conducting the same type of interviews similarly. These tapes may be seen by the researchers and clinicians involved with this clinic. We will keep and use these tapes for up to 10 years

Videotaping is entirely optional. If you consent to the videotape, you can withdraw your consent at any time and tapes can be erased during or after the interview. If you do not consent, or later decide to withdraw your consent, it will not affect your participation in this research study or in treatment at the New York State Psychiatric Institute in any way.

We will do our utmost to ensure the confidentiality of the videotape. However, there is a slight risk that someone will learn about your personal information after viewing this videotape. To minimize the chances of this happening, the videotape and written material presented with it will not include your name. All videotapes will be strictly confidential and will be kept in locked files. Only the research staff will have access to them, and they will view them only for research purposes.

Statement of Consent:

I reserve the right to withdraw this consent at any time.

_____

Patient's Name (print)

_____ _____

Patient's Signature **Date**

I have discussed the proposed videotaping procedures with this subject and in my opinion, this subject understands the benefit, risks and alternatives (including non-

participation) and is freely capable of consenting to participate in the videotaping component of this study.

_____	_____	_____
Signature of person obtaining consent	**Print Name**	**Date**

CAPACITY ADDENDUM

I have examined _____on_____for the purpose of determining whether he/she is capable of understanding the purpose, nature, risks, benefits, and alternatives (including non-participation) of the research, making a decision about participation, and understanding that the decision about participation in the Research will involve no penalty or loss of benefits to which the patient is otherwise entitled, for Dr. Ragy Girgis' research project: "**Tocilizumab, An Il-6 Receptor Antibody, As Add-On Treatment For Residual Positive, Negative, And Cognitive Symptoms Of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial**"

On the basis of my examination, I have arrived at the conclusion that:

_____1) This patient has this capacity at this time.

_____2) There is a question about this patient's capacity at this time.

_____3) This patient clearly lacks this capacity.

Print Name _____

Signature_____Date_____