Official title: *Exploratory Study of Efficacy of Ocrelizumab in Autoimmune Encephalitis*

NCT number: NCT03835728

IRB Approval date: March 21, 2019 (Ver.3.0)

Form A

IRB #	STU 2018-0185
26776	

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

Purpose:

1) To determine if the use of an immunotherapy that targets CD20 (Ocrelizumab) will prevent relapses in patients with autoimmune encephalitis with antibodies to cell-surface proteins.
2) To identify markers of immune activity that may predict response to CD20 therapy in autoimmune encephalitis.

Hypothesis:
Ocrelizumab will be safe and effective (compared to placebo) in preventing relapse (and improving symptoms) in patients with autoimmune encephalitis associated with cell-surface antibodies (NMDAR, LGI1, CASPR2, DPPX) antibodies.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Autoimmune encephalitis (AE) is a group of disorders caused by an immune-mediated disruption of brain function characterized by seizures, cognitive impairment, movement disorders and behavioral changes. These disorders have been increasingly recognized over the past 10 years as a treatable cause of rapidly progressive dementia, intractable seizures or psychosis. The best characterized forms of AE are associated with autoantibodies targeting cell surface or synaptic proteins. The most common encephalitis autoantibodies are specific for the N-methyl-D-aspartate receptor (NMDAR), leucine rich, glioma-inactivated 1 protein (LGI1) and contactin associated protein-like 2 (Caspr2). However, as of 2017, over a dozen other autoantibodies have been associated with AE and some patients with treatable AE have no recognized antibody marker.[1, 2]

AE affects patients across all age groups, with some forms of the disease preferentially affecting pediatric patients. Increasing awareness and clinical experience indicates that AE is not rare as previously thought. At UT Southwestern Medical Center, for example, we retrospectively identified 64

AE cases over a 6 year period (2010-2015), and this is certainly an underestimation since awareness and clinical laboratory diagnostic tests have improved significantly in the past 4 years.

References

1. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology 2016;15:391-404.
2. Dubey D, Sawhney A, Greenberg B, et al. The spectrum of autoimmune encephalopathies. J Neuroimmunol 2015;287:93-97.
3. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. The Lancet Neurology 2013;12:157-165.

b. Current practice

Despite the burden of this potentially treatable condition, there have been no controlled prospective treatment trials for AE. Current treatments for the disease are based on expert opinion, retrospective case series, or open label immunotherapy. Most of the therapies utilized in AE are off label uses of therapies approved for other disorders, including corticosteroids, intravenous immunoglobulin, plasma exchange, "traditional" immunosuppression (e.g. cyclophosphamide), cytokine inhibition (e.g. tocilizumab) or B cell depletion (e.g. rituximab). There is particular interest in anti-CD20 therapy because of the demonstrated role of B cells in the pathogenesis of antibody-mediated disorders and the success of anti-CD20 therapy (ocrelizumab) in the treatment of multiple sclerosis, another autoimmune disorder of the brain. Additionally, unpublished data from Dr. Nancy Monson (one of the co-investigators on this proposal) shows that the characteristics of CSF lymphocytes may be predictive of response to therapy. Specifically, those patients with a large population of autoreactive plasmablasts anectodally seem to have a better outcome than those with a large population of mature plasma cells or autoreactive memory B-cells. Targeting plasmablasts and other CD20-positive B cells acutely should be effective therapy for these disorders and prevent progression.

There is an urgent need to carry out systematic controlled studies to evaluate the efficacy of immunotherapy in AE. Retrospective data suggests that a significant number of patients will relapse without ongoing immunotherapy.[3] However, immunotherapeutic drugs carry serious potential risks, so evidence of clinical efficacy is critical in order to offer such treatment to patients. We propose to conduct a prospective double-bind placebo-controlled pilot study to evaluate the efficacy of ocrelizumab in AE. These results can then be used to design a larger multi-center phase III study for the use of this drug in AE patients. This proposed pilot study will also allow the development and evaluation of biomarkers for AE which could ultimately be used to guide selection of therapy and monitor disease activity.

IRB #	STU 2018-0185
26776	

3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

These study is comprised of two phases.

Phase 1 is a study of biomarkers and clinical features of autoimmune encephalitis. Many of the patients from this portion of the study will come from the inpatient setting, though patients meeting the criteria may also be identified as outpatients. Individuals fitting criteria for possible autoimmune encephalitis will be invited to participate. Consenting patients will have blood and CSF samples collected for antibody testing and testing of B-cell activity. They will also undergo a brief formal neuropsychological assessment. During phase 1, all patients will receive standard of care acute therapies for encephalitis (typically high dose IV steroids and plasma exchange at our institution). They will again undergo biomarker and neuropsychological assessments within seven days of finishing treatments.

In Phase 2, individuals with a detectable antibody in serum or CSF associated with autoimmune encephalitis will be invited to participate in a randomized double-blinded placebo-controlled trial on the efficacy of ocrelizumab for autoimmune encephalitis. Individuals will undergo a screening process to insure they can safely enroll in the trial. They will then be randomized in a 1:1 fashion to receive infusion of Ocrelizumab or matched placebo. The drug will be administered via infusion three times throughout the trial period: after the initial screening, at two weeks from initial infusion, and at 6 months. Individuals will attend clinical study visits every 3 months, during which a full panel of tests will be performed to assess clinical worsening.

Individuals who meet the definition of clinical worsening within the first 6 months of enrollment will be offered the opportunity to participate in open label treatment with ocrelizumab at the investigator's discretion.

The primary outcome this study will be proportion of patients who fail to complete the 12 month study period without worsening, as defined in the protocol. Secondary outcomes include the time to treatment failure and change in neuropsychological assessment at 6 and 12 months compared to baseline.

4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

We will identify adult patients with clinical features of possible autoimmune encephalitis according to consensus criteria adapted from a recent consensus group (Table 1). Patients that meet inclusion/exclusion criteria (Table 2) will be invited to participate in phase 1 of this study. Phase 1 is a study of biomarkers and clinical features of AE. Consenting patients will have blood and CSF collected for antibody testing and biomarker studies before and after initial treatment. Rapid screening for encephalitis autoantibodies will be done at UT Southwestern using standard cell-based assay (EuroImmun), and biomarkers for B cell activity will be conducted in the laboratory of Dr. Nancy Monson. Patients will also be evaluated with quantitative functional measures administered by a neuropsychologist including the Texas functional living scale as well as Quality of Life measures.

All patients will receive treatment with the current acute standard of care treatment. At UT Southwestern, this consists of treatment with iv solumedrol (1000mg daily for 5 days) and plasma exchange (5 exchanges

typically given every other day). Biomarker testing and functional assessment will be repeated within one week of completing this initial treatment.

Table 1: Diagnostic criteria for possible autoimmune encephalitis (AE)
1. Reasonable exclusion of alternative causes 2. Subacute onset (< 3 months) of memory deficits, altered consciousness, and/or psychiatric symptoms 3. One or more of the following: • CSF pleocytosis (>5 cells/µl corrected, if necessary, for traumatic lumbar puncture) • EEG with epileptiform or focal slow wave abnormalities involving temporal lobes • Brain abnormalities on T2/FLAIR MRI restricted to the mesial temporal (limbic) lobes • Associated dyskinesias (faciobrachial dystonic movements or orofacial dyskinesias)

Table 2: Inclusion/Exclusion criteria (Study Phase 1)
Inclusion criteria 1. Age 18 or greater 2. Able to obtain informed consent from patient or appropriate designee 3. Possible autoimmune encephalitis as defined by Table 1
Exclusion criteria 1. Prior immunosuppression treatment in past year (prior treatment steroids is allowed) 2. Treatment with intravenous immunoglobulin in past year

Subjects completing Phase 1 must be re-screened to subsequently participate in Phase 2 of this study. Phase 2 of the study is the double-blind placebo-controlled trial for which we are requesting funding support through Genentech.

Patients who meet the inclusion/exclusion criteria (Table 3) will be eligible to participate in the randomized double-blind placebo-controlled treatment trial. Subjects who meet the eligibility criteria for the treatment trial can participate even if they were not enrolled in Phase1 of this study. Patients will be consented separately for the treatment trial.

Table 3: Inclusion/Exclusion criteria (Treatment Trial)
Inclusion criteria 1. Age 18 or greater 2. Able to obtain informed consent from patient or appropriate designee 3. Possible autoimmune encephalitis as defined by Table 1 4. Completed initial treatment with iv steroids (at least 3000mg solumedrol) and plasma exchange (at least 3 exchanges) within the past 4 weeks

5. Presence of one (or more) of the following autoantibodies in serum or CSF
    - NMDA receptor
    - LGI1
    - CASPR2
    - DPPX

Exclusion criteria

1. Prior immunosuppression treatment in past year (other than steroids and plasma exchange)
2. Treatment with intravenous immunoglobulin in past year
3. Active malignancy requiring chemotherapy
4. Pregnancy
5. Evidence of active hepatitis or tuberculosis infection
6. Medical condition that (in investigators opinion) precludes the use of ocrelizumab

Patients in Phase 2 (treatment trial) will be evaluated with neuropsychological functional measures at baseline and during treatment (every 3 months). The complete battery of tests listed in Table 4 can be completed in about 40 minutes. The Texas Functional Living Scale (TFLS) and self-reported ADL score are part of the clinical outcome assessment.

Table 4: Neuropsychological testing battery

Test	**Rationale**
Texas Functional Living Scale (TFLS)	Objective measure of functional ability/instrumental ADLs
Lawton & Brody Instrumental Activities of Daily Living (IADL) Rating Scale	Self-report measure of instrumental IADLs Patient and informant administrations
Symbol-digit Modalities Test (SDMT)	Written and /or oral processing speed
Trail Making Test Parts A & B (TMT)	Visuomotor processing speed (TMTA) and set shifting/divided attention (TMTB)
Controlled Oral Word Association Test (FAS)	Phonemic verbal fluency
Hopkins Verbal Learning Test-Revised (HVLT-R)	Episodic verbal memory
Test of Premorbid Functioning (TOPF)	Estimate for premorbid intellectual ability
Montreal Cognitive Assessment (MOCA)	Commonly used multimodality bedside cognitive test

The TFLS is a validated instrumented functional test administered by a trained assessor. The score reflects ability to perform activities of daily living and higher level tasks. The 50 point raw score is converted to a T score (0 – 100) based on normative data. A change in T score of 5 points corresponds to a change of 0.5 standard deviations in the TFLS and is considered a significant meaningful change. The IADL is a simple 8 point self-administered questionnaire; a change of one point is considered significant.
After baseline procedures, subjects will be randomized to receive either intravenous ocrelizumab or matched placebo in a 1:1 ratio. Investigators, patients and treating physicians will be blinded to the treatment assignment. Patients will receive an initial dose of 300mg study medication followed by a second dose of 300mg 2 weeks later. Study medications will be handled and allocated by the research pharmacy, and infusions given in either the inpatient or outpatient clinical trials infusion center at UT Southwestern. At 6 months, patients who remain in the study will receive an additional dose of study medication (ocrelizumab 600mg or matched placebo).
Subjects will be monitored closely throughout the study with clinical assessments at months 1, 2, 3, 6, 9, and 12 as well as telephone assessments every 2 weeks between clinical visits.

Outcome assessment
The primary outcome of the treatment trial will be the proportion of patients who fail to complete the 12 month study without clinical worsening. Secondary outcomes will be time to treatment failure and change in TFLS scores at 6 and 12 months compared to baseline. We anticipate that patients treated with ocrelizumab will be much less likely to show clinical worsening compared to placebo.

Table 5: Definition of clinical worsening (treatment failure)

1. Clinician or patient/caregiver perception of clinical decline
2. Worsening of patient/family reported IADL (by one point or more)
3. One of the following additional features:
   - Significant worsening of Texas Functional Living Scale (by ≥ 5 T points, 0.5 st deviation)
   - Other clinical worsening leading to hospitalization

We also anticipate that ocrelizumab-treated subjects will show higher functional scores.

The criteria for the primary endpoint, treatment failure, is described in Table 5. At each clinical study visit, subjects will complete the global impression and IADL questionnaire, and the full panel of assessment tests will be performed every 3 months. Between study visits, the study coordinator will contact the subject every 2 weeks by telephone to inquire about adverse events and clinical status. If a subject or caregiver reports clinical worsening, the subject will complete the IADL questionnaire. Subjects with concern for clinical worsening will be brought in for unscheduled clinical assessment and completion of the TFLS.

Subjects who meet criteria for treatment failure will complete the final study visit procedures (12 month visit). At the investigators' discretion, subjects with early treatment failure during the first 6 months will be offered open label treatment with ocrelizumab (one dose of 600mg) or may proceed with best available alternative treatment in consultation with their primary doctors.

IRB #	STU 2018-0185
26776	

Estimated number of subject

We expect to identify up to 60 patients eligible for the phase 1 biomarker study, and we plan to enroll 22 patients in the double-blind treatment study (phase 2). Based on our previous retrospective studies, we anticipate that we can achieve this enrollment in 12-18 months.

Based on our own experience and case reports related to rituximab, we will be expecting a large effect size. Assuming a relapse rate of 15-20% in the ocrelizumab group and an 75-80% relapse rate in the placebo group, a sample size of 22 achieves 80% power to detect an effect size (W) of 0.6 (20% vs 80%) using a 1 degree of freedom Chi-Square Test with a significance level (alpha) of 0.05. This sample size would have a 73% power to detect and effect size of 0.55 and 65% power to detect and effect size of 0.5

With 22 subjects, the Chi Square for this effect size would be significant (p=0.03) even for an effect size of 46% (e.g. 3 treatment failures out of 11 in the ocrelizumab group and 8 treatment failures in placebo group).

Setting for each phase:

For phase 1, subjects may be initially enrolled during hospitalization at Zale Lipshy Hospital or Clements University Hospital. Patients identified in the neurology clinics of the investigators may also be identified.

For phase 2, all visits and drug administrations will occur in the Clinical Research Units at UT Southwestern Medical Center.

Schedule of Phase 2 Study Procedures/Assessments

Study Week (Study Month)	**Screening/Baseline**	**0**	**2**	**4 (1)**	**6**	**8 (2)**	**10**	**12 (3)**	**16 (4)**	**20 (5)**	**24 (6)**
infusion #		**1 300mg**	**2 300mg**								**3 600mg**
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Medical History	X										
Pregnancy Test (females only)	X										
Telephone Contact					X		X		X	X	
Vital signs, physician exam	X	X	X	X		X		X			X
Concomitant Medications			X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X
Safety Labs (CBC/CD19)	X			X		X		X			X
Safety Labs (Quantiferon, Hepatitis & JCV Serology)	X										
Serum AE Ab	X			X				X			X
Serum/CSF for B cell testing (Biorepository)	X										
Subject/Caregiver Impression			X	X	X	X	X	X	X	X	X
Seizure Frequency Report	X		X	X	X	X	X	X	X	X	X
Clinician Global Impression	X		X	X		X		X			X
Testing[4] - TFLS	X			X				X			X

IRB #	STU 2018-0185
26776	

Testing[4]- IADL	X		X	X	X[3]	X	X[3]	X	X[3]	X[3]	X		X[3]	X
Testing[4]– SDMT	X			X				X			X			
Testing[4]- TMT	X			X				X			X			
Testing[4]– FAS	X			X				X			X			
Testing[4]– HVLT-R	X			X				X			X			
Testing[4]– TOPF	X													
Testing[4]- MOCA	X			X				X			X			
Study Drug Administration (placebo/ocrelizumab)		X	X								X			

[1] If subject terminates study early (reaches progression endpoint)
[2]Telephone contact/assessments will take place every 2 weeks between scheduled clinic visit
[3]The IADL questionnaire will be completed at telephone contact if the patient/caregiver impression suggests clinical worsening
[4]TFLS: Texas Functional Living Scale; IADL: Lawton & Brody Instrumental Activities of Daily Living Rating Scale; SDMT: Symbol-digit Modalities Test; TMT: Trail Making Test Parts A & B; FAS: Controlled Oral Word Association Test; HVLT-R: Hopkins Verbal Learning Test-Revised; TOPF: Test of Premorbid Functioning; MOCA: Montreal Cognitive Assessment

4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	Administration of drug Ocrelizumab	☒ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

IRB #	STU 2018-0185
26776	

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

IRB #	STU 2018-0185
26776	

4.c.
Study Intervention #1
Administration of Ocrelizumab

List each group exposed to this intervention on a separate line.	
Experimental Arm (group randomized to ocrelizumab)	We anticipate that patients receiving ocrelizumab will have a reduced rate of worsening compared to placebo.
Open Label Arm (patients with early worsening who opt to receive drug open label)	

4.d. List ALL other research procedures or components not listed in table 4.b.
The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.

Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)

#	Research component • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Phase 1 assessments**			
	History and Physical	x		
	Antibody testing (serum and CSF)		X	
	Biomarker testing (serum and CSF)		X	
	Neuropsychological Assessment		x	
2	**Phase 2 Elligibility**			
	History and Physical	x		
	Laboratory testing (safety labs for ocrelizumab)		X	
	Laboratory Testing (antibody testing)		X	
	Questionnaires		X	
	Neuropsychological testing		x	
3	**Drug Adminstration**			
	History and Physical Exam		x	
	Questionnaire (Advserse Events)		x	
4	**Clinic Visits**			
	History and Physical		x	

Questionnaires (Adverse Events, seizure frequency, impression)		x	
Laboratory Testing (safety labs for ocrelizumab		x	
Neuropsychological Testing		x	
5 Telephone Visits			
Questionnaires (Adverse Events, seizures, impression)		x	
Testing (IADL)		x	

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Laboratory monitoring (blood work for blood counts, CD19, and autoantibody testing) will be done at study visits. Since the subject, principal investigator and study personnel must remain blinded to treatment assignment, the laboratory results will be reviewed by an independent safety monitor (physician) who has no contact with the research subjects.

In addition, throughout the study, participates will be regularly contacted (either during clinical visits, or during telephone visits) and specifically asked about adverse events.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

The sponsor (Genetech) will be independently review all AE & SAE for this study. They provided a safety data exchange agreement Will the safeguards be different between/among groups?

☐ Yes ■ No

If yes, describe here