Brief Title: Ublituximab for Acute Neuromyelitis Optica (NMO) Relapses

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Document: Informed Consent Form

ClinicalTrials.gov ID: NCT02276963

If you are using Epic for this study, fax a copy of the signed consent form to 410-367-7382.

Patient I.D. Plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: Phase I, Open Label Safety Study of Ublituximab for the Treatment of Acute Optic Neuritis and/or Transverse Myelitis in Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD)

Application No.: IRB00052958

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1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in it. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.
- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.
- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.

- Biospecimens will be collected in this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.
- 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.
- If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

2. Why is this research being done?

This research is being done to study the safety of the investigational drug ublituximab (UTX) when used as an add-on therapy to standard of care for the treatment of acute optic neuritis and/or transverse myelitis in people with neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD). We will also be looking at the effects of UTX on your neurological status.

High dose steroids are the first line standard of care treatment for acute NMO/NMOSD attacks. Ublituximab (UTX) is a monoclonal antibody that causes lysis (destruction) of B cells. We want to find out what effects (good and bad) people experiencing these attacks get when they take ublituximab in addition to the standard of care and if it is effective in reducing the inflammation and damage in the spinal cord and/or optic nerves during an attack.

Ublituximab is not approved by the Food and Drug Administration (FDA) for use in NMO or NMOSD and therefore its use in this study is investigational. The FDA is allowing the use of ublituximab in this research study.

We will assess the safety and compare the clinical and radiographic outcomes following acute optic neuritis and/or transverse myelitis in NMO/NMOSD in patients who receive 1 dose of 450 mg of ublituximab in addition to standard medical therapy.

We hope to determine the:
- safety and tolerability of 1 dose of 450 mg ublituximab given by infusion into a vein
- frequency of adverse events with ublituximab in this patient population with NMO/NMOSD
- effect of ublituximab on NMO/NMOSD neurological function after relapse
- effect of ublituximab on Magnetic Resonance Imaging (MRI) lesion size and extent.

People aged 18-100 years, diagnosed with NMO or NMOSD and experiencing optic neuritis and/or transverse myelitis may join.

How many people will be in this study?

About 5 people are expected to take part in this study.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

First, you will be started on treatment for your attack according to standard of care. That involves five (5) daily infusions of high dose steroids (1000 mg of methylprednisolone) intravenously. Steroids are the first line treatment for acute NMO attacks.

In addition to high dose steroids, if you join this study, you will receive 1 dose of ublituximab (450 mg) by infusion into a vein on the first day of your treatment. You will not receive any further ublituximab

during your hospitalization. If you received steroid treatment for this relapse prior to transfer to Johns Hopkins, you will complete your 5-day steroid course and receive ublituximab on the first day of hospitalization at Johns Hopkins.

Every day that you are in the hospital receiving treatment for this NMO/NMO exacerbation, you will have a neurologic examination, as per standard of care. If you join this study, there will be additional neurologic examinations that will take place at the bedside. These include timed walking and basic vision tests.

At the end of the 5 doses of steroids, your doctors will evaluate you to see if they need to escalate your treatment to plasma exchange, according to standard of care. The decision to escalate your care is made by considering your improvement in muscle strength, sensory function and bowel/bladder control.

If your doctor decides not to escalate your care:
If you have improved to the point that you do not need plasma exchange in your doctor's opinion, a Magnetic Resonance Imaging (MRI) may be performed as part of your standard of care, to confirm that your exacerbation has been effectively treated.

Based on the MRI, your doctor may discharge you home or change the plan to escalate your care.

Typically, 33 - 50% of NMO/NMOSD patients improve from a relapse with just steroids alone. The other 50 - 66% require escalated care with plasma exchange.

If your doctor decides to escalate your care:
If your doctor decides to escalate your care to plasma exchange, you will receive plasma exchange according to standard of care practice for NMO relapses. You will not receive any additional doses of ublituximab.

At the end of your plasma exchange therapy, your doctor will make another decision about your progress, again perhaps aided by a standard of care MRI. If your doctor notes improvement, you may be discharged from the hospital.

Typically about 95% of NMO/NMOSD patients who complete plasma exchange are discharged following completion of the plasma exchange. The other 5% require escalated care with additional immunosuppression.

Follow-up Visits:
Before discharge from the hospital, two appointments for follow-up outpatient clinic visits will be made—one visit 90 days (3 months) from discharge and one visit 180 days (6 months). At the 90 day visit, you will obtain a research MRI similar to the MRI scans obtained at the hospital. At both clinic visits, you will undergo repeat neurological and visual testing to assess changes that may have taken place since discharge.

Also, every month after discharge, you will obtain a blood test for the CD19/20 B cell marker, complete blood count and liver function tests at your local lab. The results will be automatically sent to us for review. You will need to repeat this monthly blood test until your B cells begin to repopulate, which could take up to 9 months or perhaps longer.

Incidental Findings:

One of the MRIs you are having 90 days after hospitalization as part of this research study will be reviewed by a qualified person just as it would be if you were having the MRI as part of your routine medical care.

There is a possibility that while reviewing MRI we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding."

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, it may affect your current or future life or health insurance coverage. This risk will vary depending on the type of insurance plan involved.

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

How long will you be in the study?

You will be in this study for up to 9 months or perhaps longer. The first 5-15 days are in the hospital. The rest of the time, you will be at rehabilitation or home.

4. What are the risks or discomforts of the study?

Possible side effects of ublituximab listed below are based on studies of ublituximab in humans. These side effects may be a minor inconvenience or could be severe enough to be life threatening or fatal. In addition, there is always the risk that you could experience other presently unknown side effects. You will be watched closely for any side effects and if serious side effects occur the drug will be stopped and you will be treated appropriately.

Below are the most common risks of ublituximab reported in humans. For the most part, most of these are short-term risks lasting a few days to a few weeks. The most important long term risk lasting up to 9 months risk of infections due to immunosuppression.

It possible that getting plasma exchange soon after ublituximab administration may reduce the possible effectiveness of ublituximab.

Very Common (greater than or equal to 10%)

- **Blood and lymphatic system disorders:** Neutropenia (low white blood cell levels), Thrombocytopenia (low blood platelet count)
- **Gastrointestinal disorders:** Nausea
- **General disorders and administration site conditions:** Fever, allergic reactions such as rash, low blood pressure, shortness of breath,, Asthenia (weakness), Chills
- **Infections and infestations:** Bronchitis, Nasopharyngitis (inflammation of nasal passages and throat), Rhinitis (inflammation of mucous lining of the nose), Sinusitis (inflammation of the sinuses), Oral herpes

- **Investigations:** Liver test abnormalities
- **Nervous system disorders:** Headache
- **Respiratory, thoracic and mediastinal disorders:** Cough

Common (greater than or equal to 1% and less than 10%)

- **Blood and lymphatic system disorders:** Anemia, Pancytopenia (low levels of all blood cells), Febrile neutropenia (fever with other signs of infection), Autoimmune hemolytic anemia (a condition in which the immune system attacks the red blood cells, resulting in fewer of these oxygen-transporting cells), Anemia (low blood cell count), Evans syndrome (an autoimmune disease in which an individual's antibodies attack their own red blood cells and platelets)
- **Cardiac disorders:** Cardiac flutter, arrhythmia
- **Ear and labyrinth disorders:** Tinnitus (noise or ringing in the ears)
- **Endocrine disorders:** Thyroid cyst
- **Eye disorders:** Conjunctivitis (inflammation or infection of the transparent membrane (conjunctiva) that lines the eyelid and covers the white part of the eyeball), Lacrimation (shedding of tears) decreased
- **Gastrointestinal disorders:** Lip edema (swelling), Gingival (gum) bleeding, Oral paresthesias (mouth tingling/numbness), Stomatitis (swelling of mouth or lips), Esophagitis (inflammation or irritation of the esophagus), Abdominal pain, Upper Abdominal pain, Gastric ulcer, Constipation, Colonic polyp, Diverticulitis (inflammation of the large bowel), Diarrhea
- **General disorders and administration site conditions:** Chest pain, Fatigue, Injection site hemorrhage, Swelling in the arms and legs
- **Hepatobiliary disorders:** Cholestasis (decrease in bile flow), Cholecystitis acute (inflammation of the gallbladder), other forms of liver injury and toxicity.
- **Immune system disorders:** Drug hypersensitivity, Hypogammaglobulinemia (immune deficiency disease)
- **Infections and infestations:** Influenza, Lung infection, Upper respiratory tract infection, Tracheitis, Laryngitis, Tonsillitis, Parotitis (inflammation of salivary glands), Otitis media (inflammation of middle ear), Urinary tract infection, Anal abscess, Bronchopulmonary aspergillosis (allergic lung reaction), Febrile infection, Listeriosis (bacterial infection), Septic shock, Staphylococcal sepsis, Streptococcal sepsis, Hepatitis C, Genital herpes, Herpes zoster,
- **Injury, poisoning and procedural complications:** Wrong technique in drug usage process, Subcutaneous hematoma (bruise)
- **Investigations:** Weight decreased, Serum IgA increased, O2 saturation decreased
- **Metabolism and nutrition disorders:** Diabetes mellitus inadequate control, Hypercholesterolemia, Hyperglycemia, Hyperuricemia (excessive uric acid in blood)
- **Musculoskeletal and connective tissue disorders:** Back pain, Musculoskeletal pain, Muscle spasms, Myalgia (muscle pain), Arthralgia (joint pain), Tendonitis
- **Neoplasms benign, malignant and unspecified (including cysts and polyps):** Squamous cell carcinoma, Basal cell carcinoma, Leukemia, Neuroendocrine carcinoma of the skin
- **Nervous system disorders:** Somnolence (sleepiness), Paraesthesia (burning or prickling sensation), Syncope vasovagal (fainting), Ischemic stroke
- **Psychiatric disorders:** Anxiety, Aggression, Depression, Insomnia
- **Renal and urinary disorders:** Hematuria (blood in urine)
- **Reproductive system and breast disorders:** Genital prolapse, Vulva cyst
- **Respiratory, thoracic and mediastinal disorders:** Epistaxis (nosebleed), Throat irritation, Bronchopneumopathy (type of pneumonia)

- **Skin and subcutaneous tissue disorders:** Erythema (redness of skin), Urticaria (hives), Allergic dermatitis, Perivascular dermatitis (skin irritation associated with inflammation around the blood vessels), Skin hemorrhage, Hyperhidrosis (excessive sweating), Night sweats
- **Vascular disorders:** Hypertension (high blood pressure), Hypotension (low blood pressure), Hot flush

Should you develop these reactions during the study, we will make every effort to treat you.

Infusion Process:
The most common risks related to the infusion process include fever, infection at the infusion site, clotting or swelling at the infusion site, accidental infusion into the tissue around the vein.

Confidentiality:
There is the risk that information about you may become known to people outside this study.

We will make every effort to maintain confidentiality of your personal medical information by keeping all data on password-protected computers and files and minimizing use of paper records.

5. Are there risks related to pregnancy?

This research may hurt an embryo or fetus and affect reproduction capacity in ways we do not currently know.

Women who are pregnant may not participate in this study. If you are able to have children, you will have a pregnancy test at screening. This test must be negative in order for you to take part in this study.

6. Are there benefits to being in the study?

There may or may not be a direct benefit to you from being in the study.

If you take part in this study, you may help others in the future.

7. What are your options if you do not want to be in the study?

If you decide not to join this study, other options are available. You do not have to join this study to get treatment. The treatment you will receive if you do not join this study will be the standard of care treatment of high dose steroids (1000 mg methylprednisone daily) intravenously and, if necessary, plasma exchange.

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

8. Will it cost you anything to be in this study?

It will not cost you anything to be in this study.

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).

- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. Will you be paid if you join this study?

No.

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.
- If you leave the study early, Johns Hopkins may use or give out your health information that it already has if the information is needed for this study or any follow-up activities**.**

11. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You fail to follow instructions.
- You become pregnant.
- The study is cancelled.
- Join an additional medical research study during this time.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it already has if the information is needed for this study or any follow-up activities**.**

12. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records ([which may include information about HIV, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

The research team will know your identity and that you are in the research study. Other people at Johns Hopkins, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study. If you are in a cancer study that receives federal funding, the National Cancer Institute (NCI) now requires that we report identifiable information (such as, zip code) about your participation. You may contact the NCI if you have questions about how this information is used.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other health care providers in order to verify your diagnosis of NMO/NMOSD. You will be asked to give us a list of other health care providers that you use.

14. What treatment costs will be paid if you are injured in this study?

Johns Hopkins does not have a program to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

TG Therapeutics, manufacturer of ublituximab, will cover costs associated with injury due to use of the drug in this trial.

15. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine Institutional Review Board (IRB) reviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?
Call the principal investigator, Dr. Michael Levy at 443-287-4412 (office). If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?
If you think you are injured or ill because of this study, call Dr. Michael Levy at 443-287-4412 during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call Dr. Michael Levy at 443-287-4412 during regular office hours and at 410-979-8297 (cell) after hours and on weekends.

d. What happens to Data and Biospecimens that are collected in the study?
Johns Hopkins and our research partners work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, Johns Hopkins may share your biospecimens and information with our research sponsors and partners.

16. What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form; you accept the provisions in the form and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

_____

Signature of Participant (Print Name) Date/Time

_____

Signature of Person Obtaining Consent (Print Name) Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

_____

Signature of Participant, LAR or Parent/Guardian (Print Name) Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.