Providence Brain & Spine Institute
9135 S.W. Barnes Road, Suite 461
Portland, OR 97225
www.providence.org/oregon

PROVIDENCE
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CONSENT FORM FOR A RESEARCH STUDY

Title:	Evaluating the Efficacy and Safety of Transitioning Patients from Natalizumab to Ocrelizumab (OCTAVE)
PH&S IRB #	STUDY2017000156
Principal Investigator:	Kyle Smoot, MD
Study Sponsor:	Providence Health & Services
Sponsor Study Number:	ML39655

INTRODUCTION AND PURPOSE

You are being asked to take part in this research study because you have relapsing multiple sclerosis (MS) and you and your doctor have decided you will transition your treatment from natalizumab to ocrelizumab. This consent form will explain this study to you, and what you need to do if you take part. Make sure you understand what is written, and ask as many questions as needed before you decide whether to take part. After this study has been explained to you, and if you choose to take part, you will be asked to sign this consent form.

Standard care for your condition is a broad approach which may include: disease modifying therapy (DMT), corticosteroids for relapses, and symptom management. This study is examining the transition of DMT from natalizumab to ocrelizumab. This is an observational study, meaning all patients will receive commercially available ocrelizumab (OCREVUS™) as standard of care.

Ocrelizumab has been shown to be very effective at preventing disease progression, is well tolerated, and was recently approved by the US Food and Drug Administration (FDA) for the treatment of Multiple Sclerosis. Ocrelizumab may have certain advantages over natalizumab including less frequent dosing and decreased risk of developing progressive multifocal leukoencephalopathy (PML). The rate of PML in patients receiving natalizumab is about 4 out of 1000 patients, and this often limits how long you can receive natalizumab.

If you choose to take part in this study, you will receive the FDA approved dose and frequency of ocrelizumab which is 600 mg IV (delivered via a plastic tube in your vein) every 24 weeks. The first dose is divided into two infusions of 300 mg each, because there is a possibility for infusion-related reaction with this treatment.

The purpose of this study is to see how safe and effective the transition from natalizumab to ocrelizumab might be. Quality of life of patients on ocrelizumab will be examined with questionnaires at different time points during the study. About 50 people in 5 different centers

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will take part in this study. Your participation will last about 1 year (12 months).

STUDY PROCEDURES

Visit 1 or Screening Visit- (time commitment about 5 hours)

- History including demographic information, vital signs (blood pressure and pulse, disease history, neurological exam)
- Review of medications, including lifetime MS treatment history.
- JC virus status and date of testing
- Blood sample, about 10 milliliters (mL) (2 teaspoons) to check your health.
- Urine pregnancy test for women who can become pregnant.
- EDSS (expanded disability status scale) method of ranking how multiple sclerosis impacts your abilities
- Reason for switching to ocrelizumab
- Magnetic Resonance Imaging (MRI) of the brain with and without contrast (You may not need to repeat a brain MRI at the screening visit if you have completed one within 6 weeks before the Baseline Visit.)

Visit 2 Baseline Visit (Day 0) - (time commitment about 6-7 hours)

- Neurological exam, including vital signs
- EDSS (expanded disability status scale)
- Medication review since last visit
- MSIS-29 questionnaire (Multiple Sclerosis Impact Scale) this asks you to rate how MS symptoms have impacted you, it should take about 5 minutes.
- CBC and CMP (These are blood tests that measure the amount and types of your blood cells and levels of electrolytes and other markers of kidney and liver health), about 7mL (1 ½ teaspoons)
- Urine pregnancy test for women who can become pregnant.
- Ocrelizumab infusion 300 mg IV (intravenous) over 2.5 hours. Baseline Day 0 is defined as the day of first day you receive ocrelizumab.
- To prevent infusion related reaction, you may receive preventative drugs: Solumedrol, acetaminophen (Tylenol), and an anti-histamine such as diphenhydramine (Benadryl) before the ocrelizumab is started.

Visit 2.1 (Day 14 from baseline) - (time commitment about 4.5 hours)

- Ocrelizumab infusion 300 mg IV (intravenous) over 2.5 hours.
- To prevent infusion related reaction, you may receive preventative drugs: Solumedrol, acetaminophen (Tylenol), and an anti-histamine such as diphenhydramine (Benadryl) before the ocrelizumab is started.

Visits 3 (About 3 months from baseline) - (time commitment about 4 hours)

- Neurological exam including vital signs
- Review of current medications and side effects
- EDSS (expanded disability status scale)
- Blood sample, about 7mL (1 ½ teaspoons) to check your health
- Magnetic Resonance Imaging (MRI)of the brain, with and without contrast

Visit 4 (About 24 weeks or 6 months from baseline) - (time commitment about 10 hours)

- Neurological exam including vital signs
- Review of current medications and side effects

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- EDSS (expanded disability status scale)
- MSIS-29 questionnaire (Multiple Sclerosis Impact Scale)
- Blood sample, about 7mL (1 ½ teaspoons) to check your health
- Urine pregnancy test for women who can become pregnant.
- Magnetic Resonance Imaging (MRI)
- Ocrelizumab infusion 600 mg IV (intravenous) over 3.5 hours.
- To prevent infusion related reaction, you may receive preventative drugs: Solumedrol, acetaminophen (Tylenol), and an anti-histamine such as diphenhydramine (Benadryl) before the ocrelizumab is started.

Visit 5 (About 36 weeks or 9 months from baseline) - (time commitment about 1 hour)

- Neurological exam including vital signs
- Review of current medications and side effects
- EDSS (expanded disability status scale)
- Blood sample, about 10 mL (2 teaspoons) to check your health.
- Urine pregnancy test for women who can become pregnant.

Visit 6 (About 48 weeks or 12 months from baseline) - (time commitment about 10 hours)

- Neurological exam including vital signs
- Review of current medications and side effects
- EDSS (expanded disability status scale)
- MSIS-29 questionnaire (Multiple Sclerosis Impact Scale)
- Blood sample, about 7mL (1 ½ teaspoons) to check your health
- Urine pregnancy test for women who can become pregnant.
- Magnetic Resonance Imaging (MRI)
- Ocrelizumab infusion 600 mg IV (intravenous) over 3.5 hours.
- To prevent infusion related reaction, you may receive preventative drugs: Solumedrol, acetaminophen (Tylenol), and an anti-histamine such as diphenhydramine (Benadryl) before the ocrelizumab is started.

End of Study Phone Contact (30 days after final visit)-(time commitment about 15 minutes)

- Review of side effects

Early termination visit - (time commitment about 2 hours)

If you discontinue ocrelizumab for any reason, you may continue in the study if you choose. However, if you no longer wish to take part, an early termination visit should be done as soon as possible. If the discontinuation of study drug occurs at an infusion visit, an early termination visit must be completed within 7 days

- Neurological exam including vital signs
- Review of current medications and side effects
- EDSS (Expanded Disability Status Scale)
- MSIS-29 questionnaire (Multiple Sclerosis Impact Scale)
- Blood sample, about 7mL (1 ½ teaspoons) to check your health.
- Urine pregnancy test for women who can become pregnant.
- Main reason for early discontinuation

Unscheduled Visits

If you experience a relapse of your MS, or any undesired symptoms during the study, you will be asked to return for an unscheduled visit to assess your symptoms. This includes:

- Neurological exam with vital signs
- Review of current medications and side effects
- EDSS (Expanded Disability Status Scale)
- Magnetic Resonance Imaging (MRI), if the study doctor thinks it is necessary
- Blood sample, about 7mL (1 ½ teaspoons) to check your health.
- Urine pregnancy test for women who can become pregnant, if the study doctor thinks it is necessary

STUDY TREATMENT

Procedure/Visit	Screening Visit #1	Baseline Visit #2 (Day 0)	Month 3 Visit #3	Month 6 Visit #4	Month 9 Visit #5	Month 12 Visit #6	End of Study Phone Contact	Premature Termination Visit	UNS Visit
Disease and Medical History	X								
Reason(s) for switching to OCR	X								
Vital Signs	X	X	X	X	X	X		X	X
Neuro Exam	X	X	X	X	X	X		X	X
EDSS	X	X	X	X	X	X		X	X
MSIS-29		X		X		X		X	
Blood tests	X	X	X	X	X	X		X	X
Urine pregnancy test[1]	X	X	X	X	X	X		X	X
JCV Antibody Status	X								
MRI	X[2]		X	X		X			X
OCR Administration		X		X		X			
Primary Reason for Discontinuation								X	
Medication Review	X	X	X	X	X	X		X	X
Side Effect Review		X	X	X	X	X	X	X	X

EDSS = Expanded Disability Status Scale; MSIS-29 = Multiple Sclerosis Impact Scale; MRI = magnetic resonance imaging; UNS=Unscheduled visits

[1] Only for women able to become pregnant

[2] You may not need to repeat a brain MRI if you have completed one within 6 weeks before the Baseline Visit

POSSIBLE RISKS

There are minimal risks to you if you take part in this study. There is a risk of loss of privacy or confidentiality of your personal information that is collected for the study. However, steps have been taken to keep your personal information confidential, and the risk of this happening is very small.

You will be assigned a patient code number. Only your treating doctor and the research staff will have access to your personal information such as your name or address. Genentech will only refer to your information by the code number, and at no time will your personal information be shared with Genentech or any other group without your permission.

Prior to FDA approval of ocrelizumab, this medication was closely studied in over 2200 patients with multiple sclerosis. As with any medication, there is a risk of side effect and your doctor will discuss these with you so you can weigh the risks and benefits for yourself. Some of the risks are similar to natalizumab, but not exactly the same.

Potential risks related to switching to other MS treatments after ocrelizumab

If you withdraw from the study, you may receive a different treatment for your MS as instructed by your study doctor. However, since there is no information available regarding potential risks related to switching from ocrelizumab to another MS treatment, certain treatments for MS that remove lymphocytes (a type of white blood cell) are strongly discouraged for as long as your B-cell count is low. Your study doctor will discuss possible treatment options with you at this time.

Risks Associated with Anti-histamine Pre-medications

If you receive antihistamines prior to your ocrelizumab infusions, you may experience drowsiness and/or impaired ability to drive or operate machinery. It is important to plan transportation to your clinic visits with this in mind.

Risks related to Childbearing

If you are pregnant or breastfeeding, you cannot take part in this study. The risks of ocrelizumab to an unborn baby or nursing child may cause harm. If you are a woman able to become pregnant, you will have a urine pregnancy test to see if you are pregnant before you begin this study treatment. You will also have a urine pregnancy test before each dose of study drug is given. If the urine test is positive, study drug will not be given and you will have a blood pregnancy test done. If the blood test is positive, you will not receive any more doses of study drug.

If you are sexually active, you must take adequate precautions to avoid the possibility of becoming pregnant. You must discuss these precautions with your study doctor before agreeing to take part in this study.

If you become pregnant during this study, you should tell your study doctor immediately.

For women: If you become pregnant, you will no longer be given ocrelizumab. Information about your pregnancy, including its outcome, will be collected.

After you complete your treatment, it is important that you continue to take adequate precautions to avoid the possibility of becoming pregnant for at least 6 months (24 weeks) after your last dose of ocrelizumab.

POSSIBLE BENEFITS
There are no guaranteed benefits to you for taking part in this study. This study treatment may even harm you. However, if effective, this study treatment might stabilize, or potentially improve the signs and symptoms of your MS.

The information learned from this study will help researchers learn more about ocrelizumab, and may help future patients with MS.

OTHER TREATMENTS
You may choose not to take part in this study. Other treatments available to you include:
- Standard treatment with medications that are approved by the FDA
- Ocrelizumab therapy without participating in a research study.
- Other research study treatments, if available
- No treatment

GENERAL INFORMATION
Your taking part in this study is voluntary. Refusing to take part will not affect the health care benefits you have. If you decide to take part, you are free to stop at any time without any effect on your medical care, your relationship with your doctor(s) or Providence Health & Services.

While in this study, any important new information that may affect your wish to continue taking part will be given to you.

Providence St. Vincent Medical Center is receiving funding from Genentech to conduct this study and gather information gained in the study. The study doctors who work at Providence and enroll patients on this study may also receive money from the study sponsor for speaker's fees, advisory boards, and consulting that they provide about MS treatments. Some doctors may own stock in companies sponsoring research. The study doctor or the study staff may have travel expenses covered by the sponsor in order to attend study training meetings. The doctors do not believe that this affects how this study is being conducted or the results. If you have concerns, you should discuss this with your study doctor, or you may call the Providence Institutional Review Board (IRB) at 503 215-6512; the IRB is a committee that reviewed this research to protect your rights.

Withdrawing from the Study
Your study doctor may remove you from this study at any time if he/she thinks it is medically necessary, you have a serious side effect, you do not follow the study plan, or the study has been cancelled. If the study is cancelled or you decide to stop using ocrelizumab, your study doctor will ask you to return to the clinic for safety follow-up visits described in the study procedures above.

If you are continuing to benefit from treatment with ocrelizumab, your doctor may continue to treat you with ocrelizumab following completion of the study.

COSTS
You will not be paid to take part in this study.

You are responsible and must pay for the costs of your routine medical care and medications; however, these costs may be covered, at least in part, by most major insurance companies or Medicare. You and/or your insurance company will be charged for ocrelizumab during this

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study.

The study will pay for:

- At the baseline visit: Neurological exam, CBC, and CMP
- At month 3: MRI
- Pregnancy tests if required during the study.

All other study visits, procedures, MRIs and tests related to receiving ocrelizumab will be billed to your insurance which may result in co-payments or co-insurance fees for you. It is important for you to know that the frequency of visits may be increased during the transition from natalizumab to ocrelizumab because changing DMT requires more monitoring. The study doctor and the research coordinator will be responsible for making sure the study activities are billed properly.

LIABILITY

If you are injured as a result of taking part in this study, all of the necessary medical facilities are available for treatment, as is reasonably possible.

If you are injured during this study, immediate care for any physical injury will be billed to your insurance company. You may be responsible for co-payment or deductibles.

Providence Health & Services is not able to offer you financial payment, nor pay for the costs of medical treatment should you be injured as a result of taking part in this research.

Genentech does not have plans to provide any payment for injury.

You do not give up any of your legal rights by signing this consent form and taking part in this study.

PRIVACY

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) gives you certain rights to protect the privacy of your medical information and records. Under HIPAA, you must give your permission before anyone uses or shares your medical information. This information is also called protected health information (PHI). Your rights, as well as the reasons for using your PHI, are described below.

Your medical and study records are personal and private and only your study doctor, yourself and anyone you allow have the right to look at your records. It is important that the research staff, the FDA, the Center for Medicare and Medicaid Services (CMS), the Providence Health & Services Institutional Review Board (IRB – a committee that reviewed this research to protect your rights), and representatives of Genentech Inc. (a member of the Roche Group) be able to look at your medical and study records. When you sign this consent form, you agree to allow this. If results of this study are reported in medical journals or at meetings, your identity will remain secret.

The sponsor and your study doctor(s) will need to use your PHI for this study. Your study information is protected by the use of a patient identification number, which is a number specific to you. Only a unique patient identification number for the study will link the data or samples to you. Your data and samples will not be labeled with your name, picture, or any other personally identifying information.

By signing this consent form, you agree to allow your study doctor and the research staff to use and share your PHI for the following reasons:

- Make decisions about your medical care
- Evaluate the results of this study
- Make conclusions about the study results
- Provide study results to other study doctors
- Re-evaluate study results in the future, as needed
- Include your study information with results from other similar studies
- Send study information to government health agencies (for example, to the FDA to request approval of the treatment used in this study); this may also include government agencies in other countries
- Report side effects to the FDA and other government agencies
- Send study information to representatives of the study sponsor
- Any other purposes as described in this consent form.

If you are not willing to allow your PHI to be shared, you will not be able to take part in this study.

The study sponsor and their representatives, the IRB and any regulatory agencies may review your medical records and make copies. The reasons this might happen is to make sure this study is being done properly, study information is being collected correctly, and for other purposes allowed by law.

Once your PHI is shared with others, it is no longer protected by HIPAA law. However, it will be kept as confidential as possible.

Your permission to use and share your PHI will not end unless you change your mind. You may cancel your permission at any time by sending a written notice to your study doctor. Your PHI for this study will no longer be collected for this study. In some circumstances, your study doctor will need to use or share your PHI that has already been collected to continue this research study.

If you cancel your permission, you will no longer be able to take part in this study. The sponsor will still use any PHI they received before you cancel your permission.

If you have questions about your privacy rights, please call the Providence Health & Services HIPAA Privacy Officer at (503) 574-9123.

QUESTIONS

Any questions you have about this research study can be answered by:

Study Investigator: _____at_____

Study Coordinator: _____at_____

Any questions you have about your rights as a research subject will be answered by the Providence Health & Services Institutional Review Board at (503) 215-6512.

You are free to ask questions about this study at any time.

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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.

CONSENT

I have read all of the above, asked questions and received satisfactory answers about what I did not understand. I agree to take part in this research study. I will be given a signed copy of this consent form for my records.

_____

Name of Patient (Please Print)

_____

Signature of Patient Date

_____

Name of Person Obtaining Consent (Please Print)

_____

Signature of Person Obtaining Consent Date

Required only if short form is used:

_____

Name of Interpreter/Witness Date

_____

Signature of Interpreter/Witness Date

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