A Single-Center Phase 2 Open-Label Trial Evaluating the Efficacy and Safety of OBINUTUZUMAB in Treatment of Immunosuppression-Dependent or Immunosuppression/Treatment-Resistant Primary FSGS, or Contraindication/Patient Refusal to Take High Dose Corticosteroids

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OBINUTUZUMAB IN THE TREATMENT OF PATIENTS WITH PRIMARY FSGS

Study Summary

Title	A single-center phase 2 open-label trial evaluating the efficacy and safety of OBINUTUZUMAB in treatment of immunosuppression-dependent or immunosuppression/treatment-resistant primary FSGS, or contraindication/patient refusal to take high dose corticosteroids
Running Title	OBINUTUZUMAB IN PRIMARY FSGS
Protocol Number	21-003887
Phase	Phase 2
Methodology	Open-label, Proof of Concept
Overall Study Duration	24 months
Subject Participation Duration	24 months
Single or Multi-Site	Single center
Objectives	Is Obinutuzumab effective and safe in treating patients with primary FSGS
Number of Subjects	20
Diagnosis and Main Criteria	Patients with primary FSGS who have contraindication/refuse to take high dose corticosteroids or are resistant/dependent on immunosuppression therapy to remain in remission
Study Product, Dose, Route, Regimen	Obinutuzumab 1g IV on day one and 1 g IV on day 15, followed by identical course at month 6
Duration of Administration	6 months
Reference therapy	No reference therapy
Statistical Methodology	A paired t-test will be performed for proteinuria and renal function at Baseline (Day 0), 6 month and 12 months.

INTRODUCTION

1.1 Background

Primary FSGS is a primary podocytopathy in which patients present with nephrotic syndrome characterized by heavy proteinuria and hypoalbuminemia. The pathogenesis of primary FSGS is not as well understood but there is growing evidence that B-cells play a major role. Potential mechanisms include local production of IL-4 by B-cells as shown in murine models, production of IgG-antibody against Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCHL1) in addition to their interactions with T-cells.[1,2] Most importantly, rituximab an anti-CD20 monoclonal antibody has been used in treatment of patients with primary FSGS with some success. The best evidence for the use of rituximab is for treatment of recurrent FSGS post kidney transplantation. There is also good evidence that patients with steroid-responsive primary FSGS respond favorably to rituximab but evidence in patients with steroid-resistant FSGS is inconclusive.[3-5] In a study of eight patients with steroid-resistant FSGS, only three patients responded.[6] Other treatment modalities for primary FSGS include long courses of corticosteroids which are associated with significant toxicity and side effects and up to 60% may not respond or have relapses.[7] Calcineurin inhibitors have also been used with some success but the rate of relapse with discontinuation is high.[8,9]

1.2 Investigational Agent

Obinutuzumab (also known as RO5072759, GA101, GAZYVATM, GAZYVAROTM) is a humanized glycoengineered Type II anti-CD20 monoclonal antibody(mAb). Obinutuzumab is licensed for use for oncological indications and relevant oncology data is available in the Obinutuzumab Oncology IB Version 14, July 2019. Some of the oncology information is considered relevant to inform the investigation of non-oncology indications at this stage of development and is therefore included in this IB. To date, obinutuzumab, in combination with chlorambucil (GClb), has received regulatory approval for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) in many countries including the US, Switzerland, and the EU (exact wording of the indication varies from country to country). Obinutuzumab has also been approved globally for follicular lymphoma (FL) for patients who did not respond to a rituximab-containing regimen or had their FL return after such treatment and for the treatment of adult patients with previously untreated FL. As per investigator brochure, an estimated 3745 oncology patients and 150 non-oncology patients were analyzed for safety in obinutuzumab clinical studies. These data are derived from oncology patients with CLL or non-Hodgkin lymphoma (NHL) from obinutuzumab doses of 50−2000 mg mostly in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); fludarabine plus cyclophosphamide (FC); bendamustine; or chlorambucil (Clb) or as monotherapy. Data from non-oncology patients are derived from patients with LN where obinutuzumab was given in combination with mycophenolate and corticosteroids and patients with end stage renal disease (ESRD) where obinutuzumab administration was followed by high dose intravenous immunoglobulin (IVIG). The properties of obinutuzumab, a humanized Type II anti-CD20 antibody, include increased direct cell death induction and reduced complement-dependent cytotoxicity (CDC) activity as compared to rituximab, a chimeric Type I CD20 antibody. Obinutuzumab is the product of glycoengineering that results in increased binding affinity for FcγRIII, which leads to significantly improved cellular cytotoxicity in in-vitro antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis

(ADCP)-based assays. In particular, the binding affinity of obinutuzumab to the low affinity FcγRIIIa (F158) is substantially increased, such that it exceeds that of rituximab for the high affinity FcγRIIIa (V158) receptor.[10] As a result of improved direct cell death induction and ADCC/ADCP potency, obinutuzumab has the potential to deplete CD20+ B-cells, including tissue-resident CD20+ B-cells, to a greater degree than other anti-CD20 antibodies, which may lead to better clinical efficacy. Data from the primary analysis of Stage II of Study BO21004/CLL11 (GClb vs rituximab + chlorambucil [RClb]) in patients with CLL demonstrated this improved blood and tissue depletion for obinutuzumab versus rituximab. These properties have also identified obinutuzumab as a potential new therapy in specific immunological diseases where the unmet need remains high and where rituximab may be less effective due to incomplete depletion of pathogenic B-cells in secondary lymphoid organs and tertiary lymphoid structures

1.3 Clinical Data to Date

We propose to use obinutuzumab, a Type II anti-CD20 monoclonal antibody, for treatment of treatment-resistant or treatment-dependent primary FSGS, or contraindication/patient refusal to take high dose corticosteroids. Obinutuzumab has been shown to be superior to rituximab in management of several conditions in which B-cells play a major role including several hematological malignancies.[11] Recently, we showed the successful use of obinutuzumab in three patients with membranous nephropathy who had failed to respond to rituximab.[12] In addition, obinutuzumab has been shown to be effective in treatment of patients with lupus nephritis.[13,14]. Therefore, there is growing evidence that in kidney diseases in which B-cells play a role in the pathophysiology targeting B-cells with more "potent" anti-CD20 may be effective. We have also recently successfully treated three patients with primary FSGS resistant to all therapies (including rituximab) with obinutuzumab.

1.4 Dose Rationale and Risk/Benefits

The pharmacokinetics of obinutuzumab has also been characterized in LN patients from Study WA29748 treated with single IV doses of 1000 mg on Days 1, 15, 168, and 182 using a population PK approach. A total of 61 patients contributed 612 serum concentration values to the analysis. The pharmacokinetics of obinutuzumab in patients with LN was well described by a two-compartment linear population PK model in which total clearance is the sum of two elimination pathways, (i) time-varying clearance that decreases with time with a decay coefficient (kdes), likely related to CD20 target reduction and proteinuria improvement over time and (ii) time-independent clearance related to the endogenous catabolic processes of IgG. The covariates found to influence obinutuzumab PK parameters in LN patients were body weight (BW), serum albumin (ALB) at baseline and serum IgG levels at baseline. The variability between patients was low for clearance and volume parameters (less than 30%), but high for the time-dependent clearance (above 50%).

Overall, the safety of obinutuzumab in the non-oncology studies is acceptable and manageable. The most frequently observed adverse drug reactions (ADRs) in patients receiving Obinutuzumab for any indication were IRRs which occurred predominantly during infusion of the first 1000 mg. (Investigator's Brochure: obinutuzumab TM F. Hoffmann-La Roche Ltd CONFIDENTIAL Version Number 6, September 2019 134) In patients with CLL who received the combined measures for prevention of IRRs (adequate corticosteroid, oral analgesic/anti-histamine, omission of antihypertensive medication), a decreased incidence of IRRs of all grades was observed. The rates of Grade 3-4 IRRs (which were based on a relatively small number of

patients) were similar before and after mitigation measures were implemented. The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of obinutuzumab. In majority of patients, irrespective of indication, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumor burden and/or high circulating lymphocyte count in CLL [> 25 x 109/L] may be at increased risk of severe IRR. The most frequently reported related SAEs are febrile neutropenia (5.4%), IRR (3.4%), thrombocytopenia (2.5%) and neutropenia (2.9%). To date, no new safety signal has been identified as a result of the post-marketing experience of obinutuzumab.

2. STUDY OBJECTIVE

We propose a pilot study (hypothesis generating) to enroll 20 patients with immunosuppression-dependent or immunosuppression/treatment-resistant primary FSGS, or contraindication/patient refusal to take high dose corticosteroids, to test the efficacy and safety of obinutuzumab in inducing complete or partial remission of proteinuria.

3. STUDY DESIGN

Patients with immunosuppression-dependent or immunosuppression/treatment-resistant primary FSGS or contraindication/patient refusal to take high dose corticosteroids, will receive obinutuzumab 1 gram on day 1 and 1 gram on day 15, given intravenously and then an identical course at 6 months.

3.1 Primary endpoint

Change in proteinuria from baseline to 6 months and 12 months post treatment with Obinutuzumab

3.2 Secondary endpoints

- Rate of complete or partial remission (Complete remission: Proteinuria < 0.3g/24 hrs. and no more than 20% decline in eGFR, Partial remission: 50% reduction in proteinuria and proteinuria < 3.5 g/24hrs and no more than 20% decline in eGFR) at 6 months and 12 months
- Improvement in serum albumin at 6 months and 12 months
- Stabilization of kidney function (no more than 20% decline in eGFR at 6 months and 12 months)
- Rate of all Serious Adverse Events (SAEs) including serious infection defined as severe UTI or pyelonephritis, pneumonias or other systemic infections requiring hospitalization
- Sustained effect on proteinuria up to 18 and 24 months

4. SUBJECT SELECTION

4.1 Inclusion criteria

- ≥18 years of age
- Biopsy proven FSGS lesion
- Foot process effacement ≥80% on electron microscopy
- Presence of nephrotic syndrome (proteinuria >3.5g/24hrs and serum albumin <3.5 g/dl) prior to initiation of immunosuppressive therapy
- Resistant or dependent on therapy, including corticosteroids or calcineurin inhibitors or who have failed rituximab. Patient who have contraindication to or refuse to take high dose corticosteroids are allowed

4.2 Exclusion criteria

- Genetic or secondary forms of FSGS
- Hepatitis B, C or HIV positive
- Pregnant or breast-feeding
- Active infection
- Kidney transplant
- Anemia with Hgb < 8.0 g/dL
- Thrombocytopenia with platelet count < 100'000
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complication
- Patients who have received cyclophosphamide in the last 6 months
- Patients who have received ACTH and/or mycophenolate mofetil in the last 30 days
- Patient who are on prednisone therapy at a dose > 10 mg/day in the last 30 days
- Patients who received rituximab previously with CD20 count of < 5 cells/microliter at the time of enrollment
- For women who are not postmenopausal (greater than or equal to [>/=] 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of less than (<) 1 percent (%) per year, during the treatment period and for at least 18 months after the last dose of study drug
- For men: agreement to remain abstinent or use two adequate methods for contraception, including at least one method with failure rate of less than 1% per year during the treatment period and for at least 6 months (180 days) after the last dose of drug

4.3 Subject Recruitment, Enrollment and Screening

Patients will be recruited from the principal investigator or co-investigator clinical practices within the Division of Nephrology and Hypertension at Mayo Rochester by reviewing available renal biopsies and lab values.

4.4 Subject Withdrawal

4.4.1 When to Withdraw Subjects

- Subjects decision to withdraw from the study (withdrawal of consent)
- Failure of subject to adhere to protocol requirements. If a patient experiences an adverse event and the PI determines the next dose must be delayed, the dose may be delayed for up to 4 weeks and continue the protocol schedule without being withdrawn.
- Disease progression (proteinuria increase by > 50% from baseline that is persistent for > 2 months)
- Given this is a proof of concept study if a patient withdraws within 30 days after enrollment, they will be replaced
- If Hgb < 8.0 g/dL or platelet <50,000 or WBC < 3.0 or absolute neutrophil count (ANC) < 500, the infusion will be held and restarted once blood counts have improved.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

- Subjects that withdraw consent or are withdrawn from the study due to safety issues or not following through with the protocol will be followed clinically by the PI or co-investigators or will be sent back to the referring nephrologist

5. STUDY DRUG

5.1 Description

Obinutuzumab is a humanized glycoengineered Type II anti-CD20 monoclonal antibody(mAb). It appears in liquid form and is administered intravenously.

5.2 Treatment Regimen

The drug will be given intravenously at a dose of 1000 mg on day 1 and 1000 mg on day 15, followed by identical protocol at 6 months.

5.3 Method for Assigning Subjects to Treatment Groups

This study is non-randomized trial and all 20 patients that are enrolled in this study will receive obinutuzumab.

5.4 Preparation and Administration of Study Drug

Study drug will be prepared in the research pharmacy.

Pretreatment: Fifteen minutes prior to the first infusion, 100 mg methylprednisolone will be administered via IV along with 1000 mg acetaminophen and 50 mg diphenhydramine given by mouth. Fifteen minutes

prior to all subsequent infusions, only 1000 mg acetaminophen and 50 mg diphenhydramine will be administered by mouth.

First Infusion (1000 mg): IV infusion in 250 mL 0.9% NaCl, beginning at 50 mg/hr. Increase by 50 mg/hr every 30 minutes, as tolerated, to a maximum rate of 400 mg/hr. Vital signs will be taken every 15 minutes for first hour, then every hour until end of infusion, and then again after IV flush.

Second Infusion (1000mg): IV infusion in 250 mL 0.9% NaCl starting at 100 mg/hr if there was no infusion reaction greater than Grade 1 during previous infusion and the final rate was 100 mg/hr or faster. Rate may be increased by 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour., If the first infusion was not well tolerated (infusion-related reaction > Grade 1), then instructions for the first infusion should be used. Vital signs will be taken every 15 minutes for first hour, then every hour until end of infusion, and then again after IV flush.

Infusions at months 6 (1000 mg) each will follow identical protocol as infusions on day 1 and day 15.

Infusion related reactions: Diphenhydramine 25 mg IV can be given every 4 hours as needed and may repeat once if symptoms are not relieved within 15 minutes of initial dose. Methylprednisolone 100 mg IV can be given as needed for infusion related reactions.

Post-infusion: Beginning the day after their first obinutuzumab infusion, patients will also start single strength Bactrim, orally, once a day (or its equivalent) to prevent opportunistic infections, including pneumocystis pneumonia. Treatment with Bactrim will continue until there is evidence of B cell reconstitution.

The drug will be prepared in the following steps:

1. Prepared in the non-hazardous sterile hood.
2. Utilize 0.9% normal saline 250 mL.
3. Infusion rate instructions:
    a. Continuous Infusion: Start infusion at 50 mg/hr. Rate may be increased by 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. (For pump set up at mL/hr: start at 12.5 mL/hr; if tolerated, increase the rate by 12.5 mL/hr every 30 minutes to a maximum of 100 mL/hr.)
    b. Subsequent doses: Start infusion at 100 mg/hr if there was no infusion reaction greater than Grade 1 during previous infusion and the final rate was 100 mg/hr or faster rate may be increased by 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. (For pump set up at mL/hr: start at 25 mL/hr; if tolerated, increase the rate by 25 mL/hr every 30 minutes to a maximum of 100 mL/hr.)

5.5 Management of Infusion Related Reactions

If a patient experiences an infusion-related of any grade during infusion, adjust the infusion as follows:

Infusion Reactions	CTCAE Version 5.0 Description	Recommendations per Prescribing Information
Grades 1-2 (mild to moderate)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications for ≤ 24 hrs	Reduce infusion rate or interrupt infusion and manage symptoms • Upon resolution of symptoms, continue or resume Obinutuzumab infusion, and if patient does not experience any further infusion-related reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment regimen
	Mild reaction; infusion interruption not indicated; intervention not indicated	
Grade 3 (severe)	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Interrupt infusion and manage symptoms • Upon resolution of symptoms, consider restarting Obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion-related reaction occurred), and if patient does not experience any further infusion-related reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment regimen • Permanently discontinue treatment if patients experience a Grade 3 infusion-related reaction at rechallenge
Grade 4 (life-threatening)	Life-threatening consequences: pressor or ventilatory support indicated	Stop infusion immediately and permanently discontinue Obinutuzumab therapy

CTCAE, Common Terminology Criteria for Adverse Events

- Closely monitor patients during the entire infusion.
- Refer to section 5.4 for medical management for infusion reactions as needed

Other Adverse Reactions

Consider treatment interruption if patients experience an infection, Grade 3 or 4 cytopenia, or a Grade 2 or higher non-hematologic toxicity.

5.6 Subject Compliance Monitoring

This drug is administered intravenously in the Clinical Research Trials Unit (CRTU) and we can ensure compliance.

5.7 Prior and Concomitant Therapy

Patients must have a minimal washout period before initiating Obinutuzumab to avoid over immunosuppression and consequent risk of morbidity. However, to avoid risk of worsening of their underlying FSGS disease in those with partial response these patients are to discontinue or reduce other immunosuppressive therapies as follows:

- Cytotoxic therapy discontinued at least 6 months prior to initiation of Obinutuzumab
- ACTH and/or MMF discontinued at least 30 days prior to initiation of Obinutuzumab
- CNI tapered and discontinued beginning 60 days after the first Obinutuzumab dose
- Prednisone reduced to ≤ 10 mg/day 30 days prior to Obinutuzumab
- If patient has received rituximab prior to the study, there should be evidence of B-cell reconstitution prior to enrollment (CD 20 count>5).

Patients must be on an ACE-I or ARB (unless intolerance) while enrolled in the study but dose adjustment is not allowed unless down titration for safety reasons.

Rescue treatment is not permitted while receiving obinutuzumab. If patient is failing treatment with evidence of disease progression (> 50% increase in proteinuria that is persistent over 2 months), the subject will be withdrawn from the study and can then receive other immunosuppressive therapy per discretion of the treating physician.

5.8 Packaging

Commercially available supplies of obinutuzumab will be provided by Genentech, Inc.

5.9 Masking/Blinding of Study

This is an open-label study and all participants will be receiving the study drugs. There will be no blinding or masking.

6. STUDY PROCEDURES

Please see flow chart below.

Tests/ Assessments	Screening	Day 1 (1st Infusion- Round 1)	Day 15 (2nd Infusion –Round 1) ± 2 days	Day 90 Month 3 ± 7 days	Day 180 Month 6 (1st Infusion – Round 2) ± 7 days	Day 195 (2nd infusion – Round 2) ± 7 days	Day 270 Month 9 ± 14 days	Day 365 Month 12 ± 14 days	Day 548 Month 18 ± 14 days	Day 730 Month 24 ± 14 days
History/Exam	X			X	X		X	X	X	X
Informed Consent	X									
CBC with 5-part WBC differential	X			X	X		X	X	X	X
Comprehensive Metabolic Panel	X			X	X		X	X	X	X
TBNK [b]		X		X	X			X	X	X
Minimal residual B cells (HSFC) and B cell subsets [b]		X		X	X			X	X	X
T cell markers (flow) [b]		X		X	X			X	X	X
Hepatitis B tests	X									
Hepatitis C tests	X									
HIV test	X									
Pregnancy test, serum	X									
Lipid panel	X				X			X	X	X
Urinalysis w/microscopy	X				X			X	X	X
24 hr. creatinine clearance	X			X	X		X	X	X	X
Protein total, 24 hr. urine	X			X	X		X	X	X	X
Pregnancy Test, urine		X	X		X	X				
Pretreatment medications (methylprednisolone, acetaminophen and Diphenhydramine)		X	X		X	X				
Obinutuzumab IV		X	X		X	X				
Adverse Events		X	X	X	X	X	X	X	X	X

a) Urine biomarker sample may be taken from 24-hour urine collection.

b) Samples will be drawn in duplicates before administration of study drug infusions and pre-infusion medications on dosing days. a) one sample will be mailed to COVANCE b) the second sample will be sent to Dr. Sadighi Akha, at Mayo Clinic, Rochester

7. ANCILLARY STUDIES

We will evaluate the effect of obinutuzumab on key circulating B cell subsets by flow cytometry (e.g. naïve and memory B cells, and plasmablasts), as well as T cells subsets (e.g. CD4+, CD8+ and Tregs).

The B cell subset flow cytometry will include total B cells, naive B cells, memory B cells (unswitched, switched), double negative B cells, IgD+ transitional B cells, Plasmablasts/plasma cells. We will study regulatory T Cell Panel 3, which reports the frequency of CD4+ CD25+ Tregs and their expression of common Treg markers: CD127, and FoxP3, as well as the negative costimulatory molecule PD1, and negative regulator of Tregs, OX40. The T cell panel sample should be collected in a green top sodium heparin tube. A 5 mL tube (purple and black speckled Cyto-Chex® tube) and a 5 mL green top sodium heparin tube are sufficient to run all the flow cytometry panels.

Samples will be mailed to Covance laboratories for analysis and to Dr. Sadighi Akha, at Mayo Clinic, Rochester.

Recently, advances have been made in understanding the pathogenesis of primary FSGS. These include evaluation of antibodies at the slit diaphragm of the podocytes on a kidney biopsy slide. Our goal is to obtain kidney biopsy slides of patients enrolled in the study and to send the slides to our collaborator, Dr. Paola Romagnani, at the **Meyer Children's Hospital IRCCS**, whose registered office is located at Viale Gaetano Pieraccini 24, 50139 Firenze, Italy,in order to test for the presence of auto-antibodies.

STATISTICAL PLAN

7.1 Sample Size Determination

This is a pilot study and therefore power analysis was not done prior to this study. The primary endpoint of this study is to assess the efficacy of obinutuzumab in patients with primary FSGS and the secondary endpoint is the safety of this drug in this population.

7.2 Statistical Methods

7.2.1 Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables including proteinuria, serum albumin and serum creatinine in each response category will be tabulated. A paired t-test will be performed for proteinuria, serum creatinine, serum albumin, and renal function at baseline (Day 0), 6 months and 12 months. For binary outcomes (e.g. stabilization of kidney function) McNemar's test will be used.

7.2.2 Handling of Missing Data

This is a study of only 20 patients and expect that majority of patients will have complete data available.

7.2.3 Subject Population(s) for Analysis

All-treated population: Any subject that received at least one dose of study drug.

8. SAFETY REPORTING AND ADVERSE EVENTS

8.1 Assessment of Safety

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

8.1.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), 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 FSGS 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

8.1.2 Serious Adverse Events

An AE should be classified as an SAE if any of 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)

8.2 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).

8.2.1 Adverse Event Reporting Period

The study period during which AEs and SAEs where the patient has been exposed to Genentech product must be reported begins after informed consent is obtained and initiation of study treatment 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.

8.2.2 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 the obinutuzumab, and actions taken.

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

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the obinutuzumab, 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 the obinutuzumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of the obinutuzumab or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than the obinutuzumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to obinutuzumab 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 (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current 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.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

8.3 Procedures for Eliciting, Recording, And Reporting Adverse Events

8.3.1 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?"

8.3.2 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 acceptable 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 9.2.1), 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. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE □ National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0) which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a) Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b) Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c) If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d) Grade 4 and 5 events must be reported as serious adverse events

F. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 18 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 180 days, a report should be completed and expeditiously submitted to 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 the study drug should be reported as an SAE.

G. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law
- Treatment-emergent ALT or AST □ 3 □ ULN in combination with total bilirubin □ 2 □ ULN
- Treatment-emergent ALT or AST □ 3 □ ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

The Obinutuzumab Events of Special Interest are:

Infusion-related reactions

Grade 3 or higher infections

Hepatitis B reactivation

Progressive multifocal leukoencephalopathy (PML)

Drug-related neutropenia

Drug-related thrombocytopenia

Gastrointestinal perforations

Worsening of pre-existing cardiac conditions

H. Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

I. Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

J. Post-Study Adverse Events

For studies involving extended follow up period the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period (quarterly) to ensure successful transmission of Single case reports.

K. Exchange of Single Case Reports with Genentech

The investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch form should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	Timelines

Serious Adverse Events (Related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and Pregnancy)	
Product Complaints (With or without AE)	
AESI	

8.3.3 Case Transmission Verification of Single Case Reports

The parties will verify that all single case reports have been adequately received by Genentech via the investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by the investigator to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

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. The sponsor shall receive reconciliation guidance documents within the 'Activation Package.'

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Dr. Fernando Fervenza to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

MEDWATCH 3500A REPORTING GUIDELINES

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

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- 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)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

8.3.4 Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

Dr. Fernando Fervenza will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

Dr. Fernando Fervenza as the Sponsor of the Study, will be responsible for the preparation of six-monthly Suspected Unexpected Serious Adverse Reaction (SUSAR) reports and their submission to Investigators, Regulatory Authorities and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), where applicable.

Dr. Fernando Fervenza will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Other Reports

Dr. Fervenza will forward a copy of the publication to Genentech upon completion of the study.

And Dr. Fernando Fervenza will be responsible for the distribution of safety information to Site IRB:

Mayo Clinic Institutional Review Board
201 Building 4-60
200 First Street SW
Rochester, MN 55905
Phone: 507-266-4000

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

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:

Email: ga101-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

8.4 Queries

Queries related to the Study will be answered by Dr. Fernando Fervenza. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between Dr. Fervenza and Genentech and that Genentech shall have the final say and control over safety queries relating to Obinutuzumab. Dr. Fernando Fervenza agrees that he shall not answer such queries from regulatory authorities and other sources relating to Obinutuzumab independently but shall redirect such queries to Genentech.

8.5 Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that Dr. Fernando Fervenza, as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If Dr. Fernando Fervenza issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study), this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Dr. Fernando Fervenza with signal and risk management activities related to the Product within the study.

Genentech will also provide Dr. Fernando Fervenza with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

8.6 Compliance with Pharmacovigilance Agreement/Audit

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in

good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

8.7 Stopping Rules

Patients should not receive further obinutuzumab infusions if they experience:

A. acute life-threatening respiratory symptoms
B. Grade 4 (i.e., life-threatening) IRR or
C. a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion)

8.8 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.9 Internal Data and Safety Monitoring Board

A four person DSMB (clinical researchers) not affiliated with the study will be responsible for evaluating the progress of the study and will be provided data on a regular basis to monitor patient safety. This committee will communicate by meeting every 6 months. They will be responsible for determining if and when the study must be discontinued as a result of excessive adverse events. Study data will be provided to the DSMB by the data coordinating center (including all adverse event reports and the GFR data). The Committee will make its recommendations by periodically monitoring progress, data, outcomes, toxicity, safety and other confidential data, and may recommend stopping the clinical trial if an excessive number of serious adverse events are observed.

9. DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The investigator will review, approve and sign/date each completed CRF; the investigator signature serving as attestation of the investigator responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

9.4 Data Management

Investigators will enter the information required by the protocol into electronic Case Report Forms (eCRFs). This study will use REDCap which allows web-based data entry, has edit checks, audit trails, controlled access, and undergoes frequent back-up.

9.4.1 Data Security and Confidentiality

All clinical data will be processed in a secure electronic environment that includes virus protection, and restricted access. Electronically stored data are subject to extensive security measures including virus detection, and restricted access. Security measures in place for the database management system proposed for this study include: browser security, firewall protection, username/password protection, user re-authentication, and inactivity time-out.

9.4.2 Data Quality Assurance

Quality control will take place at time of data entry (range, consistency checks) and will be ensured by oversight by the P.I. Before the enrollment of any subject in this study, designated study personnel will review with the investigator and personnel the following documents: protocol, Investigator's Brochure,

eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs. Information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered, safety information will be reviewed for completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Mayo Clinic agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol and accepted standards of Good Clinical Practice.

9.4.3 Data Clarification Process

Data queries generated by identification of incomplete or inconsistent data will be raised directly within the electronic eCRF and should be resolved by the study coordinator or PI in a timely manner. Corrections or changes in the data management system are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel.

9.4.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for:

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual – "Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717, whichever is longer.

10. Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes

any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

11. STUDY FINANCES

11.1 Funding Source

This study is funded by Genentech Inc.

12. PUBLICATION PLAN

A policy similar to the NIH policy on publication of study results will apply to this study. Details regarding policy statements may be found on the website at http://www1.od.nih.gov/oma/manualchapters.

The PI will hold the primary responsibility for publication of the results of the study. The study will be registered at ClinicalTrials.gov and results will be posted within 12 months of final data collection for the primary outcome.

13. Safety Reporting Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX

COVER SHEET Genentech

Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials
Enter a dash if patient has no middle name)
[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

14. REFERENCES

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