

A Single Center Pilot Trial of Rituximab in the Treatment of Fibrillary Glomerulonephritis

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Study Title

A Single Center Pilot Trial of Rituximab in the Treatment of Fibrillary
Glomerulonephritis

Study Drug

Rituximab (Rituxan®)

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1.0 INTRODUCTION

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Disease Background

Fibrillary glomerulonephritis (FGN) is generally recognized as an uncommon and untreatable form of nephritis. The largest series of 66 cases comes from the Mayo Clinic. During an average of 52.3 months of follow-up for 61 patients with available data, 13% had complete or partial remission, 43% had persistent renal dysfunction, and 44% progressed to ESRD, despite treatment with a variety of immunosuppressive agents.⁴ Biopsy appearance on light microscopy is variable, but it is specific using electron microscopy. Randomly oriented fibrils of approximately 20 nm in length that do not stain with Congo Red define the process. It can be visually confused with fibronectin deposits, but fibronectin can be distinguished by a family history and differential tinctorial properties.⁹⁻¹² Some authorities lump immunotactoid nephropathy with FGN, but we will separate the two for research purposes.

Treatment of FGN has been attempted with prednisone, cytotoxics, pheresis, NSAIDs and colchicine. Improvement has been inconsistent but generally poor.^{3,5,7} Thus, effective treatment is urgently needed. No animal models exist.

In the majority of cases, the disease is considered idiopathic, although it has also been seen in association with B cell lymphomas, hepatitis C, cryoglobulinemia and lupus. B cells mediate immune responses, and depletion of the CD 19 – 20 subtypes has proven effective in treating other glomerulopathies of various etiologies, especially membranous nephropathy, ANCA associated vasculitis and lupus nephritis.

This together with anecdotal case reports and small series^{1,2,6,8} and observation that glomerular deposits in fibrillary GN are IgG4 dominant¹³ (similar to membranous nephropathy) suggest that FGN is immune mediated and is the rationale for using an agent such as Rituximab that is capable of depleting CD 20+ B cells and preventing the production of nephrotoxic immune globulins that initiate or mediate the disease.

1.2 Rituximab Background

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG₁ κ immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of

213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM.

1.2.1 Safety Profile

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, asthenia, and hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate.

Fatal Infusion Reactions: Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

Tumor Lysis Syndrome: Tumor lysis syndrome, some with fatal outcome, has been reported and is characterized in patients with a high number of circulating malignant cells ($\geq 25,000/\text{ul}$) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

Renal Events: Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has led to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ($\geq 25,000/\text{mm}^2$) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported in patients treated with rituximab. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia.

Infectious Events: Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulins in a minority of

patients; the lymphopenia lasted a median of 14 days (range, 1-588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Hepatitis B Reactivation: Hepatitis B virus (HBV) reactivation in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including Rituxan. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

Other Serious Viral Infections: The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

Progressive multifocal leukoencephalopathy (PML)

PML is a rare disease caused by the reactivation of latent JC virus in the brain. Immunosuppression allows reactivation of the JC virus which causes demyelination and destruction of oligodendrocytes resulting in death or severe disability. Rare cases of PML, some resulting in death, have been reported in patients with hematologic malignancies who have received rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Cases of PML resulting in death have also been reported following the use of rituximab for the treatment of autoimmune diseases. The reported cases had multiple risk factors for PML, including the underlying disease and long-term immunosuppressive therapy or chemotherapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Physicians should consider PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, rituximab should be discontinued and reductions or discontinuation of any concomitant chemotherapy or immunosuppressive therapy should be considered.

Posterior Reversible Encephalopathy Syndrome (PRES)/ Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include

visual disturbance, headache, seizures and altered mental status, with or without associated hypertension.

Bowel Obstruction and Perforation: Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1–77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Immunogenicity: Patients may develop a human anti-chimeric antibody (HACA) response with rituximab treatment. The clinical significance of this is unclear.

Pregnancy: B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in utero.

Immunization: Response rates may be reduced with non- live vaccines.

Additional Safety Signals: The following serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), eye disorders (uveitis and optic neuritis), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), that may result in fatal outcomes, and fatal cardiac failure.

See the rituximab Investigator Brochure for additional details regarding safety experience with rituximab.

1.3 Study Rationale

Although fibrillary nephritis may be a single pathological pathway for kidney injury of multiple etiologies, the immunofluorescent studies are clear that the fibrillary process is mediated by immune mechanisms. Biopsies typically stain for C3 and IgG (especially the IgG4 and IgG1 subclasses). A minority of the patients also have monoclonal proteins in circulation and in the biopsy. B cells mediate immune responses, and destruction of the CD 19 – 20 subtypes has proven effective in treating other glomerulopathies of various etiologies, especially membranous glomerulopathy and lupus nephritis. This together with anecdotal case reports and small series suggests rituximab has a rational role in the treatment of fibrillary GN.

Thus it appears that FGN is immune mediated. This is the rationale for using an agent such as Rituximab that is capable of depleting CD 20+ B cells and preventing the production of nephrotoxic immune globulins that initiate or mediate the disease.

2.0 OBJECTIVES

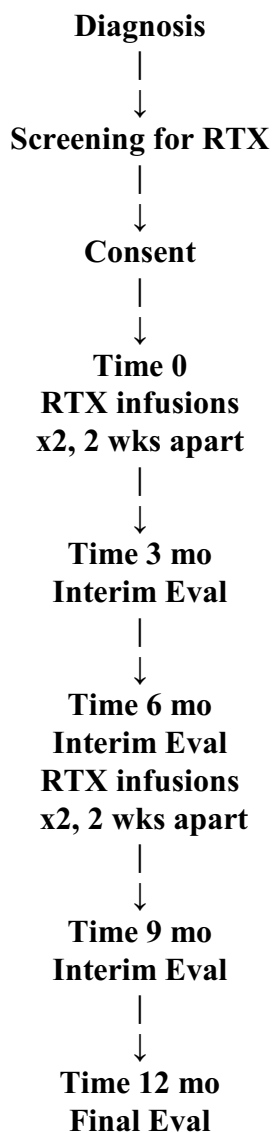
2.1 Primary

Preservation of kidney function at 12 months as defined by stable or improved 24 hour creatinine clearance.

2.2 Secondary

- a. Reduction in proteinuria at 12 months
 - Complete remission: < 300 mg proteinuria/24 hours
 - Partial remission: < 3500 mg proteinuria/24 hours
- b. Improved quality of life at 12 months by validated questionnaire

3.0 STUDY DESIGN



3.1 Description of the Study: Eleven (11) patients will be enrolled in the study and followed for 12 months. In all patients, proteinuria and other clinical laboratory parameters will be evaluated at study entry and at Day 28, Day 90, Day 180, Day 270, and Day 365 according to the test schedule listed below. These tests are: full blood cell count with white cell differential, serum creatinine, BUN, sodium, potassium, calcium, glucose, uric acid, bicarbonate, AST, alkaline phosphatase, total bilirubin, total serum protein, albumin, lipid screen, urinalysis, and 24 hour urine collection for creatinine clearance, sodium, and total protein. After successful enrollment, patients will be treated with an infusion dose of rituximab at Day 1 and at Day 15. CD 20+ cell count will be drawn pre and post infusion at Time 0, Day 28, Day 180, and Day 365. Patients will be retreated with a second dose of rituximab at 6 months independently of CD 20+ cell count.

Test Schedule and Monitoring for Rituximab Treatment

1. PBFC: Peripheral blood flow cytometry. Quantitate B and T cell subsets. This test is performed on

Tests	Time 0	Day 1	Day 15	Day 28	Day 90 (3 mo)	Day 180 (6 mo)	Day 181	Day 195	Day 270 (9 mo)	Day 365 (12 mo)
History/Exam	X			X	X	X			X	X
CBC with diff ²	X			X	X	X			X	X
BUN, creat, sodium, potassium, uric acid, tot prot, alb, bicarbonate, glucose, calcium, AST, alk phos, total bili ²	X			X	X	X			X	X
CD 20+ cells (PBFC) ¹	X			X		X				X
Lipid panel ²	X				X	X			X	X
Urine Pregnancy		X	X				X	X		
UA ²	X				X	X			X	X
24h urine for protein	X			X	X	X			X	X
24h creatinine for CrCl	X			X	X	X			X	X
24h urinary Na ⁺	X				X	X			X	X
Pre-infusion medication (i.e. Tylenol, Benadryl)		X	X				X	X		
Pre-infusion medication (i.e. methylprednisolone)		X					X			
Rituximab Infusion		X	X				X	X		
Quality of life-KDQOL	X					X				X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Optional Research Labs for antibodies (blood/urine) ⁴	X				X	X			X	X
HIV, HBsAg, anti-HBc ³	X									
Serum Pregnancy	X									

anticoagulated blood to identify the presence of various types of B and T lymphocytes, specifically CD 19-20+, which should be eradicated by Rituximab treatment.

2. At screening (Time 0), if patients had any Time 0 study specific labs drawn clinically at Mayo within 30 days, those values may be appropriate to use upon the investigator's review.

3. At screening (Time 0), if patients have had a negative Hepatitis b, Hepatitis c, or HIV value documented within two years of enrollment, those values may be appropriate to use upon the investigator's review.

4. Blood from a 5 mL red top tube will be drawn and aliquoted into five 1 mL cryovials to be frozen and stored. 50 mL of urine will be drawn from the 24 hour collection and then will be aliquoted into five 10 mL conical tubes to be frozen and stored.

3.2 Rationale for the Study Design

This is a pilot study. There is not enough treatment data to justify a head-to-head trial or even a placebo controlled trial yet. The number of patients required for more extensive studies will require a multi-centered trial, but that is premature until there is better evidence for effectiveness of rituximab treatment.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measures

Preservation of kidney function at 12 months as defined by stable or improved 24 hour creatinine clearance

3.3.2 Secondary Outcome Measures

- a. Reduction in proteinuria at 12 months
 - Complete remission: < 300 mg proteinuria/24 hours
 - Partial remission: < 3500 mg proteinuria/24 hours
- b. Quality of life at 12 months as determined by validated questionnaire

3.3.3 Safety Outcome Measures

Favorable experience with the use of rituximab in populations of patients with other forms of glomerulonephritis argues against the need for a data safety monitoring board in this small trial. We will monitor important laboratory parameters and other clinical manifestations as described above.

4.0 STUDY POPULATION

4.1 Inclusion Criteria

Patients must meet the following inclusion criteria to be eligible for study entry:

- Fibrillary Glomerulonephritis with diagnostic biopsy performed within the last 2 years
- Proteinuria > 1 gm
- Age \geq 18 years but < 80 years
- Patients need to have adequately controlled blood pressure (BP < 140/90 mmHg in > 75% of the readings) for at least 3 months prior to enrollment with the use of ACEi and/or ARB, if tolerated.
- Women must be post- menopausal, surgically sterile or practicing a medically approved method of contraception
- Able and willing to give written informed consent and comply with the requirements of the study protocol
- Adequate renal function as indicated by estimated GFR \geq 25 mL/min using CKD/EPI formula or a quantified creatinine clearance > 25 mL/min, and/or serum creatinine < 3.0 mg/dL in the presence of ACEi/ARB therapy
- Adequate liver function, as indicated by total bilirubin, AST, and alkaline phosphatase levels (< 2 times the upper normal limit)

- Adequate bone marrow function, as indicated by hemoglobin >7.0 gm/dL, white count >3.0 x 10⁹, platelet count >100 x 10⁹
- Negative chest x-ray within one year
- Negative serum pregnancy test (for women of child bearing age)
- Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for twelve month (1 year) after completion of treatment

General Medical Concerns:

- Normal organ function.
- Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for twelve months after completion of treatment
- Subject has provided written informed consent
- Subjects may continue to take their usual medications, except routine use of non-steroidal anti-inflammatory drugs

Rituximab-Specific Concerns:

- Documentation of CD20 + status.
- ANC: > 1000/ mm³
- Adequate bone marrow function as indicated by
 - Platelets: > 100 x 10⁹
 - Hemoglobin: >7 gm/dL
 - White count > 3.0 x 10⁹(A bone marrow biopsy is not necessary prior to study entry)
- Adequate renal function as indicated by estimated GFR \geq 25 ml/min using CKD-EPI formula and/or serum creatinine < 3.0 mg/dL in the presence of ACE inhibitor/ARB therapy
- Adequate liver function, as indicated by AST, alkaline phosphatase and total bilirubin < 2x upper limit or normal unless related to primary disease

4.2 Exclusion Criteria

Patients will be excluded from the study based on the following concerns:

General Medical Concerns:

- Pregnancy (a negative serum pregnancy test should be performed for all women of childbearing potential within 7 days of treatment), or lactating.
- Known history of diabetes mellitus or a Hemoglobin A1c result \geq 6.0% within 90 days prior to enrollment.
- Inability to comply with study and/or follow-up procedures.

Rituximab-Specific Concerns:

- History of HIV (as documented as a positive lab value within one year of enrollment)
- Presence of active infection

- New York Heart Association Classification III or IV heart disease (See Appendix D)
- Concomitant malignancies or previous malignancies within the last five years, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix
- History of psychiatric disorder
- At the Investigator's discretion, receipt of a live vaccine within 4 weeks prior to randomization
- Positive hepatitis B or C serology is considered a potential exclusion criterion. Hepatitis B screening should include hepatitis B surface antigen (HBsAg) and core antibody (anti-HBc) in all patients. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during Rituxan treatment. For inclusion into the study, the patient must have a negative HBsAg and anti-HBc lab value **within** 2 years of signing consent.

4.3 Immunization during B-Cell Depletion

Efficacy and/or safety of immunization during periods of B-cell depletion have not been adequately studied. It is recommended that a patient's vaccination record and possible requirements be reviewed. Per the investigator's discretion, the patient may have any required vaccination/booster administered at least 4 weeks prior to the initiation of study treatment. Review of the patient's immunization status for the following vaccinations is recommended: tetanus; diphtheria; influenza; pneumococcal polysaccharide; *Varicella*; measles, mumps and rubella (MMR); and hepatitis B. Patients who are considered to be at high risk for hepatitis B virus (HBV) infection and for whom the investigator has determined that immunization is indicated should complete the entire HBV vaccine series at least 4 weeks prior to participation in the study.

5.0 TREATMENT PLAN

This is a Phase II, open-label study. Each patient will be treated with 2 intravenous infusions of rituximab 1000 mg, two weeks apart for a total of 2 doses. Each patient will be retreated with identical 2 intravenous infusions of rituximab, two weeks apart at 6 months after the first infusion, irrespective of CD 20+ cell counts. Thus each patient will receive 4 infusions of rituximab.

Given the risk of *Pneumocystis* pneumonia for rituximab-treated patients and the associated significant mortality,¹⁴ study patients will be started on double strength Bactrim three times a week (or its equivalent) for *Pneumocystis* pneumonia prophylaxis. This treatment will continue until the end of the study (12 months) and the B cells (CD19/20+) have been repleted (>15 cells/microliter on peripheral blood flow cytometry). B cells (CD19/20+) are expected to be replete by Month 12. In the rare event that B cells (CD19/20+) are not replete by Month 12, flow cytometry should be repeated at Month 18 (see table 2b) and prophylaxis continued to that point of repletion.

This research study protocol allows the subject to receive up to “4” infusions of rituximab. Even if the treatment is shown to be of benefit, additional infusions of rituximab beyond that allowed in the protocol cannot be given to the subject while she/he is participating in this study.

Patients who flare will receive no additional treatment, because there is no known alternative. However, this should not be a concern because fibrillary glomerulonephritis is not a disease subject to flares, unlike ANCA associated vasculitis.

Patients who drop out of the study will be encouraged to return for their usual nephrology follow-up visits.

After study completion, patients will receive ongoing care from their usual nephrologist indefinitely.

6.0 STUDY MEDICATION

6.1 Rituximab

Rituximab is a highly purified, 1328-amino acid antibody with an approximate molecular mass of 145 kD. The chimeric mouse/human anti-CD20 antibody is a glycosylated IgG₁ κ immunoglobulin containing murine light and heavy chain variable regions and human γ_1 heavy chain and κ light chain constant regions.

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

“Rituximab will be provided free of charge by Genentech and Biogen IDEC. The Sponsor/Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (C.F.R.), Part 312.57 and 312.62 and Genentech requirements.”

6.1.1 Rituximab Dosage and Administration

The dosage of rituximab to be used is 1000 mg given as an IV infusion once every 2 weeks for two doses. Rituximab may be administered in an outpatient setting and will be repeated in 6 months.

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Do not infuse rituximab concomitantly with another IV solution or other IV medications.

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Infusion and hypersensitivity reactions may occur. Premedication, consisting of methylprednisolone, acetaminophen and diphenhydramine, should be considered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

For women of child bearing potential (WOCBP) a serum pregnancy test will be required at the screening visit. For each WOCBP a urine pregnancy test will be required prior to each infusion.

See Appendix E for more information.

Administration Guidelines for Adult Patient Population

First Infusion of both courses (Day 1 and Day 181): The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy

Subsequent Infusions (Day 15 and Day 195): If the subject tolerated the first infusion well, subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the first infusion was not well tolerated, the guidelines for the first infusion should be followed for the subsequent infusions.

Subjects will remain in the Clinical Research Unit for a one hour observation period following each infusion.

6.1.2 Rituximab Storage

Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight.

Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 24 hours. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2° to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

6.1.3 Rituximab Overdosage

There has been no experience with overdosage of rituximab in human clinical trials. Single doses higher than 500 mg/m² have not been tested in controlled studies.

7.0 DOSE MODIFICATION/TOXICITY MANAGEMENT

A number of measures will be taken to ensure the safety of patients participating in this study. These measures will be addressed through exclusion criteria (see Section 4.2) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Subjects will remain in the Clinical Research Unit for a one hour observation period following each infusion.

7.1 Rituximab

The dose of rituximab will remain constant throughout the trial. Rituximab infusion should be interrupted for severe reactions, e.g., rapid tumor lysis. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to rituximab (e.g., anaphylaxis). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms and laboratory abnormalities have completely resolved.

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Subjects who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions.

Carriers of hepatitis B and patients with a history of hepatitis B infection or positive serology should be excluded from clinical trials except in situations where the potential benefit is determined to justify the risk of possible hepatitis B reactivation, which can be fatal. Patients with positive serology should have viral DNA levels checked and a gastrointestinal consultation obtained. If treated with rituximab, such patients should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation.

8.0 CRITERIA FOR SUBJECT DISCONTINUATION

8.1 Rituximab-Specific Criteria

Subjects who meet the following criteria should be discontinued from the study:

- Active HBV infection or hepatitis
- Severe or life-threatening anaphylaxis or hypersensitivity reaction

8.2 General Criteria

- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy

Subjects who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.

9.0 CRITERIA FOR STUDY DISCONTINUATION

Determination by the investigator that it is not in the best interest of the patients to continue with study.

10.0 CLINICAL AND LABORATORY EVALUATIONS

10.1 Pre-Treatment Evaluations

The following evaluations must be performed within four weeks prior to the date of each patient's initial treatment with rituximab:

- Pregnancy test (serum or urine) for women of childbearing potential.

- Medical history and documentation of the rationale for treatment of the patient's disease with rituximab.
- Physical examination, including vital signs, blood pressure, performance status and tumor assessment.
- Hematology (within 2 weeks of treatment): complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, total protein, albumin, SGOT(AST), and calcium.
- Immunology: Screening of patients at high risk for HBV infection and other evaluations as appropriate for trial. Please note: Rituximab will compete with CD20 antibodies used in flow cytometry; use of CD20 to monitor B cells may provide false negative results for up to 6 months following treatment.

10.2 Evaluations During Treatment

Each patient will have a clinical evaluation at study entry and then at Day 28, Day 90, Day 180, Day 270, and Day 365 following the first rituximab infusion to include relevant medical history regarding response and potential side effects, and relevant physical examination to determine response and potential side effects. At subsequent visits, proteinuria and other clinical laboratory parameters will be evaluated according to the test schedule in section 3.1. These tests are: full blood cell count with white cell differential, serum creatinine, BUN, sodium, potassium, calcium, glucose, uric acid, bicarbonate, AST, alkaline phosphatase, total bilirubin, total serum protein, albumin, lipid screen, urinalysis, and 24 hour urine collection for creatinine clearance, sodium, and total protein. Each patient will be asked to complete a quality of life- KDQOL questionnaire at study entry, Day 180, and at Day 365.

Please include hydration where appropriate, and the following institutional guidelines for blood pressure monitoring:

- HR every 15 minutes x 4; every 30 minutes x 2; then hourly during the rest of the infusion
- BP every 15 minutes x 4; every 30 minutes x 2; then hourly during the rest of the infusion
- RR every 15 minutes x 4; every 30 minutes x 2; then hourly during the rest of the infusion

10.3 Post-Treatment Evaluations

Please note that subjects of both sexes must practice adequate birth control for a minimum of twelve months post-treatment.

11.0 REPORTING OF ADVERSE EVENTS

Safety Reporting of Adverse Events Assessment of Safety

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to {study drug}, all events of death, and any study specific issue of concern.

11.1 Adverse Event and Reporting Definitions

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with fibrillary glomerulonephritis that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Methods and Timing for Assessing AND Recording Safety variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment or initiation of any study procedures and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to rituximab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

There is a plausible temporal relationship between the onset of the AE and administration of rituximab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to rituximab; and/or the AE abates or resolves upon discontinuation of rituximab or dose reduction and, if applicable, reappears upon re-challenge.

Evidence exists that the AE has an etiology other than rituximab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to rituximab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

Procedures for Eliciting, Recording, and Reporting Adverse Events

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy

should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to rituximab should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior rituximab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

11.2 Reporting of Serious Adverse Events Associated With Rituximab

Investigators must report all SAEs to Genentech within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682

OR

(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to the Rituximab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the Rituximab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with the Rituximab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participants and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow up and reporting required.

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
<http://www.fda.gov/medwatch/getforms.html>

11.3 Safety Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of Rituximab. An unexpected adverse event is one that is not already described in the Rituximab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of Rituximab. An unexpected adverse event is one that is not already described in the Rituximab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

Randomization Codes for blinded clinical trials.

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-5288

IND Annual Reports

Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

rituxan-immunology-gsur@gene.com

11.4 Safety Reporting Requirements for IND Exempt Studies

For **Investigator Sponsored IND Exempt Studies** there are some reporting requirements for the FDA in accordance with the guidelines set forth in 21 CFR 314.80.

Postmarketing 15 Day “Alert Report”:

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of rituximab. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be submitted to the FDA (2 copies) at the following address: Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852.

All Postmarketing 15 Day “Alert Reports” submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-1683

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission, it is also provided on Rituxan CD-ROM).

For questions related to safety reporting, contact:

Genentech Drug Safety

Tel: 1-888-835-2555

Or

Fax: (650) 225-1682 or (650) 225-1683

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission).

12.0 EVALUATION OF RESPONSE

It is recommended that an evaluation of response be carried out no earlier than one month following completion of therapy. Re-evaluation of response should be carried out at a minimum of yearly intervals.

Please denote at which timepoint subject response will be evaluated and documented.

For consistency across studies, GNE/Biogen IDEC requests that the investigators refer to the NCI proposed guidelines, Cheson, JCO 17: 1244-53 (for NHL).

Response Criteria [Time to progression, overall survival, etc.]

13.0 STATISTICAL CONSIDERATIONS

13.1 Determination of Sample Size:

This is a pilot study in a population of patients with a rare disease for which only a few case reports are available. As such, it is impossible to calculate a sample size. We plan to recruit 11 (eleven) patients as described above. We do not think we can recruit more patients than this in 2 years.

13.2 Planned Efficacy Evaluations

13.2.1 Primary Efficacy Variables

- a. Preservation of kidney function at 12 months as determined by stable or increased 24h creatinine clearance

13.2.2 Secondary Efficacy Variables

- a. Reduction in proteinuria
 - Complete remission: < 300 mg proteinuria/24 hours
 - Partial remission: < 3500 mg proteinuria/24 hours
- b. Quality of life at 12 months by validated questionnaire

13.3 Methods of Analysis

- a. Pre- and post-treatment proteinuria and estimated glomerular filtration rate will be compared by t-test. Proteinuria will be log transformed.
- b. Quality of life will be measured pre- and post-treatment by a validated kidney disease questionnaire.

14.0 RETENTION OF RECORDS

We will retain all documentation of adverse events, records of trial drug receipt and dispensation, and all IRB correspondence for at least 2 years after the investigation is completed according to 21 CFR 312.57..

REFERENCES/BIBLIOGRAPHY

Publication Numbers below are 3 abstracts presented at the 2012 American Society of Nephrology:

1. Pub Number: [SA-PO382]
Long-Term Follow Up of Rituximab Treatment for Fibrillary Glomerulonephritis
Jonathan J. Hogan, MD, Michaela Restivo, MD, Pietro A. Canetta, MD, Jai Radhakrishnan, MD, FASN, Gerald B. Appel, MD, FASN, Andrew S. Bomback, MD
2. Pub Number: [SA-PO1043]
Favorable Response to Rituximab in Diffuse Sclerosing Variant of Fibrillary Glomerulonephritis
Asad J. Chaudhary, MD, Geeta G. Gyamlani, MD, Barry M. Wall, MD
3. Czarnecki PG, Lager DJ, Leung N et al. Long-term outcome of kidney transplantation in patients with fibrillary glomerulonephritis or monoclonal gammopathy with fibrillary deposits. *KI* 75: 420-7, 2009
4. Collins, M, Navaneethan SD, Chung M et al. Rituximab treatment of fibrillary glomerulonephritis. *Am J Kid Dis* 52: 6, 1156-62, 2008
5. Nasr SH, Valeri AM, Cornell LD et al. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. *J Am Soc Nephrol* 6: 775-84, 2011
6. Pub Number: [SA-PO350]
Immunosuppressive Therapy in Fibrillary Glomerulonephritis
7. Vincent Javaugue, Alexandre Karras, MD, Francois Glowacki. Long Term Disease Outcomes in Fibrillary Glomerulonephritis: A Case Series of 27 Patients. *Am J Kid Dis* 2013; 62:679.
8. Bhat P, Weiss S, Appel GB, Radhakrishnan J. Rituximab Treatment of Dysproteinemias Affecting the Kidney: A Review of 3 Cases. *Am J Kid Dis* 2007; 50: 641.
9. Alpers CE, Rennke HG, Hopper J Jr, Biara CG. Fibrillary Glomerulonephritis: An Entity with Unusual Immunofluorescent Features *Kid Int* 1987; 31:781.
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11. Rosenstock JL, Markowitz GS, Valeri AM, et al. Fibrillary and Immunotactoid Glomerulonephritis: Distinct Entities with Different Clinical and Pathological Features. Kid Int 2001; 63:1450.
12. Fogo A, Qureshi N, Horn RG. Morphological and Clinical Feature of Fibrillary Glomerulonephritis versus Immunotactoid. Am J Kid Dis 1993; 22:367.
13. Bridoux F, Hugue V, Coldefy O, Goujon JM, Bauwens M, Sechet A, Preud'Homme JL, Touchard G. Fibrillary glomerulonephritis and immunotactoid (microtubular) glomerulopathy are associated with distinct immunologic features. Kidney Int 2002; 62: 1764.
14. Martin-Garrido I, Carmona E, Specks U, Limper A. Pneumocystis Pneumonia in Patients Treated with Rituximab. Chest 2013; 144 (1): 258-265.

APPENDIX A: STUDY FLOW CHART/SCHEMA

[test schedule located under section 3.1]

APPENDIX B: CURRENT NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

[please refer to the following web link:]

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX C: FDA MEDWATCH 3500A FORM

[provided as separate document on Rituxan CD-ROM]

APPENDIX D: NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES

[provided as separate document on Rituxan CD-ROM]

APPENDIX E: GUIDELINES FOR RITUXIMAB PREPARATION AND ADMINISTRATION

[provided as separate document on Rituxan CD-ROM]

APPENDIX F: PHARMACOKINETICS / HACA LABORATORY INSTRUCTIONS

[provided as separate document on Rituxan CD-ROM]

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SAFETY REPORTING FAX COVER SHEET

Investigator Sponsored Trials

SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-4683

Study Number (Genentech study number)	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date (DD/MON/YYYY)	___ / ___ / ___
Follow-up Report Date (DD/MON/YYYY)	___ / ___ / ___

Subject Initials (Please enter a dash if the patient has no middle name)	___ - ___ - ___
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PLEASE PLACE MEDWATCH REPORT or IND SAFETY REPORT BEHIND THIS
COVER SHEET

**Please contact Genentech Safety for any questions regarding SAE or IND Safety
reporting at (888) 835-2555**