The attached includes:

Consent Document for Protocol: A Phase 2 clinical trial of tolebrutinib, a brain-penetrant Bruton's tyrosine kinase inhibitor, for the modulation of chronically inflamed white matter lesions in multiple sclerosis

NCT#: 04742400

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PRINCIPAL INVESTIGATOR: Daniel Reich, MD, PhD

STUDY TITLE: A Phase 2 clinical trial of tolebrutinib, a brain-penetrant Bruton's tyrosine kinase inhibitor, for the modulation of chronically inflamed white matter lesions in multiple sclerosis

STUDY SITE: NIH Clinical Center

Cohort: *Patient (60 mg)*

Consent Version: 3/27/2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

Daniel Reich, MD, PhD, 301-496-1801, daniel.reich@nih.gov

Shari Sawney, MS, 301-496-3825, shari.sawney@nih.gov

KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

- Participation in this research study is voluntary.
- In this study, we will test whether a drug called tolebrutinib can reduce inflammation in multiple sclerosis (MS) brain lesions. This type of inflammation is not treated by available medications for treatment of multiple sclerosis.
- Tolebrutinib is an investigational drug that decreases disease activity in multiple sclerosis. This has been seen in previous magnetic resonance imaging (MRI) studies.
- Tolebrutinib reduces the function of a certain type of immune cell that contributes to brain inflammation. We will use this medication in the doses that have previously been studied. It is a drug that is taken by mouth.
- The study will take approximately 96 weeks from the time you enroll. Should you decide to continue taking tolebrutinib, you may remain in the study beyond that point, until tolebrutinib either becomes approved for prescriptions or stops being developed for clinical use. You will not be able to participate in any other treatment research studies during this time.
- If you qualify for the study and decide to participate, you will have scheduled visits at the NIH.
- You will not be able to participate in this study if you have metal in your body or if you are pregnant. We will discuss other exclusions with you during your baseline visit.
- There will be at least 15 required study visits while you are taking tolebrutinib. If you decide to continue taking tolebrutinib, we will schedule additional study visits at least

every 24 weeks. At each study visit, you will have a clinic exam, bloodwork, and a brain MRI.

- Brain MRIs will be performed.
- A lumbar puncture (also known as a spinal tap), will be performed three times during the course of the study (Baseline, Week 12, and Week 48).
- If fertile, you must use an effective method of birth control one month before your first dose of study drug. You must continue using birth control until 12 weeks after the last dose of study drug.
- Tolebrutinib is a pill taken by mouth once a day. One pill is 60 mg. In this study, you will take one pill once a day (with food) for at least 96 weeks. You will have a clinic visit at the NIH every 12 weeks while you are taking the medication. You can have the option to continue taking tolebrutinib until tolebrutinib either becomes approved for prescriptions or stops being developed for clinical use.
- We will ask you to track your daily dosage of study drug. We will count the number of remaining pills and bottles at each follow up visit.
- If you miss a dose of tolebrutinib, you must inform the Neuroimmunology Clinic as soon as possible. The Neuroimmunology Clinic can be reached at 301-496-3825.
- If the treatment is stopped early for any reason, you will still have one post-treatment follow-up visit after stopping the drug.
- All of the information collected during this study will be stored for future studies This includes clinical information, MRIs, blood and cerebrospinal fluid (CSF) samples. We may publish information based on these studies in the medical and scientific literature, without personal identifying information.
- All study-related visits will take place in the outpatient clinic of the NIH Clinical Center and may last up to one full day. For convenience, you and the study team may choose to split your visits over several days. You may also have a study visit as an inpatient in the NIH Clinical Center.
- Clinical labs may be performed at a local site (home MD or Quest/LabCorp).
- After you complete study participation, continued medical care will not be offered at NIH. You will return to the care of your primary outside provider. If you are eligible, you may choose to participate in other multiple sclerosis research studies at NIH.
- The risks or discomforts of being in the study are explained in detail in this consent form.
- Tolebrutinib is an investigational drug so information about its side-effects are limited to information reported from a few previous studies. Overall, the drug was considered generally safe and was well-tolerated.
- Tolebrutinib is in a drug class called Bruton's tyrosine kinase (BTK) inhibitors. A drug class is a set of medications that work in the body in a similar way and have a similar chemical structure.
- BTK inhibitors may increase the risk of bleeding, infections, abnormal blood counts, or abnormal heart rhythms.
- Tolebrutinib may cause abnormal liver function, also known as drug-induced liver injury. Side-effects can be very mild, where only laboratory tests would show that this was occurring, to more severe, where you could require hospitalization which is very rare.

You will have liver function testing and will be monitored regularly throughout the study. Drinking excess amounts of alcohol might put you at higher risk for this condition.

- During the entire study, female participants should not consume more than 1 drink per day. Male participants should not consume more than 2 drinks per day.
- We will ask you to report any bleeding signs such as petechiae (tiny red spots on the skin) and easy bruising.
- An electrocardiogram (ECG) is a test that measures the electrical activity of the heart. This test provides information about how the heart is functioning. You will have an ECG at baseline, and at each visit while taking the medication.
- Tolebrutinib may affect how other medications work. It is important to tell the study team what medications you are taking and to check if it is safe to take a new medication while on this investigational drug.
- You might not receive direct benefit from taking part in this research study. However, the potential benefit to you might be a decrease in chronic inflammation in multiple sclerosis. However, even if tolebrutinib reduces brain inflammation, this may not improve your symptoms. We hope to learn more about multiple sclerosis and whether or not we can treat chronic inflammation in multiple sclerosis. This inflammation may play an important role in disease progression.
- You may choose not to take part, or you may leave the study at any time, for any reason. In either case, you will not lose any benefit to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation. Additionally, if you choose to leave the study, please inform your study team.
- We will not compensate you for time and research-related inconveniences.
- We may provide travel and/or lodging compensation if you will be coming from out-of-town or if traveling to NIH for you is a hardship. In such cases, an escort fee may be provided.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you

must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This is a research study. The purpose of this research study is to see if a drug called tolebrutinib can help clear inflammation in multiple sclerosis lesions.

This drug is still investigational which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat multiple sclerosis. Previous studies of tolebrutinib have shown a decrease in disease activity associated with multiple sclerosis by MRI.

Some multiple sclerosis lesions remain inflamed for very long periods of time (sometimes years). This type of inflammation is not affected by any of the available multiple sclerosis medications. We can see these lesions using advanced MRI scans. Research has shown that these lesions can lead to slow clinical worsening of symptoms in multiple sclerosis (often called “progressive MS”). In this research study, we will test whether tolebrutinib can help clear the inflammation in these lesions by seeing if tolebrutinib can change how the plaques appear on MRI.

We are asking you to join this research study because we think you may be a good candidate for this trial.

WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this study, you will be asked to come to the NIH for a baseline visit. The baseline visit may last over a few days. If you currently participate in our natural history study of multiple sclerosis, some previous procedures may not need to be repeated if it has happened within a short time frame.

You will have at least 10 visits to the NIH. This table shows you what tests will be done at each study visit:

Procedures	Baseline (≤14 days prior to Day 0)	Day 0	24 – 48 Hours Follow-Up	Week 2 (±7 days)	Week 4 (±7 days)	Week 6 (±7 days)	Week 8 (±7 days)	Week 10 (±7 days)	Week 12 (±7 days)	Week 24 (±14 days)	Week 36 (±14 days)	Week 48 (±14 days)	Week 60 (±14 days)	Week 72 (±14 days)	Week 84 (±14 days)	Week 96 (±14 days)	Every 24 weeks (±28 days)
Informed consent	X																
Medical history	X																
Interval history/neurological exam	X								X	X	X	X	X	X	X	X	X
Vital signs	X	X							X	X	X	X	X	X	X	X	X
Clinical measures# (EDSS, 9HPT, 25FTW, SNRS, SDMT)	X									X		X		X		X	X
Clinical labs	X			X[2]	X[1]	X[2]	X[1]	X[2]	X[2]	X	X[2]	X	X[2]	X	X[2]	X	X
Research labs	X								X	X	X	X	X	X	X	X	X
Pregnancy test (if applicable)	X	X							X	X	X	X	X	X	X	X	X
Brain MRI (7-tesla)##	X									X		X		X		X	X
Brain MRI									X		X		X		X		
ECG	X								X	X	X	X	X	X	X	X	X
Lumbar puncture	X								X			X					
Tolebrutinib first dose		X															
Follow-up phone call			X														
Tolebrutinib study drug dispensed		X							X	X	X	X	X	X	X	X	X

#Expanded Disability Status Scale (EDSS), 9-hole peg test (9HPT), 25-foot timed walk (25FTW), Scripps Neurological Rating Scale (SNRS), Symbol Digit Modalities Test (SDMT)

##This MRI scanner uses a powerful 7-tesla magnetic field and radio waves to create three-dimensional images of your brain.

Clinical labs may be performed at a local site (home MD or Quest/LabCorp).

1 Safety labs

2 Liver-specific Safety labs

If you miss a dose of tolebrutinib, you must inform the Neuroimmunology Clinic as soon as possible. You will restart the next day with the same dose. You should not take a higher dose or more than one dose per day.

If you request, we may email you to schedule appointments.

History and examination, including clinical scales

We will ask you about your medical history and do a physical examination. This physical examination is for research purposes only and does not replace any examination you may receive from your own physicians.

We may repeat the clinical scales twice if we need more data to analyze.

Blood work
We will collect blood for this study. Blood will be drawn from a vein. This may require a needle stick in your arm or hand, or if you already have an IV catheter in place, we may be able to draw through that. Blood will be collected both for clinical and for research testing. We may draw up to 10 tablespoons of blood for research purposes at any study visit. Please tell the study staff if you are participating in other studies that have blood draws.

We may repeat the blood draw twice if we need more samples to perform the research tests.

Contraception
For women who are able to become pregnant: You must agree to use an effective method of contraception (birth control) at least 1 month before you start taking the study drug until 12 weeks after your last dose of study drug.

For males of reproductive potential (who can father a child): You must agree to use condoms or other methods to ensure effective contraception (birth control) with your partner. You must agree not to donate sperm during the study and for up to 12 weeks after your last dose of study drug.

Pregnancy Test

We will collect less than 1 cup of urine to test for possible pregnancy in women who are able to become pregnant. If applicable, a urine pregnancy test will be done before every MRI and before getting your first dose of tolebrutinib. If you are unable to provide a urine specimen, a pregnancy test can also be obtained from a blood specimen.

MRI

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. We will obtain pictures of your brain for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner for about 2 hours. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time.

We will be using the MRI for investigational research. This means that the way the MRI is generating the images may be different than what is normally done in a routine clinical scan. However, all studies done under this protocol will be performed within FDA safety guidelines. We may also to use research coils (antennae). These are parts of the machine that help generate the imaging. This use of research tools in the MRI has not been approved by the FDA and is considered investigational. Additionally, some of the MR machines that we may use are considered investigational (not yet approved by the FDA for this use) but are used within the FDA safety guidelines. There is no known increase of risk in the use of these research scan techniques compared with those used

in clinical scans. It is unavoidable that results obtained with research devices will sometimes have diagnostic implications in the context of this study. However, the diagnosis will always be confirmed by another, medically established diagnostic product or procedure.

We may repeat the MRI twice if the images are not adequate.

Lumbar Puncture (Spinal Tap)

You will undergo a lumbar puncture (sometimes called a "spinal tap") to obtain cerebral spinal fluid (CSF) samples at baseline, week 12, and week 48. This procedure involves inserting a small needle into your lower back. The study staff will help position you either on your side or sitting up. If you are having the lumbar puncture using x-ray guidance, you will lie on your belly or rotated slightly. The lower part of your back will first be cleaned with antiseptic, and then the study clinician will inject a small amount of local anesthetic to numb the area. Once numb, a very thin needle will be inserted into the spinal canal in your lower back, well below where the spinal cord ends. About 4 ½ teaspoons of cerebrospinal fluid (CSF) will be removed for analysis and storage. Your body usually replaces this fluid within 1–2 hours.

After the lumbar puncture is complete, you will be monitored for about 30 minutes. To prevent side effects, it is important that you not do any strenuous physical activity for 24 hours following the procedure. This includes lifting, bending, doing housework and gardening, or exercising.

We may repeat the lumbar puncture twice if we need more samples to perform the research tests.

Study Drug: Tolebrutinib

We will give you a 12-week supply of tolebrutinib at Day 0, week 12, week 24, week 36, week 48, week 60, week 72, week 84 visits. You will take 60 mg (one pill) every day for 96 weeks. Every 12 weeks we will ask you how you are doing and see if you are experiencing any side effects of the medication or if the lesions on your MRI already appear improved. If you decide to continue taking tolebrutinib after your Week 96 visit, we will give you a new 24-week supply every 24 weeks.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your participation is expected to last for at least 96 weeks from the time you enroll. You will have a baseline visit; 16 visits while taking tolebrutinib, and then additional visits every 24 weeks should you decide to continue taking tolebrutinib. Visits will last 4-6 hours.

If you are interested and eligible, you may be followed under another Neuroimmunology Clinic protocol.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 30 people participate in this study at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

History and examination, including clinical scales

There is minimal medical risk or discomfort from the physical exam or clinical scales.

Blood work

Blood draws may cause pain, redness, bruising or infection at the site of the needle stick. Rarely some people faint. The study team member may apply numbing cream to the area so that the needle stick won't hurt as much.

Urine collection

There is minimal medical risk or discomfort from giving a urine sample.

MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

In this study, we are using an MRI scanner that has a strong 7-tesla magnet. Because of the strong magnetic field, some people have brief periods of muscle twitching, eye discomfort, dizziness, mild nausea, headache, a metallic taste in their mouth or a sensation of flashing lights. Many of these effects are from moving too quickly in the magnetic field, so you will be asked to walk slowly to the MRI table. Once you lie down, we will move the table slowly into the scanner. You can ask us to stop the scan at any time if you feel too uncomfortable. There is no evidence that scanning at high magnetic field strengths is dangerous, but we do not know if there are any long-term effects.

Lumbar Puncture (Spinal Tap)

The lumbar puncture may cause pain at the site where the needle goes in and the spinal fluid is taken. There is a small risk of infection or bleeding. After the lumbar puncture you may get a headache. About a third of adults report a headache after a lumbar puncture. To minimize the risk

of a headache, the doctor will use a small needle and may prescribe bed rest for one or more hours after the procedure. If a headache occurs, it is usually mild and can be controlled by bed rest, drinking lots of fluids and a pain pill, such as acetaminophen. Rarely, the headache is severe and may require additional treatment with a "blood patch." In this procedure, a small amount of your own blood is injected into the lumbar puncture site. This procedure is generally effective in stopping the headache. A rare but serious complication of a lumbar puncture, if it is done when the pressure inside the head is higher than normal (such as when a brain tumor is present), is known as medullary herniation, which can result in death. Increased intracranial pressure is very unlikely to be present. The lumbar puncture will not be done if there are any clinical indications that you have increased intracranial pressure, a skin infection in the lower back area, or bone malformation of the lower back (including severe scoliosis) which would make a lumbar puncture difficult.

To minimize these risks, the lumbar puncture procedure will be performed by a medical professional specifically trained to do this procedure.

Radiation

What if you are pregnant? If you are pregnant or nursing, you cannot be in this research study because the radiation may harm your baby. If you are nursing a baby, please tell your doctor. If you are able to have a baby and are not pregnant now, and you want to be in this study, we will give you a pregnancy test. If you join in this study, you should use contraception to keep from getting pregnant while you are in the study. If you get pregnant while you are in this study, or if you think you are pregnant, please tell the study doctor right away.

During your participation in this research study, you may be exposed to radiation from a fluoroscopy guided lumbar puncture each year. This is considered a low exposure. The risk of this exposure is too low to be reliably measured.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body. The radiation you will get by participating in this study is less than the average yearly background radiation in the United States.

Study Drug: Tolebrutinib

Tolebrutinib is an experimental medication that has not yet been approved for use by the FDA. Doses as high as double the dose used in this study have been shown to be safe in clinical trials in people with multiple sclerosis. The most common side effects were headache, upper respiratory tract infection, and mild liver enzyme elevation.

Drugs similar to tolebrutinib have been approved and are used for the treatment of blood cancers; these medications have a good track record for safety. The most common side effects in these medications have been infections, bleeding, cardiac arrhythmia (abnormal heart rhythm), low white blood counts, low platelets and anemia (low red blood cell count). Although these side effects have not been seen with tolebrutinib, we will be monitoring you closely during this study for these possible side effects.

Drug-induced liver injury (DILI) is liver injury caused by a medication and has been seen with tolebrutinib. The injury can range from mild to severe. One participant with MS outside of NIH experienced severe DILI that led to a liver transplant, and death as a result of complications after surgery. We will monitor your liver function throughout the study. If your liver function test is abnormal, you may have additional testing to further evaluate your liver such as blood tests and an ultrasound of your abdomen. You may have a visit with a liver specialist.

The combination of BTK inhibitors and rituximab, a drug similar to ocrelizumab, is FDA approved for the treatment of some blood cancers. This drug combination has been found to be safe with the same side effects as when taking these drugs alone.

Certain medications cannot be taken while you are taking tolebrutinib. We will provide you with a separate document that contains a list of those medications.

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails while you are in the study. If you think or know you have become pregnant while participating in this research study, please contact the study team as soon as possible. If you plan to become pregnant in the future, please discuss with the study team how long you need to wait before becoming pregnant after completing the study.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during your participation in this study. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during your participation in this study, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after your participation in this study, please discuss this with the study team.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from fluoroscopy (x-ray guidance), if you are unable to have a lumbar puncture at the bedside. This is considered a low exposure. The risk of this exposure is too low to be reliably measured.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called “background radiation.” No one knows for sure whether exposure to these low amounts of radiation is harmful to your body. The radiation you will get by participating in this study is less than the average yearly background radiation in the United States.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the potential benefit to you might be a decrease in chronic inflammation in MS. If tolebrutinib has no effect on multiple sclerosis inflammation in the brain, you may not benefit. Even if tolebrutinib reduces brain inflammation, this may not improve your symptoms.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because we may be able to learn more about multiple sclerosis, how we can best study inflammation in multiple sclerosis and whether or not we can treat inflammation in multiple sclerosis with tolebrutinib.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose to continue treating your multiple sclerosis as you are now. Tolebrutinib is an investigational drug and is not yet available outside of a clinical trial.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

We may discuss the results of the research tests with you. If we learn information during this study that may be important for your health, we will share that information with you.

All participants in MRI research studies will have an MRI scan read by a credentialed neuroradiologist. Sometimes there are unexpected findings on an MRI scan or on other testing that we will perform. Some findings are of unknown significance or importance to your health, which may make you anxious. We will inform you about any finding that may require further evaluation or care. We are not able to provide evaluation or treatment for these conditions at NIH. If needed, we will refer you to a health care provider.

EARLY WITHDRAWAL FROM THE STUDY

We may stop your participation in the study for any of the following reasons:

- You develop any serious side effects that we believe are due to tolebrutinib
- You are unable to tolerate the medication due to significant side effects
- You develop a clinical relapse
- You develop new or gadolinium-enhancing lesions on MRI
- You become pregnant
- Under the investigator's discretion for safety, behavioral, compliance or administrative reasons

If you take tolebrutinib for any length of time during the course of this study, even if you do not finish the full 96 weeks of treatment, we will ask that you come back for a follow-up visit within 3 months, and ideally within 1 month, after stopping the investigational drug.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding multiple sclerosis, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and

data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

We may publish papers based on data collected during this study in the clinical and scientific literature. Your private identifying information will not be included in these publications.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH possibly indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

This study will offer reimbursement for, or payment of, travel or lodging if you will be coming from out-of-town or if traveling to NIH for you is a hardship. In such cases, an escort fee may be provided.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- You will receive study treatment at no charge to you. This may include medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH)
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using tolebrutinib developed by Sanofi-Genzyme through a collaboration between your study team and the company. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor: National Institute of Neurological Disorders and Stroke (NINDS)

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Daniel Reich, MD, PhD, daniel.reich@nih.gov, 301-496-1801. Other researchers you may call are: Shari Sawney, MS at 301-496-3825. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.