

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:
BLA 103705 / S-5344

Trade Name: Rituxan

Generic Name: Rituximab

Sponsor: Genentech, Inc.

Approval Date: April 19, 2011

Indications: This prior approval efficacy supplement provides for the use of Rituxan in combination with glucocorticoids for the treatment of patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA).

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APPROVAL LETTER



BLA 103705/5344

SUPPLEMENT BLA APPROVAL

DATE: April 19, 2011

Genentech, Inc.
1 DNA Way MS#241B
South San Francisco, CA 94080-4990

Attention: Yasameen Qazen, Manager
Regulatory Affairs

Dear Ms. Qazen:

Please refer to your Supplemental Biologics License Application (sBLA), dated October 15, 2010, received October 18, 2010, submitted under section 351 of the Public Health Service Act for Rituxan (rituximab).

We acknowledge receipt of your amendments dated January 12, February 10 and 11, March 24 and 25, and April 8, 11, 14, and 15, 2011.

This Prior Approval efficacy supplement to your biologics license application provides for the use of Rituxan in combination with glucocorticoids for the treatment of patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry

titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved BLA STN 103705/5344.**”

Also within 14 days, amend all pending supplemental applications for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 15, 2010, submission containing final printed carton labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known risks of infusion reactions and infections and identify unexpected serious risks related to long-term treatment with Rituxan (rituximab) or repeat courses of Rituxan in patients with Wegener’s Granulomatosis and Microscopic Polyangiitis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1 Conduct a prospective, observational registry study of 100 rituximab-treated patients with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) followed for 4 years to evaluate long term safety and retreatment with rituximab or other therapies.

The timetable you submitted on April 11, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 2011
Study Completion:	March 2018
Final Report Submission:	March 2019

Submit the protocol to your IND 11831, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

/Badrul A. Chowdhury/
Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton Labeling

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Rituxan safely and effectively. See full prescribing information for Rituxan.

Rituxan (rituximab)
Injection for Intravenous Use
Initial U.S. Approval: 1997

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

See full prescribing information for complete boxed warning.

- Fatal infusion reactions within 24 hours of Rituxan infusion occur; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).
- Tumor lysis syndrome (5.2).
- Severe mucocutaneous reactions, some with fatal outcomes (5.3).
- PML resulting in death (5.4).

RECENT MAJOR CHANGES

Indications and Usage, NHL (1.1)	01/2011
Indications and Usage, WG and MPA (1.4)	04/2011
Dosage and Administration, NHL (2.2)	01/2011
Dosage and Administration, WG and MPA (2.6)	04/2011
Dosage and Administration, Recommended Concomitant Medications (2.7)	04/2011
Warnings and Precautions, HBV Reactivation (5.5)	01/2011
Warnings and Precautions, Concomitant Use with Biologic Agents and DMARDs other than Methotrexate in RA, WG and MPA (5.12)	04/2011
Warnings and Precautions, Retreatment in Patients with WG and MPA (5.14)	04/2011

INDICATIONS AND USAGE

Rituxan is a CD20-directed cytolytic antibody indicated for the treatment of patients with:

- Non-Hodgkin's Lymphoma (NHL) (1.1)
- Chronic Lymphocytic Leukemia (CLL) (1.2)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3)
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4)

Limitations of Use: Rituxan is not recommended for use in patients with severe, active infections (1.5).

DOSAGE AND ADMINISTRATION

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- The dose for NHL is 375 mg/m² (2.2).
- The dose for CLL is 375 mg/m² in the first cycle and 500 mg/m² in cycles 2–6, in combination with FC, administered every 28 days (2.3).
- The dose as a component of Zevalin® (Ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m² (2.4).
- The dose for RA in combination with methotrexate is two-1000 mg IV infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.5).
- The dose for WG and MPA in combination with glucocorticoids is 375 mg/m² once weekly for 4 weeks (2.6).

DOSAGE FORMS AND STRENGTHS

- 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial (3).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Tumor lysis syndrome - administer aggressive intravenous hydration, anti-hyperuricemic agents, and monitor renal function (5.2).
- PML - monitor neurologic function. Discontinue Rituxan (5.4).
- Hepatitis B reactivation with fulminant hepatitis, sometimes fatal - screen high risk patients and monitor HBV carriers during and several months after therapy. Discontinue Rituxan if reactivation occurs (5.5).
- Infections - withhold Rituxan and institute appropriate anti-infective therapy (5.6).
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor patients with these conditions closely (5.7).
- Bowel obstruction and perforation - evaluate complaints of abdominal pain (5.9).
- Do not administer live virus vaccines prior to or during Rituxan (5.10).
- Monitor CBC at regular intervals for severe cytopenias (5.11, 6.1).

ADVERSE REACTIONS

- Lymphoid Malignancies: Common adverse reactions (≥25%) in clinical trials of NHL were: infusion reactions, fever, lymphopenia, chills, infection and asthenia. Common adverse reactions (≥25%) in clinical trials of CLL were: infusion reactions and neutropenia (6.1).
- Rheumatoid Arthritis (RA): Common adverse reactions (≥10%) in clinical trials: upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (6.2). Other important adverse reactions include infusion reactions, serious infections, and cardiovascular events (6.2).
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA): Common adverse reactions (≥15%) in the clinical study were infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema (6.3). Other important adverse reactions include infusion reactions (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Renal toxicity when used in combination with cisplatin (5.8).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Limited human data; B-cell lymphocytopenia occurred in infants exposed in utero (8.1).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).
- Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of Rituxan to FC (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

1 INDICATIONS AND USAGE

- 1.1 Non-Hodgkin's Lymphoma (NHL)
- 1.2 Chronic Lymphocytic Leukemia (CLL)
- 1.3 Rheumatoid Arthritis (RA)
- 1.4 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
- 1.5 Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Administration
- 2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)
- 2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)
- 2.4 Recommended Dose as a Component of Zevalin®
- 2.5 Recommended Dose for Rheumatoid Arthritis (RA)
- 2.6 Recommended Dose for Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
- 2.7 Recommended Concomitant Medications
- 2.8 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

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5 WARNINGS AND PRECAUTIONS

- 5.1 Infusion Reactions
- 5.2 Tumor Lysis Syndrome (TLS)
- 5.3 Severe Mucocutaneous Reactions
- 5.4 Progressive Multifocal Leukoencephalopathy (PML)
- 5.5 Hepatitis B Virus (HBV) Reactivation
- 5.6 Infections
- 5.7 Cardiovascular
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- 5.9 Bowel Obstruction and Perforation
- 5.10 Immunization
- 5.11 Laboratory Monitoring
- 5.12 Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA, WG and MPA
- 5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

- 5.14 Retreatment in Patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience in Lymphoid Malignancies
- 6.2 Clinical Trials Experience Rheumatoid Arthritis
- 6.3 Clinical Trials Experience in Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
- 6.4 Immunogenicity
- 6.5 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

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11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
- 14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
- 14.3 Diffuse Large B-Cell NHL (DLBCL)
- 14.4 Chronic Lymphocytic Leukemia (CLL)
- 14.5 Rheumatoid Arthritis (RA)
- 14.6 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS),**
3 **SEVERE MUCOCUTANEOUS REACTIONS, and**
4 **PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)**

5 **Infusion Reactions**

6 **Rituxan administration can result in serious, including fatal infusion reactions. Deaths**
7 **within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion**
8 **reactions occurred in association with the first infusion. Carefully monitor patients during**
9 **infusions. Discontinue Rituxan infusion and provide medical treatment for Grade 3 or 4**
10 **infusion reactions [see *Warnings and Precautions (5.1), Adverse Reactions (6.1)*].**

11 **Tumor Lysis Syndrome (TLS)**

12 **Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting**
13 **of TLS following treatment of non-Hodgkin's lymphoma (NHL) with Rituxan monotherapy**
14 **[see *Warnings and Precautions (5.2), Adverse Reactions (6)*].**

15 **Severe Mucocutaneous Reactions**

16 **Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan**
17 **[see *Warnings and Precautions (5.3), Adverse Reactions (6)*].**

18 **Progressive Multifocal Leukoencephalopathy (PML)**

19 **JC virus infection resulting in PML and death can occur in patients receiving Rituxan [see**
20 ***Warnings and Precautions (5.4), Adverse Reactions (6)*].**

21 **1 INDICATIONS AND USAGE**

22 **1.1 Non-Hodgkin's Lymphoma (NHL)**

23 Rituxan[®] (rituximab) is indicated for the treatment of patients with:

- 24 • Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- 25 • Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line
- 26 chemotherapy and, in patients achieving a complete or partial response to Rituxan in
- 27 combination with chemotherapy, as single-agent maintenance therapy.
- 28 • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single
- 29 agent after first-line CVP chemotherapy
- 30 • Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or
- 31 other anthracycline-based chemotherapy regimens

32 **1.2 Chronic Lymphocytic Leukemia (CLL)**

33 Rituxan[®] (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC),
34 for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

35 **1.3 Rheumatoid Arthritis (RA)**

36 Rituxan[®] (rituximab) in combination with methotrexate is indicated for the treatment of adult
37 patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate
38 response to one or more TNF antagonist therapies.

39 **1.4 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)**

40 Rituxan[®] (rituximab), in combination with glucocorticoids, is indicated for the treatment of adult
41 patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA).

42 **1.5 Limitations of Use**

43 Rituxan is not recommended for use in patients with severe, active infections.

44 **2 DOSAGE AND ADMINISTRATION**

45 **2.1 Administration**

46 **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**

47 Premedicate before each infusion [*see Dosage and Administration (2.7)*]. Administer only as an
48 intravenous (IV) infusion [*see Dosage and Administration (2.7)*].

- 49 • **First Infusion:** Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity,
50 increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- 51 • **Subsequent Infusions:** Initiate infusion at a rate of 100 mg/hr. In the absence of infusion
52 toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of
53 400 mg/hr.
- 54 • Interrupt the infusion or slow the infusion rate for infusion reactions [*see Boxed Warning,*
55 *Warnings and Precautions (5.1)*]. Continue the infusion at one-half the previous rate upon
56 improvement of symptoms.

57 2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

58 The recommended dose is 375 mg/m² as an intravenous infusion according to the following
59 schedules:

- 60 • **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
61 Administer once weekly for 4 or 8 doses.
- 62 • **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive,**
63 **B-Cell NHL**
64 Administer once weekly for 4 doses.
- 65 • **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**
66 Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with
67 complete or partial response, initiate Rituxan maintenance eight weeks following completion
68 of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8
69 weeks for 12 doses.
- 70 • **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP**
71 **chemotherapy**
72 Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for
73 4 doses at 6-month intervals to a maximum of 16 doses.
- 74 • **Diffuse Large B-Cell NHL**
75 Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

76 2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

77 The recommended dose is:

- 78 • 375 mg/m² the day prior to the initiation of FC chemotherapy, then 500 mg/m² on Day 1 of
79 cycles 2–6 (every 28 days).

80 2.4 Recommended Dose as a Component of Zevalin[®]

- 81 • Infuse rituximab 250 mg/m² within 4 hours prior to the administration of
82 Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of
83 Yttrium-90- (Y-90-) Zevalin.
- 84 • Administer Rituxan and In-111-Zevalin 7–9 days prior to Rituxan and Y-90- Zevalin.
- 85 • Refer to the Zevalin package insert for full prescribing information regarding the Zevalin
86 therapeutic regimen.

87 2.5 Recommended Dose for Rheumatoid Arthritis (RA)

- 88 • Administer Rituxan as two-1000 mg intravenous infusions separated by 2 weeks.
- 89 • Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent
90 30 minutes prior to each infusion are recommended to reduce the incidence and severity of
91 infusion reactions.
- 92 • Subsequent courses should be administered every 24 weeks or based on clinical evaluation,
93 but not sooner than every 16 weeks.
- 94 • Rituxan is given in combination with methotrexate.

95 **2.6 Recommended Dose for Wegener's Granulomatosis (WG) and Microscopic Polyangiitis**
96 **(MPA)**

- 97 • Administer Rituxan as a 375 mg/m² intravenous infusion once weekly for 4 weeks.
98 • Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3
99 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per
100 clinical need) are recommended to treat severe vasculitis symptoms. This regimen should
101 begin within 14 days prior to or with the initiation of Rituxan and may continue during and
102 after the 4 week course of Rituximab treatment.
103 • Safety and efficacy of treatment with subsequent courses of Rituxan have not been established
104 [*see Warnings and Precautions (5.14)*].

105 **2.7 Recommended Concomitant Medications**

106 Premedicate before each infusion with acetaminophen and an antihistamine.

107 For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30
108 minutes prior to each infusion.

109 For WG and MPA patients, glucocorticoids are given in combination with Rituxan [*see Dosage*
110 *and Administration (2.6)*].

111 Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for
112 patients with CLL during treatment and for up to 12 months following treatment as appropriate.

113 PCP prophylaxis is also recommended for patients with WG and MPA during treatment and for at
114 least 6 months following the last Rituxan infusion

115 **2.8 Preparation for Administration**

116 Use appropriate aseptic technique. Parenteral drug products should be inspected visually for
117 particulate matter and discoloration prior to administration. Do not use vial if particulates or
118 discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final
119 concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or
120 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with
121 other drugs. Discard any unused portion left in the vial.

122 **3 DOSAGE FORMS AND STRENGTHS**

123 100 mg/10 mL single-use vial

124 500 mg/50 mL single-use vial

125 **4 CONTRAINDICATIONS**

126 None.

127 **5 WARNINGS AND PRECAUTIONS**

128 **5.1 Infusion Reactions**

129 Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred
130 during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions
131 and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary
132 infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation,
133 cardiogenic shock, anaphylactoid events, or death.

134 Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients,
135 methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each
136 infusion. Institute medical management (e.g glucocorticoids, epinephrine, bronchodilators, or
137 oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the
138 required interventions, temporarily or permanently discontinue Rituxan. Resume infusion at a
139 minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following
140 patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior
141 cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells
142 ($\geq 25,000/\text{mm}^3$). [*See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1)*].

143 **5.2 Tumor Lysis Syndrome (TLS)**

144 Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from
145 tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of Rituxan in patients
146 with NHL. A high number of circulating malignant cells ($\geq 25,000/\text{mm}^3$) or high tumor burden,
147 confers a greater risk of TLS.

148 Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high
149 risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and
150 administer supportive care, including dialysis as indicated. [See *Boxed Warning, Warnings and*
151 *Precautions (5.8).*]

152 **5.3 Severe Mucocutaneous Reactions**

153 Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan.
154 These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis,
155 vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied
156 from 1–13 weeks following Rituxan exposure. Discontinue Rituxan in patients who experience a
157 severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe
158 mucocutaneous reactions has not been determined. [See *Boxed Warning, Adverse Reactions (6, 6.1).*]

159 **5.4 Progressive Multifocal Leukoencephalopathy (PML)**

160 JC virus infection resulting in PML and death can occur in Rituxan-treated patients with
161 hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic
162 malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of
163 a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent
164 immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last
165 infusion of Rituxan.

166 Consider the diagnosis of PML in any patient presenting with new-onset neurologic
167 manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist,
168 brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of
169 any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. [See
170 *Boxed Warning, Adverse Reactions (6).*]

171 **5.5 Hepatitis B Virus (HBV) Reactivation**

172 Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur
173 in patients treated with Rituxan. The median time to the diagnosis of hepatitis among patients with
174 hematologic malignancies was approximately 4 months after the initiation of Rituxan and
175 approximately one month after the last dose.

176 Screen patients at high risk of HBV infection before initiation of Rituxan. Closely monitor
177 carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months
178 following Rituxan therapy. Discontinue Rituxan and any concomitant chemotherapy in patients who
179 develop viral hepatitis, and institute appropriate treatment including antiviral therapy. Insufficient
180 data exist regarding the safety of resuming Rituxan in patients who develop hepatitis subsequent to
181 HBV reactivation. [See *Adverse Reactions (6.5).*]

182 **5.6 Infections**

183 Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during
184 and up to one year following the completion of Rituxan-based therapy. New or reactivated viral
185 infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus,
186 West Nile virus, and hepatitis B and C. Discontinue Rituxan for serious infections and institute
187 appropriate anti-infective therapy. [See *Adverse Reactions (6, 6.1).*]

188 **5.7 Cardiovascular**

189 Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac
190 monitoring during and after all infusions of Rituxan for patients who develop clinically significant
191 arrhythmias, or who have a history of arrhythmia or angina. [See *Adverse Reactions (6).*]

192 **5.8 Renal**

193 Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with NHL.
194 Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with
195 NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin
196 and Rituxan is not an approved treatment regimen. Monitor closely for signs of renal failure and
197 discontinue Rituxan in patients with a rising serum creatinine or oliguria. [*See Warnings and*
198 *Precautions (5.2).*]

199 **5.9 Bowel Obstruction and Perforation**

200 Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in
201 patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean
202 time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL.
203 Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of
204 abdominal pain. [*See Adverse Reactions (6).*]

205 **5.10 Immunization**

206 The safety of immunization with live viral vaccines following Rituxan therapy has not been
207 studied and vaccination with live virus vaccines is not recommended.

208 For RA patients, physicians should follow current immunization guidelines and administer
209 non-live vaccines at least 4 weeks prior to a course of Rituxan.

210 The effect of Rituxan on immune responses was assessed in a randomized, controlled study in
211 patients with RA treated with Rituxan and methotrexate (MTX) compared to patients treated with
212 MTX alone.

213 A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an
214 increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituxan
215 plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of
216 patients in the Rituxan plus MTX group developed detectable levels of anti-keyhole limpet
217 hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX
218 alone (47% vs. 93%).

219 A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity)
220 was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs.
221 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type
222 hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on
223 MTX alone).

224 Most patients in the Rituxan-treated group had B-cell counts below the lower limit of normal at
225 the time of immunization. The clinical implications of these findings are not known.

226 **5.11 Laboratory Monitoring**

227 In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain
228 complete blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment
229 with Rituxan and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and
230 more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. In patients with
231 RA, WG or MPA, obtain CBC and platelet counts at two to four month intervals during Rituxan
232 therapy. The duration of cytopenias caused by Rituxan can extend months beyond the treatment
233 period.

234 **5.12 Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA,
235 WG and MPA**

236 Limited data are available on the safety of the use of biologic agents or DMARDS other than
237 methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with
238 rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDS are
239 used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not
240 been studied in WG or MPA patients exhibiting peripheral B-cell depletion following treatment with
241 Rituxan.

242 **5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis**
243 **Factor (TNF) Antagonists**

244 While the efficacy of Rituxan was supported in four controlled trials in patients with RA with
245 prior inadequate responses to non-biologic DMARDs, and in a controlled trial in MTX-naïve
246 patients, a favorable risk-benefit relationship has not been established in these populations. The use
247 of Rituxan in patients with RA who have not had prior inadequate response to one or more TNF
248 antagonists is not recommended [*see Clinical Studies (14.5)*]

249 **5.14 Retreatment in Patients with Wegener's Granulomatosis (WG) and Microscopic**
250 **Polyangiitis (MPA)**

251 Limited data are available on the safety and efficacy of subsequent courses of Rituxan in patients
252 with WG and MPA. The safety and efficacy of retreatment with Rituxan have not been established
253 [*see Dosage and Administration (2.6), Adverse Reactions (6.3), and Clinical Studies (14.6)*].

254 **6 ADVERSE REACTIONS**

255 The following serious adverse reactions are discussed in greater detail in other sections of the
256 labeling:

- 257 • Infusion reactions [*see Warnings and Precautions (5.1)*]
- 258 • Tumor lysis syndrome [*see Warnings and Precautions (5.2)*]
- 259 • Mucocutaneous reactions [*see Warnings and Precautions (5.3)*]
- 260 • Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- 261 • Hepatitis B reactivation with fulminant hepatitis [*see Warnings and Precautions (5.5)*]
- 262 • Infections [*see Warnings and Precautions (5.6)*]
- 263 • Cardiac arrhythmias [*see Warnings and Precautions (5.7)*]
- 264 • Renal toxicity [*see Warnings and Precautions (5.8)*]
- 265 • Bowel obstruction and perforation [*see Warnings and Precautions (5.9)*]

266
267 The most common adverse reactions of Rituxan (incidence $\geq 25\%$) observed in clinical trials of
268 patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

269 The most common adverse reactions of Rituxan (incidence $\geq 25\%$) observed in clinical trials of
270 patients with CLL were: infusion reactions and neutropenia.

271 **6.1 Clinical Trials Experience in Lymphoid Malignancies**

272 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
273 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of
274 another drug and may not reflect the rates observed in practice.

275 The data described below reflect exposure to Rituxan in 2783 patients, with exposures ranging
276 from a single infusion up to 2 years. Rituxan was studied in both single-arm and controlled trials
277 ($n=356$ and $n = 2427=1926$). The population included 1180 patients with low grade or follicular
278 lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received
279 Rituxan as an infusion of 375 mg/m^2 per infusion, given as a single agent weekly for up to 8 doses,
280 in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses.
281 CLL patients received Rituxan 375 mg/m^2 as an initial infusion followed by 500 mg/m^2 for up to
282 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL
283 patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

284 *Infusion Reactions*

285 In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea,
286 pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia,
287 dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically
288 occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or
289 interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and
290 intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%)

291 and decreased with each subsequent infusion. [See *Boxed Warning, Warnings and*
292 *Precautions (5.1).*]

293 *Infections*

294 Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of
295 patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial
296 19%, viral 10%, unknown 6%, and fungal 1%). [See *Warnings and Precautions (5.4), (5.5), (5.6).*]

297 In randomized, controlled studies where Rituxan was administered following chemotherapy for
298 the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who
299 received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more
300 frequently in those who received Rituxan.

301 *Cytopenias and hypogammaglobulinemia*

302 In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were
303 reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia
304 (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days
305 (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of
306 transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following
307 Rituxan therapy occurred during the single-arm studies.

308 In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients
309 with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

310 *Relapsed or Refractory, Low-Grade NHL*

311 Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or
312 follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a
313 single agent [see *Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m² weekly for
314 4 doses.

Table 1
 Incidence of Adverse Reactions in $\geq 5\%$ of
 Patients with Relapsed or Refractory, Low-Grade or Follicular
 NHL, Receiving Single-agent Rituxan (N=356)^{a,b}

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
<u>Body as a Whole</u>	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
<u>Heme and Lymphatic System</u>	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
<u>Skin and Appendages</u>	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
<u>Respiratory System</u>	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
<u>Metabolic and Nutritional Disorders</u>	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
<u>Digestive System</u>	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
<u>Nervous System</u>	32	1
Dizziness	10	1
Anxiety	5	1
<u>Musculoskeletal System</u>	26	3
Myalgia	10	1
Arthralgia	10	1

Table 1 (cont'd)
 Incidence of Adverse Reactions in $\geq 5\%$ of
 Patients with Relapsed or Refractory, Low-Grade or Follicular
 NHL, Receiving Single-agent Rituxan (N=356)^{a,b}

	All Grades (%)	Grade 3 and 4 (%)
<u>Cardiovascular System</u>	25	3
Hypotension	10	1
Hypertension	6	1

^a Adverse reactions observed up to 12 months following Rituxan.

^b Adverse reactions graded for severity by NCI-CTC criteria.

316

317 In these single-arm Rituxan studies, bronchiolitis obliterans occurred during and up to 6 months
 318 after Rituxan infusion.

319 *Previously Untreated, Low-Grade or Follicular, NHL*

320 In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and
 321 neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more
 322 frequently ($\geq 5\%$) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough
 323 (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8%
 324 vs. 3%), and chest tightness (7% vs. 1%). [See *Clinical Studies (14.2)*.]

325 In Study 5, detailed safety data collection was limited to serious adverse reactions, Grade ≥ 2
 326 infections, and Grade ≥ 3 adverse reactions. In patients receiving Rituxan as single-agent
 327 maintenance therapy following Rituxan plus chemotherapy, infections were reported more
 328 frequently compared to the observation arm (37% vs. 22%). Grade 3-4 adverse reactions occurring
 329 at a higher incidence ($\geq 2\%$) in the Rituxan group were infections (4% vs. 1%) and neutropenia (4%
 330 vs. $<1\%$).

331 In Study 6, the following adverse reactions were reported more frequently ($\geq 5\%$) in patients
 332 receiving Rituxan following CVP compared to patients who received no further therapy: fatigue
 333 (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections
 334 (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or
 335 pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the
 336 only Grade 3 or 4 adverse reaction that occurred more frequently ($\geq 2\%$) in the Rituxan arm
 337 compared with those who received no further therapy (4% vs. 1%). [See *Clinical Studies (14.3)*.]

338 *DLBCL*

339 In Studies 7 and 8, [see *Clinical Studies (14.3)*], the following adverse reactions, regardless of
 340 severity, were reported more frequently ($\geq 5\%$) in patients age ≥ 60 years receiving R-CHOP as
 341 compared to CHOP alone; pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder
 342 (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was
 343 primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

344 In Study 8, a review of cardiac toxicity determined that supraventricular arrhythmias or
 345 tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0%
 346 for CHOP).

347 The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the
 348 R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung
 349 disorder (6% vs. 3%). Other Grade 3 or 4 adverse reactions occurring more frequently among
 350 patients receiving R-CHOP were viral infection (Study 8), neutropenia (Studies 8 and 9), and anemia
 351 (Study 9).

352 CLL

353 The data below reflect exposure to Rituxan in combination with fludarabine and
354 cyclophosphamide in 676 patients with CLL in Study 10 or Study 11 [see *Clinical Studies (14.4)*].
355 The age range was 30–83 years and 71% were men. Detailed safety data collection in Study 10 was
356 limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

357 Infusion-related adverse reactions were defined by any of the following adverse events occurring
358 during or within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and
359 dyspnea.

360 In Study 10, the following Grade 3 and 4 adverse reactions occurred more frequently in
361 R-FC-treated patients compared to FC-treated patients: infusion reactions (9% in R-FC arm),
362 neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and
363 pancytopenia (3% vs. 1%).

364 In Study 11, the following Grade 3 or 4 adverse reactions occurred more frequently in
365 R-FC-treated patients compared to FC-treated patients: infusion reactions (7% in R-FC arm),
366 neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%),
367 hypotension (2% vs. 0%), and hepatitis B (2% vs. <1%). Fifty-nine percent of R-FC-treated patients
368 experienced an infusion reaction of any severity.

369 **6.2 Clinical Trials Experience in Rheumatoid Arthritis**

370 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
371 observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of
372 another drug and may not reflect the rates observed in practice.

373 The data presented below reflect the experience in 2578 RA patients treated with Rituxan in
374 controlled and long-term studies with a total exposure of 5014 patient-years.

375 Among all exposed patients, adverse reactions reported in greater than 10% of patients include
376 infusion-related reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection,
377 and bronchitis.

378 In placebo-controlled studies, patients received 2 x 500 mg or 2 x 1000 mg intravenous infusions
379 of Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these
380 studies, 938 patients treated with Rituxan (2 x 1000 mg) or placebo have been pooled (see Table 2).
381 Adverse reactions reported in $\geq 5\%$ of patients were hypertension, nausea, upper respiratory tract
382 infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in
383 patients who received Rituxan 2 x 500 mg were similar to those observed in patients who received
384 Rituxan 2 x 1000 mg.

Table 2*

Incidence of All Adverse Reactions** Occurring in $\geq 2\%$
and at Least 1% Greater than Placebo Among Rheumatoid
Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo+MTX N=398 n (%)	Rituxan+MTX N=540 n (%)
Hypertension	21 (5)	43 (8)
Nausea	19 (5)	41 (8)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Arthralgia	14 (4)	31 (6)
Pyrexia	8 (2)	27 (5)
Pruritus	5 (1)	26 (5)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Rhinitis	6 (2)	14 (3)
Paresthesia	3 (<1)	12 (2)
Urticaria	3 (<1)	12 (2)
Abdominal Pain Upper	4 (1)	11 (2)
Throat Irritation	0 (0)	11 (2)
Anxiety	5 (1)	9 (2)
Migraine	2 (<1)	9 (2)
Asthenia	1 (<1)	9 (2)

*These data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 \times 1000 mg) or placebo administered in combination with methotrexate.

**Coded using MedDRA.

385

386 *Infusion Reactions*

387 In the Rituxan RA pooled placebo-controlled studies, 32% of Rituxan-treated patients experienced
388 an adverse reaction during or within 24 hours following their first infusion, compared to 23% of
389 placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the
390 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%,
391 respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash,
392 angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated
393 hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their
394 first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion.
395 The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo
396 decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1%
397 of patients in either treatment group. Acute infusion reactions required dose modification (stopping,
398 slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo,
399 respectively, after the first course. The proportion of patients experiencing acute infusion reactions
400 decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids
401 prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was
402 no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion

403 reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to
404 Rituxan infusions.

405 *Infections*

406 In the pooled, placebo-controlled studies, 39% of patients in the Rituxan group experienced an
407 infection of any type compared to 34% of patients in the placebo group. The most common
408 infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections,
409 bronchitis, and sinusitis.

410 The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo
411 group.

412 In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per
413 100 patient years. The most common serious infections ($\geq 0.5\%$) were pneumonia or lower
414 respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included
415 pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving
416 subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment
417 with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the
418 rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per
419 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per
420 100 patient years) after exposure.

421 *Cardiac Adverse Reactions*

422 In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular
423 reactions was 1.7% and 1.3% in the Rituxan and placebo treatment groups, respectively. Three
424 cardiovascular deaths occurred during the double-blind period of the RA studies including all
425 rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

426 In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was
427 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years
428 (28 events in 26 patients), which is consistent with MI rates in the general RA population. These
429 rates did not increase over three courses of Rituxan.

430 Since patients with RA are at increased risk for cardiovascular events compared with the general
431 population, patients with RA should be monitored throughout the infusion and Rituxan should be
432 discontinued in the event of a serious or life-threatening cardiac event.

433 *Hypophosphatemia and hyperuricemia*

434 In the pooled, placebo-controlled studies, newly-occurring hypophosphatemia (< 2.0 mg/dl) was
435 observed in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo.
436 Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring
437 hyperuricemia (> 10 mg/dl) was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398)
438 of patients on placebo.

439 In the experience with Rituxan in RA patients, newly-occurring hypophosphatemia was observed
440 in 21% (528/2570) of patients and newly-occurring hyperuricemia was observed in 2% (56/2570) of
441 patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and
442 was transient.

443 *Retreatment in Patients with RA*

444 In the experience with Rituxan in RA patients, 2578 patients have been exposed to Rituxan and
445 have received up to 10 courses of Rituxan in RA clinical trials, with 1890, 1043, and 425 patients
446 having received at least two, three, and four courses, respectively. Most of the patients who received
447 additional courses did so 24 weeks or more after the previous course and none were retreated sooner
448 than 16 weeks. The rates and types of adverse reactions reported for subsequent courses of Rituxan
449 were similar to rates and types seen for a single course of Rituxan.

450 In RA Study 2, where all patients initially received Rituxan, the safety profile of patients who
451 were retreated with Rituxan was similar to those who were retreated with placebo [*see Clinical*
452 *Studies (14.5), and Dosage and Administration (2.5).*]

453 **6.3 Clinical Trial Experience in Wegener's Granulomatosis (WG) and Microscopic** 454 **Polyangiitis (MPA)**

455 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
456 observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of
457 another drug and may not reflect the rates observed in practice.

458 The data presented below reflect the experience in 197 patients with WG and MPA treated with
459 Rituxan or cyclophosphamide in a single controlled study, which was conducted in two phases: a
460 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and
461 an additional 12 month remission maintenance phase. In the 6-month remission induction phase,
462 197 patients with WG and MPA were randomized to either Rituxan 375 mg/ m² once weekly for
463 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function,
464 white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission
465 was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group
466 received azathioprine to maintain remission. The Rituxan group did not receive additional therapy
467 to maintain remission. The primary analysis was at the end of the 6 month remission induction
468 period and the safety results for this period are described below.

469 Adverse reactions presented below in Table 3 were adverse events which occurred at a rate of
470 greater than or equal to 10% in the Rituxan group. This table reflects experience in 99 WG and
471 MPA patients treated with Rituxan, with a total of 47.6 patient-years of observation and 98 WG and
472 MPA patients treated with cyclophosphamide, with a total of 47.0 patient-years of observation.
473 Infection was the most common category of adverse events reported (47-62%) and is discussed
474 below.

Table 3
 Incidence of All Adverse Reactions
 Occurring in $\geq 10\%$ of Rituxan-treated WG and MPA Patients
 in the Clinical Study Up to Month 6*

Preferred Term	Rituxan N=99 n (%)	Cyclophosphamide N=98 n (%)
Nausea	18 (18%)	20 (20%)
Diarrhea	17 (17%)	12 (12%)
Headache	17 (17%)	19 (19%)
Muscle spasms	17 (17%)	15 (15%)
Anemia	16 (16%)	20 (20%)
Peripheral edema	16 (16%)	6 (6%)
Insomnia	14 (14%)	12 (12%)
Arthralgia	13 (13%)	9 (9%)
Cough	13 (13%)	11 (11%)
Fatigue	13 (13%)	21 (21%)
Increased ALT	13 (13%)	15 (15%)
Hypertension	12 (12%)	5 (5%)
Epistaxis	11 (11%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Leukopenia	10 (10%)	26 (27%)
Rash	10 (10%)	17 (17%)

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

475

476 *Infusion Reactions*

477 Infusion-related reactions in the active-controlled, double-blind study were defined as any adverse
 478 event occurring within 24 hours of an infusion and considered to be infusion-related by
 479 investigators. Among the 99 patients treated with Rituxan, 12% experienced at least one infusion
 480 related reaction, compared with 11% of the 98 patients in the cyclophosphamide group.
 481 Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor.
 482 In the Rituxan group, the proportion of patients experiencing an infusion related reaction was 12%,
 483 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were
 484 pre-medicated with antihistamine and acetaminophen before each Rituxan infusion and were on
 485 background oral corticosteroids which may have mitigated or masked an infusion reaction; however,
 486 there is insufficient evidence to determine whether premedication diminishes the frequency or
 487 severity of infusion reactions.

488 *Infections*

489 In the active-controlled, double-blind study, 62% (61/99) of patients in the Rituxan group
 490 experienced an infection of any type compared to 47% (46/98) patients in the cyclophosphamide
 491 group by Month 6. The most common infections in the Rituxan group were upper respiratory tract
 492 infections, urinary tract infections, and herpes zoster.

493 The incidence of serious infections was 11% in the Rituxan-treated patients and 10% in the
494 cyclophosphamide treated patients, with rates of approximately 25 and 28 per 100 patient-years,
495 respectively. The most common serious infection was pneumonia.

496 *Retreatment in Patients with WG and MPA*

497 In the active-controlled, double-blind study, subsequent courses of Rituxan were allowed for
498 patients experiencing a relapse of disease. The limited data preclude any conclusions regarding the
499 safety of subsequent courses of Rituxan with WG and MPA [*see Dosage and Administration (2.6),*
500 *and Warnings and Precautions (5.14)*].

501 **6.4 Immunogenicity**

502 As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence
503 of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several
504 factors including assay sensitivity and specificity, assay methodology, sample handling, timing of
505 sample collection, concomitant medications, and underlying disease. For these reasons, comparison
506 of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be
507 misleading.

508 Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of
509 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the
510 four patients had an objective clinical response.

511 A total of 273/2578 (11%) patients with RA tested positive for HACA at any time after receiving
512 Rituxan. HACA positivity was not associated with increased infusion reactions or other adverse
513 reactions. Upon further treatment, the proportions of patients with infusion reactions were similar
514 between HACA positive and negative patients, and most reactions were mild to moderate. Four
515 HACA positive patients had serious infusion reactions, and the temporal relationship between
516 HACA positivity and infusion reaction was variable.

517 A total of 23/99 (23%) Rituxan-treated patients with WG and MPA tested positive for HACA by
518 18 months. The clinical relevance of HACA formation in Rituxan-treated patients is unclear.

519 **6.5 Postmarketing Experience**

520 Because these reactions are reported voluntarily from a population of uncertain size, it is not
521 always possible to reliably estimate their frequency or establish a causal relationship to drug
522 exposure. Decisions to include these reactions in labeling are typically based on one or more of the
523 following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal
524 connection to Rituxan.

- 525 • Hematologic: prolonged pancytopenia, marrow hypoplasia, and late-onset neutropenia,
526 hyperviscosity syndrome in Waldenstrom's macroglobulinemia.
- 527 • Cardiac: fatal cardiac failure.
- 528 • Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like
529 syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- 530 • Infection: viral infections, including progressive multifocal leukoencephalopathy (PML),
531 increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence
532 of Grade 3 and 4 infections in patients with previously treated lymphoma without known HIV
533 infection.
- 534 • Neoplasia: disease progression of Kaposi's sarcoma.
- 535 • Skin: severe mucocutaneous reactions.
- 536 • Gastrointestinal: bowel obstruction and perforation.
- 537 • Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.
- 538 • Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible
539 Posterior Leukoencephalopathy Syndrome (RPLS).

540 **7 DRUG INTERACTIONS**

541 Formal drug interaction studies have not been performed with Rituxan. In patients with CLL,
542 Rituxan did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of
543 patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the
544 pharmacokinetics of rituximab.

545 **8 USE IN SPECIFIC POPULATIONS**

546 **8.1 Pregnancy**

547 Category C: There are no adequate and well-controlled studies of rituximab in pregnant women.
548 Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can
549 occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of
550 infants exposed in-utero.

551 Non-Hodgkin's lymphoma, moderate-severe rheumatoid arthritis, Wegener's Granulomatosis and
552 Microscopic Polyangiitis are serious conditions that require treatment. Rituximab should be used
553 during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
554 Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic
555 exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced
556 in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic
557 function was restored within 6 months of birth [*See Non-Clinical Toxicology (13.2)*].

558 **8.3 Nursing Mothers**

559 It is not known whether Rituxan is secreted into human milk. However, Rituxan is secreted in the
560 milk of lactating cynomolgus monkeys, and IgG is excreted in human milk. Published data suggest
561 that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.
562 The unknown risks to the infant from oral ingestion of Rituxan should be weighed against the known
563 benefits of breastfeeding.

564 **8.4 Pediatric Use**

565 FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients
566 ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of
567 B-cell depletion in the developing juvenile immune system.

568 The safety and effectiveness of Rituxan in pediatric patients have not been established.

569 **8.5 Geriatric Use**

570 *Diffuse Large B-Cell NHL*

571 Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients
572 received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater
573 and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed
574 between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular
575 arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions
576 were also more common among the elderly, including pneumonia and pneumonitis.

577 *Low-Grade or Follicular Non-Hodgkin's Lymphoma*

578 Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to
579 Rituxan as single-agent maintenance therapy (n = 505) or observation (n = 513) after achieving a
580 response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan
581 arm were age 65 or older. No overall differences in safety or effectiveness were observed between
582 these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular,
583 CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to
584 determine whether they respond differently from younger subjects.

585 *Chronic Lymphocytic Leukemia*

586 Among patients with CLL evaluated in two randomized active-controlled trials, 243 of
587 676 Rituxan-treated patients (36%) were 65 years of age or older; of these, 100 Rituxan-treated
588 patients (15%) were 70 years of age or older.

589 In exploratory analyses defined by age, there was no observed benefit from the addition of
590 Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 10 or
591 in Study 11; there was also no observed benefit from the addition of Rituxan to fludarabine and
592 cyclophosphamide among patients 65 years of age or older in Study 11 [see *Clinical Studies (14.4)*].
593 Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide
594 compared to younger patients, regardless of the addition of Rituxan. In Study 10, the dose intensity
595 of Rituxan was similar in older and younger patients, however in Study 11 older patients received a
596 lower dose intensity of Rituxan.

597 The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who
598 were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 10); 56%
599 vs. 39% (Study 11)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 10);
600 21% vs. 10% (Study 11)], thrombocytopenia [19% vs. 8% (Study 11)], pancytopenia [7% vs. 2%
601 (Study 10); 7% vs. 2% (Study 11)] and infections [30% vs. 14% (Study 11)].

602 *Rheumatoid Arthritis*

603 Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and
604 2% were 75 years old and older. The incidences of adverse reactions were similar between older and
605 younger patients. The rates of serious adverse reactions, including serious infections, malignancies,
606 and cardiovascular events were higher in older patients.

607 *Wegener's Granulomatosis and Microscopic Polyangiitis*

608 Of the 99 Rituxan-treated WG and MPA patients, 36 (36%) were 65 years old and over, while
609 8 (8%) were 75 years and over. No overall differences in efficacy were observed between patients
610 that were 65 years old and over and younger patients. The overall incidence and rate of all serious
611 adverse events was higher in patients 65 years old and over. The clinical study did not include
612 sufficient numbers of patients aged 65 and over to determine whether they respond differently from
613 younger subjects.

614 **10 OVERDOSAGE**

615 There has been no experience with overdosage in human clinical trials. Single doses of up to
616 500 mg/m² have been administered in clinical trials.

617 **11 DESCRIPTION**

618 Rituxan[®] (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG₁ kappa
619 antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of
620 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

621 Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a
622 nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final
623 product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous
624 administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or
625 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium
626 citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL) and Water for Injection. The pH is 6.5.

627 **12 CLINICAL PHARMACOLOGY**

628 **12.1 Mechanism of Action**

629 Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation
630 antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately
631 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on >90% of B-cell
632 non-Hodgkin's lymphomas (NHL), but the antigen is not found on hematopoietic stem cells,
633 pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early step(s) in the
634 activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion
635 channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding.
636 Free CD20 antigen is not found in the circulation.

637 B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated
638 chronic synovitis. In this setting, B cells may be acting at multiple sites in the
639 autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and
640 other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine
641 production.

642 Mechanism of Action: The Fab domain of rituximab binds to the CD20 antigen on B
643 lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*.
644 Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and
645 antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce
646 apoptosis in the DHL-4 human B-cell lymphoma line.

647 Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the
648 thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and
649 lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

650 **12.2 Pharmacodynamics**

651 *Non-Hodgkins Lymphoma (NHL)*

652 In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based
653 B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the
654 first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients.
655 B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by
656 12 months following completion of treatment.

657 There were sustained and statistically significant reductions in both IgM and IgG serum levels
658 observed from 5 through 11 months following rituximab administration; 14% of patients had IgM
659 and/or IgG serum levels below the normal range.

660 *Rheumatoid Arthritis*

661 In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the
662 majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of
663 quantification, 20 cells/ μ l) within 2 weeks after receiving the first dose of Rituxan. The majority of
664 patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients
665 (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of
666 treatment.

667 Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the
668 greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small
669 proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels
670 below the lower limit of normal (LLN). In the experience with Rituxan in RA patients during
671 repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG,
672 and IgA concentrations below LLN at any time after receiving Rituxan, respectively. The clinical
673 consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are
674 unclear.

675 Treatment with rituximab in patients with RA was associated with reduction of certain biologic
676 markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid
677 protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide
678 (anti-CCP), and RF.

679 *Wegener's Granulomatosis and Microscopic Polyangiitis*

680 In WG and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/ μ l
681 following the first two infusions of Rituxan, and remained at that level in most (84%) patients
682 through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with
683 counts >10 cells/ μ L. By Month 18, most patients (87%) had counts >10 cells/ μ L.

684 **12.3 Pharmacokinetics**

685 *Non-Hodgkins Lymphoma (NHL)*

686 Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m² Rituxan weekly
687 by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to
688 6 months after completion of treatment.

689 The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m² in
690 combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

691 Based on a population pharmacokinetic analysis of data from 298 NHL patients who received
692 rituximab once weekly or once every three weeks, the estimated median terminal elimination
693 half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or
694 larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment
695 for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect
696 on the pharmacokinetics of rituximab.

697 Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the
698 recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days
699 (range, 14 to 62 days).

700 *Rheumatoid Arthritis*

701 Following administration of 2 doses of Rituxan in patients with RA, the mean (\pm S.D.; % CV)
702 concentrations after the first infusion (C_{max} first) and second infusion (C_{max} second) were
703 157 (\pm 46; 29%) and 183 (\pm 55; 30%) mcg/mL, and 318 (\pm 86; 27%) and 381 (\pm 98; 26%)
704 mcg/mL for the 2 \times 500 mg and 2 \times 1000 mg doses, respectively.

705 Based on a population pharmacokinetic analysis of data from 2005 RA patients who received
706 Rituxan, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and
707 mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and
708 gender had no effect on the pharmacokinetics of rituximab in RA patients.

709 *Wegener's Granulomatosis and Microscopic Polyangiitis*

710 Based on the population pharmacokinetic analysis of data in 97 WG and MPA patients who
711 received 375 mg/m² rituximab once weekly by intravenous infusion for four weeks, the estimated
712 median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance
713 and volume of distribution were 0.312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21
714 to 7.52 L) respectively. Male patients and patients with higher BSA or positive HACA levels have
715 higher clearance. However, further dose adjustment based on gender or HACA status is not
716 necessary.

717 The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal
718 studies were conducted to examine the effects of either renal or hepatic impairment on the
719 pharmacokinetics of rituximab.

720 **13 NONCLINICAL TOXICOLOGY**

721 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

722 No long-term animal studies have been performed to establish the carcinogenic or mutagenic
723 potential of Rituxan or to determine potential effects on fertility in males or females.

724 **13.2 Animal Toxicology and/or Pharmacology**

725 *Reproductive Toxicology Studies*

726 An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys.
727 Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis
728 period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-
729 coitum (PC) days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36,
730 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure
731 (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the

732 monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased
733 lymphoid tissue B cells.

734 A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was
735 completed to assess developmental effects including the recovery of B cells and immune function in
736 infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75
737 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of
738 pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC
739 Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing
740 of treatment, decreased B cells and immunosuppression were noted in the offspring of
741 rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic
742 function was restored within 6 months postpartum.

743 14 CLINICAL STUDIES

744 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

745 The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in
746 3 single-arm studies enrolling 296 patients.

747 *Study 1*

748 A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or
749 refractory, low-grade or follicular, B-cell NHL who received 375 mg/m² of Rituxan given as an
750 intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with
751 > 5000 lymphocytes/ μ L in the peripheral blood were excluded from the study.

752 Results are summarized in Table 4. The median time to onset of response was 50 days.
753 Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those
754 patients with such symptoms at study entry.

755 *Study 2*

756 In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL
757 received 375 mg/m² of Rituxan weekly for 8 doses. Results are summarized in Table 4.

758 *Study 3*

759 In a multicenter, single-arm study, 60 patients received 375 mg/m² of Rituxan weekly for 4 doses.
760 All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an
761 objective clinical response to Rituxan administered 3.8–35.6 months (median 14.5 months) prior to
762 retreatment with Rituxan. Of these 60 patients, 5 received more than one additional course of
763 Rituxan. Results are summarized in Table 4.

764 *Bulky Disease*

765 In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter)
766 and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m² weekly for 4 doses. Results
767 are summarized in Table 4.
768

Table 4
Summary of Rituxan Efficacy Data by Schedule and Clinical Setting

	Study 1 Weekly×4 N=166	Study 2 Weekly×8 N=37	Study 1 and Study 3 Bulky disease, Weekly×4 N=39 ^a	Study 3 Retreatment, Weekly×4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response ^{b, c} ^d	11.2	13.4	6.9	15.0
(Months) [Range]	[1.9 to 42.1+]	[2.5 to 36.5+]	[2.8 to 25.0+]	[3.0 to 25.1+]

^a Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are provided in this table.

^b Kaplan-Meier projected with observed range.

^c "+" indicates an ongoing response.

^d Duration of response: interval from the onset of response to disease progression.

769

770 **14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**

771 The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+
772 NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

773 *Study 4*

774 A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive
775 up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan
776 375 mg/m² on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome
777 measure of the study was progression-free survival (PFS) defined as the time from randomization to
778 the first of progression, relapse, or death.

779 Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease,
780 and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by
781 a blinded, independent assessment of progression are presented in Table 5. The point estimates may
782 be influenced by the presence of informative censoring. The PFS results based on investigator
783 assessment of progression were similar to those obtained by the independent review assessment.
784

Table 5
Efficacy Results in Study 4

	Study Arm	
	R-CVP N=162	CVP N=160
Median PFS (years) ^a	2.4	1.4
Hazard ratio (95% CI) ^b	0.44 (0.29, 0.65)	

^a p < 0.0001, two-sided stratified log-rank test.

^b Estimates of Cox regression stratified by center.

785

786 *Study 5*

787 An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with
788 previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination
789 with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy,

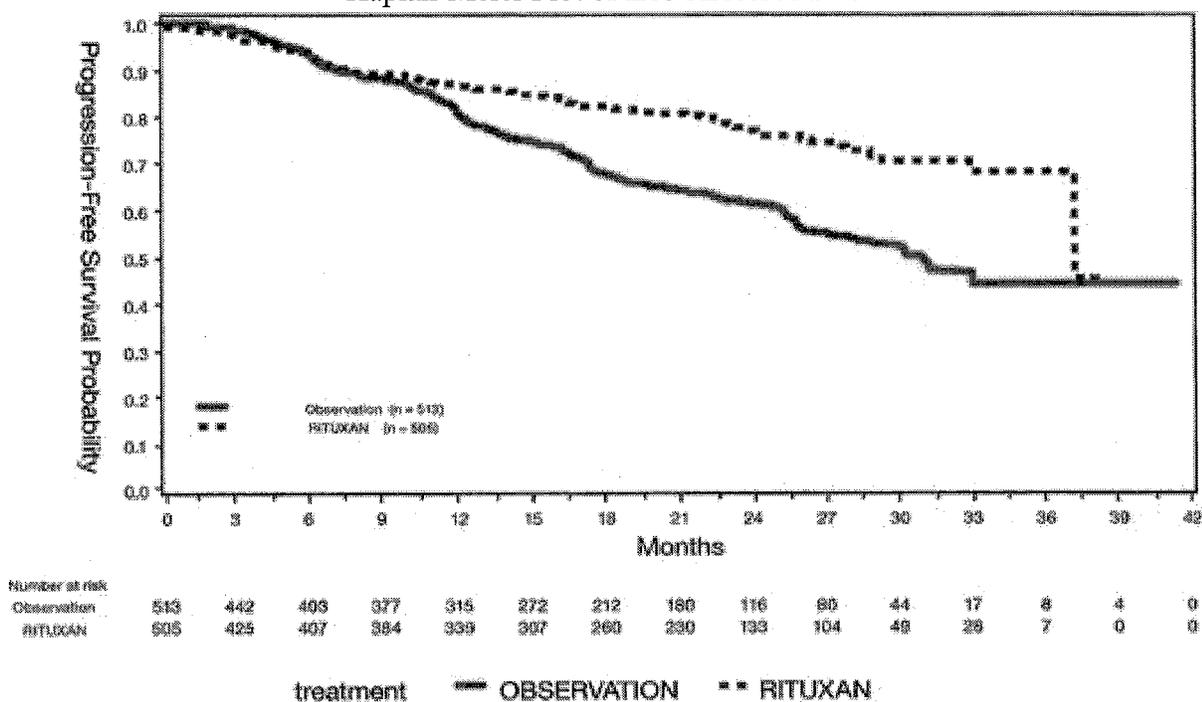
790 375 mg/m² every 8 weeks for up to 12 doses or to observation. Rituxan was initiated at 8 weeks
 791 following completion of chemotherapy. The main outcome measure of the study was
 792 progression-free survival (PFS), defined as the time from randomization in the
 793 maintenance/observation phase to progression, relapse, or death, as determined by independent
 794 review.

795 Of the randomized patients, 40% were ≥60 years of age, 70% had Stage IV disease, 96% had
 796 ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to
 797 maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71%
 798 had a complete or unconfirmed complete response and 28% had a partial response.

799 PFS was longer in patients randomized to Rituxan as single agent maintenance therapy (HR: 0.54,
 800 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar
 801 to those obtained by the independent review assessment.
 802

803
 804

Figure 1
 Kaplan-Meier Plot of IRC Assessed PFS



805
 806

807 **Study 6**

808 A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress
 809 after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized
 810 trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m² intravenous infusion, once
 811 weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The
 812 main outcome measure of the study was progression-free survival defined as the time from
 813 randomization to progression, relapse, or death. Thirty-seven percent of the study population was
 814 >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2.

815 There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the
 816 range of 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no
 817 additional treatment.

818 **14.3 Diffuse Large B-Cell NHL (DLBCL)**

819 The safety and effectiveness of Rituxan were evaluated in three randomized, active-controlled,
 820 open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with
 821 previously untreated diffuse large B-cell NHL received Rituxan in combination with

822 cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based
823 chemotherapy regimens.

824 *Study 7*

825 A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell
826 lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received
827 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses
828 of Rituxan 375 mg/m^2 on Days -7 and -3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and
829 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main
830 outcome measure of the study was progression-free survival, defined as the time from randomization
831 to the first of progression, relapse, or death. Responding patients underwent a second randomization
832 to receive Rituxan or no further therapy.

833 Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had
834 Stage III–IV disease, 56% had IPI scores ≥ 2 , 86% had ECOG performance status of < 2 , 57% had
835 elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results
836 are presented in Table 6. These results reflect a statistical approach which allows for an evaluation
837 of Rituxan administered in the induction setting that excludes any potential impact of Rituxan given
838 after the second randomization.

839 Analysis of results after the second randomization in Study 7 demonstrates that for patients
840 randomized to R-CHOP, additional Rituxan exposure beyond induction was not associated with
841 further improvements in progression-free survival or overall survival.

842 *Study 8*

843 A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive
844 CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in
845 the R-CHOP arm received Rituxan 375 mg/m^2 on Day 1 of each cycle. The main outcome measure
846 of the study was event-free survival, defined as the time from randomization to relapse, progression,
847 change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV
848 disease, 60% of patients had an age-adjusted IPI ≥ 2 , 80% had ECOG performance status scores
849 < 2 , 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites.
850 Efficacy results are presented in Table 6.

851 *Study 9*

852 A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive
853 an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main
854 outcome measure of the study was time to treatment failure, defined as time from randomization to
855 the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among
856 all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤ 1 , 99% had ECOG
857 performance status of < 2 , 29% had elevated LDH levels, 49% had bulky disease, and 34% had
858 extranodal involvement. Efficacy results are presented in Table 6.
859

Table 6
Efficacy Results in Studies 7, 8, and 9

	Study 7 (n=632)		Study 8 (n=399)		Study 9 (n=823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE ^b	NE ^b
Hazard ratio ^d		0.69 ^a		0.60 ^a		0.45 ^a
Overall survival at 2 years ^c	74%	63%	69%	58%	95%	86%
Hazard ratio ^d		0.72 ^a		0.68 ^a		0.40 ^a

^a Significant at p<0.05, 2-sided.

^b NE=Not reliably estimable.

^c Kaplan-Meier estimates.

^d R-CHOP vs. CHOP.

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In Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

14.4 Chronic Lymphocytic Leukemia (CLL)

The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients with previously untreated CLL [Study 10 (n = 817)] or previously treated CLL [Study 11 (n = 552)]. Patients received fludarabine 25 mg/m²/day and cyclophosphamide 250 mg/m²/day on days 1, 2 and 3 of each cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

In Study 10, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100% were White. In Study 11, 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67% were male and 98% were White.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to progression, relapse, or death, as determined by investigators (Study 10) or an independent review committee (Study 11). The investigator assessed results in Study 11 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 7.

Table 7
Efficacy Results in Studies 10 and 11

	Study 10*		Study 11*	
	(Previously untreated)		(Previously treated)	
	R-FC N=408	FC N=409	R-FC N=276	FC N=276
Median PFS (months)	39.8	31.5	26.7	21.7
Hazard ratio (95% CI)	0.56 (0.43, 0.71)		0.76 (0.6, 0.96)	
P value (Log-Rank test)	<0.01		0.02	
Response rate (95% CI)	86% (82, 89)	73% (68, 77)	54% (48, 60)	45% (37, 51)

*As defined in 1996 National Cancer Institute Working Group guidelines.

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Across both studies, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older and 100 Rituxan-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 8.

Table 8
Efficacy Results in Studies 10 and 11 in Subgroups Defined by Age^a

Age subgroup	Study 10		Study 11	
	Number of Patients	Hazard Ratio for PFS (95% CI)	Number of Patients	Hazard Ratio for PFS (95% CI)
Age < 65 yrs	572	0.52 (0.39, 0.70)	313	0.61 (0.45, 0.84)
Age ≥ 65 yrs	245	0.62 (0.39, 0.99)	233	0.99 (0.70, 1.40)
Age < 70 yrs	736	0.51 (0.39, 0.67)	438	0.67 (0.51, 0.87)
Age ≥ 70 yrs	81	1.17 (0.51, 2.66)	108	1.22 (0.73, 2.04)

^a From exploratory analyses.

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887 14.5 Rheumatoid Arthritis (RA)

888 *Reducing the Signs and Symptoms: Initial and Re-Treatment Courses*

889 The efficacy and safety of Rituxan were evaluated in two randomized, double-blind,
890 placebo-controlled studies of adult patients with moderately to severely active RA who had a prior
891 inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed
892 with active RA according to American College of Rheumatology (ACR) criteria, and had at least
893 8 swollen and 8 tender joints.

894 In RA Study 1, patients were randomized to receive either Rituxan 2×1000 mg+MTX or
895 placebo+MTX for 24 weeks. Further courses of Rituxan 2×1000 mg+MTX were administered in
896 an open label extension study at a frequency determined by clinical evaluation, but no sooner than
897 16 weeks after the preceding course of Rituxan. In addition to the intravenous premedication,
898 glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The
899 proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the
900 placebo-controlled period are shown in Table 9.

901 In RA Study 2, all patients received the first course of Rituxan 2 × 1000 mg + MTX. Patients who
902 experienced ongoing disease activity were randomized to receive a second course of either Rituxan
903 2 × 1000 mg MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of

904 patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at
 905 Week 48, after retreatment, are shown in Table 9.
 906

Table 9
 ACR Responses in Study 1 and Study 2 (Percent of Patients)
 (Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists							
Study 1 24 Week Placebo-Controlled (Week 24)				Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)			
Response	Placebo + MTX n = 201	Rituxan + MTX n = 298	Treatment Difference (Rituxan – Placebo) ^c (95% CI)	Response	Placebo + MTX Retreatment n = 157	Rituxan + MTX Retreatment n = 318	Treatment Difference (Rituxan – Placebo) ^{a,b,c} (95% CI)
ACR20				ACR20			
Week 24	18%	51%	33% (26%, 41%)	Week 24	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
ACR50				ACR50			
Week 24	5%	27%	21% (15%, 27%)	Week 24	27%	21%	NA
				Week 48	26%	29%	4% (-4%, 13%)
ACR70				ACR70			
Week 24	1%	12%	11% (7%, 15%)	Week 24	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

^a In Study 2, all patients received a first course of Rituxan 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 x 1000 mg + MTX or placebo + MTX at or after Week 24.

^b Since all patients received a first course of Rituxan, no comparison between Placebo + MTX and Rituxan + MTX is made at Week 24.

^c For Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive >20 IU/mL, negative <20 IU/mL) at baseline; For Study 2, weighted difference stratified by RF status at baseline and ≥20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

907 Improvement was also noted for all components of ACR response following treatment with
 908 Rituxan, as shown in Table 10.
 909

Table 10
Components of ACR Response at Week 24 in Study 1
(Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists				
Parameter (median)	Placebo + MTX (n=201)		Rituxan + MTX (n=298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment ^a	71.0	69.0	71.0	36.0
Patient Global Assessment ^a	73.0	68.0	71.0	41.0
Pain ^a	68.0	68.0	67.0	38.5
Disability Index (HAQ) ^b	2.0	1.9	1.9	1.5
CRP (mg/dL)	2.4	2.5	2.6	0.9

^a Visual Analogue Scale: 0=best, 100=worst.

^b Disability Index of the Health Assessment Questionnaire: 0=best, 3=worst.

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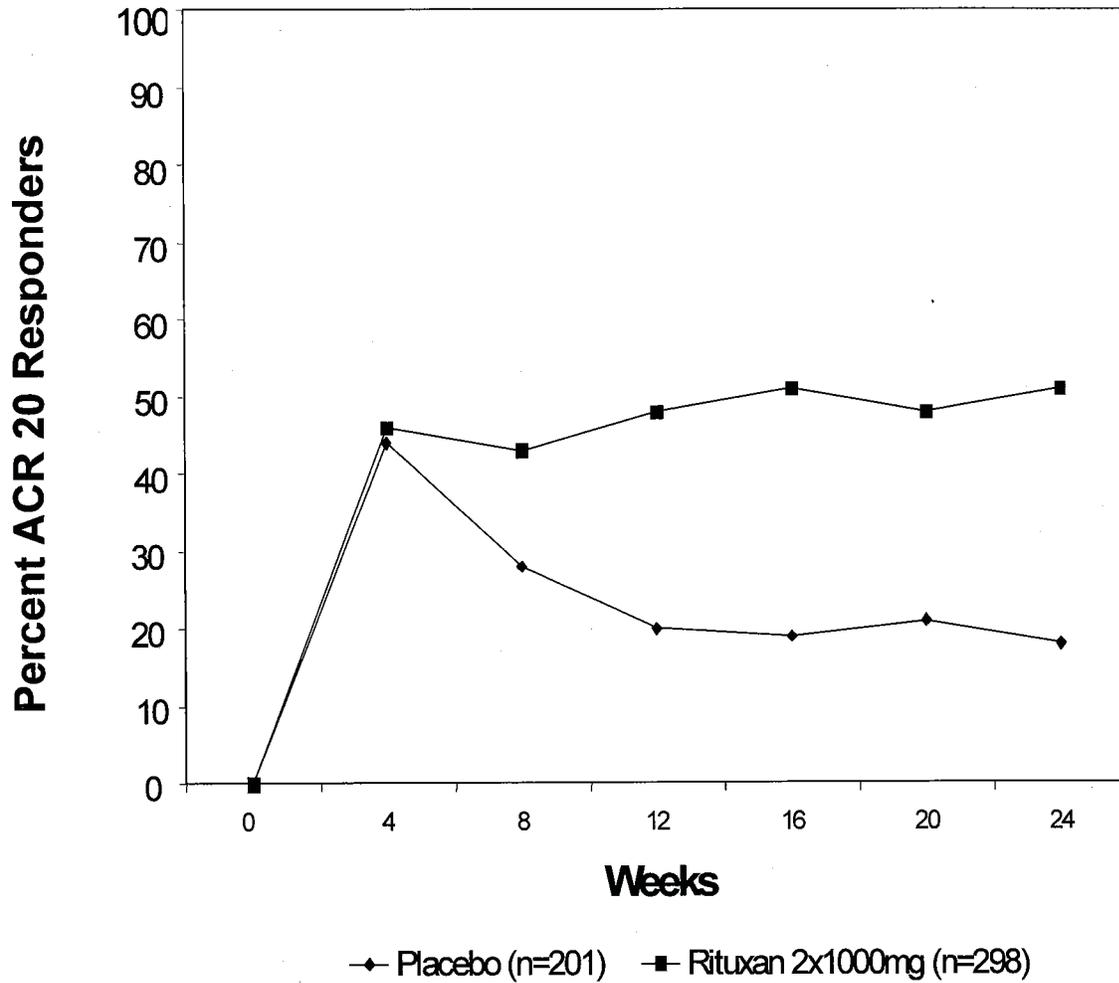
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The time course of ACR 20 response for Study 1 is shown in Figure 2. Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at Week 4, higher ACR 20 responses were observed for the Rituxan group by Week 8. A similar proportion of patients achieved these responses through Week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

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Figure 2
Percent of Patients Achieving ACR 20 Response by Visit*
Study 1 (Inadequate Response to TNF Antagonists)



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*The same patients may not have responded at each time point.

922 *Radiographic Response*

923 In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in
924 Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint
925 space narrowing (JSN) score. Rituxan +MTX slowed the progression of structural damage
926 compared to placebo +MTX after 1 year as shown in Table 11.

Table 11
Mean Radiographic Change From Baseline to 104 Weeks

Inadequate Response to TNF Antagonists				
Parameter	Rituxan 2 × 1000 mg + MTX ^b	Placebo + MTX ^c	Treatment Difference (Placebo – Rituxan)	95% CI
<u>Change during First Year</u>				
TSS	0.66	1.78	1.12	(0.48, 1.76)
ES	0.44	1.19	0.75	(0.32, 1.18)
JSN Score	0.22	0.59	0.37	(0.11, 0.63)
<u>Change during Second Year^a</u>				
TSS	0.48	1.04	—	—
ES	0.28	0.62	—	—
JSN Score	0.20	0.42	—	—

^a Based on radiographic scoring following 104 weeks of observation.

^b Patients received up to 2 years of treatment with Rituxan + MTX.

^c Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with Rituxan + MTX from Week 16 onward.

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In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 10, progression of structural damage in Rituxan + MTX patients was further reduced in the second year of treatment.

Following 2 years of treatment with Rituxan + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of Rituxan + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with Rituxan + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the Rituxan + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 Vs. 1000 mg Treatment Courses for Radiographic Outcomes

RA Study 3 is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to Rituxan 2 x 500 mg + MTX and Rituxan 2 x 1000 mg + MTX treatment courses in MTX-naïve RA patients with moderately to severely active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by Week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive re-treatment with additional courses of their assigned treatment. After one year of treatment, the proportion of patients achieving ACR 20/50/70 responses were similar in both Rituxan dose groups and were higher than in the placebo group. However, with respect to radiographic scores, only the Rituxan 1000 mg treatment group demonstrated a statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the placebo group, a 67% reduction.

Physical Function Response

RA Study 4 is a randomized, double-blind, placebo-controlled study in adult RA patients with moderately to severely active disease with inadequate response to MTX. Patients were randomized to receive an initial course of Rituxan 500 mg, Rituxan 1000 mg, or placebo in addition to background MTX.

955 Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire
 956 Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated
 957 patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference)
 958 and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 12. HAQ-DI
 959 results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment
 960 group; however radiographic responses were not assessed (see Dosing Precaution in the
 961 Radiographic Responses section above). These improvements were maintained at 48 weeks.
 962

Table 12
 Improvement from Baseline in Health Assessment
 Questionnaire Disability Index (HAQ-DI) at Week 24 in Study 4

	Placebo +MTX n=172	Rituxan 2×1000 mg+MTX n=170	Treatment Difference (Rituxan – Placebo) ^b (95% CI)
Mean Improvement from Baseline	0.19	0.42	0.23 (0.11, 0.34)
Percent of patients with “Improved” score (Change from Baseline ≥MCID) ^a	48%	58%	11% (0%, 21%)

^a Minimal Clinically Important Difference: MCID for HAQ=0.22.

^b Adjusted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥20 IU/mL, negative < 20 IU/mL) at baseline.

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964 **14.6 Wegener’s Granulomatosis (WG) and Microscopic Polyangiitis (MPA)**

965 A total of 197 patients with active, severe WG and MPA (two forms of ANCA Associated
 966 Vasculidities) were treated in a randomized, double-blind, active-controlled multicenter,
 967 non-inferiority study, conducted in two phases – a 6 month remission induction phase and a
 968 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with WG
 969 (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference
 970 criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a
 971 Birmingham Vasculitis Activity Score for Wegener’s Granulomatosis (BVAS/WG) ≥ 3, and their
 972 disease was severe, with at least one major item on the BVAS/WG. Ninety-six (49%) of patients
 973 had new disease and 101 (51%) of patients had relapsing disease.

974 Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to
 975 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive
 976 either Rituxan 375 mg/m² once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to
 977 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and
 978 acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all
 979 patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified
 980 tapering. Once remission was achieved or at the end of the 6 month remission induction period, the
 981 cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not
 982 receive additional therapy to maintain remission. The main outcome measure for both WG and
 983 MPA patients was achievement of complete remission at 6 months defined as a BVAS/WG of 0, and
 984 off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of
 985 20%. As shown in Table 13, the study demonstrated non-inferiority of Rituxan to
 986 cyclophosphamide for complete remission at 6 months.

Table 13
Percentage of Patients Who Achieved
Complete Remission at 6 Months (Intent-to-Treat Population)

	Rituxan (n=99)	Cyclophosphamide (n=98)	Treatment Difference (Rituxan – Cyclophosphamide)
Rate	64%	53%	11%
95.1% ^b CI	(54%, 73%)	(43%, 63%)	(-3%, 24%) ^a

^a non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (-3% > -20%).

^b The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

987

988 *Complete Remission (CR) at 12 and 18 months*

989 In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients
 990 achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by
 991 azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of
 992 patients achieved CR at 6, 12, and 18 months.

993 *Retreatment with Rituxan*

994 Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for
 995 treatment of relapse of disease activity which occurred between 8 and 17 months after the first
 996 course of Rituxan. The limited data preclude any conclusions regarding the efficacy of subsequent
 997 courses of Rituxan in patients with WG and MPA [See *Warnings and Precautions (5.14)*].

998 **16 HOW SUPPLIED/STORAGE AND HANDLING**

999 Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use
 1000 vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date
 1001 stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

1002 Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan
 1003 solutions for infusion have been shown to be stable for an additional 24 hours at room temperature.
 1004 However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored
 1005 refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or
 1006 polyethylene bags have been observed.

1007 **17 PATIENT COUNSELING INFORMATION**

1008 Patients should be provided the Rituxan Medication Guide and provided an opportunity to read
 1009 prior to each treatment session. It is important that the patient's overall health be assessed at each
 1010 visit and the risks of Rituxan therapy and any questions resulting from the patient's reading of the
 1011 Medication Guide be discussed.

1012 Rituxan is detectable in serum for up to six months following completion of therapy. Individuals
 1013 of childbearing potential should use effective contraception during treatment and for 12 months after
 1014 Rituxan therapy.

1015

RITUXAN[®] [rituximab]

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

10126776

Initial US Approval: November 1997

PI Revision Date 04 2011

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1016 **MEDICATION GUIDE**
1017 **RITUXAN[®] (ri-tuk'-san)**
1018 **(rituximab)**
1019 **for injection**

1020 Read this Medication Guide before you start Rituxan and before each Rituxan infusion. There may
1021 be new information. This Medication Guide does not take the place of talking to your doctor about
1022 your medical condition or your treatment.

1023 **What is the most important information I should know about Rituxan?**

1024 Rituxan can cause serious side effects that can lead to death, including:

1025 **1. Infusion reactions.** Infusion reactions are the most common side effect of Rituxan treatment.
1026 Serious infusion reactions can happen during your infusion or within 24 hours after your infusion
1027 of Rituxan. Your doctor should give you medicines before your infusion of Rituxan to decrease
1028 your chance of having a severe infusion reaction.

1029 Tell your doctor or get medical help right away if you get any of these symptoms during or after
1030 an infusion of Rituxan:

- 1031 • hives (red itchy welts) or rash
- 1032 • itching
- 1033 • swelling of your lips, tongue, throat or face
- 1034 • sudden cough
- 1035 • shortness of breath, difficulty breathing, or wheezing
- 1036 • weakness
- 1037 • dizziness or feel faint
- 1038 • palpitations (feel like your heart is racing or fluttering)
- 1039 • chest pain

1040 **2. Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection
1041 caused by a virus. People with weakened immune systems can get PML. Your chance of getting
1042 PML may be higher if you are treated with Rituxan alone or with other medicines that weaken
1043 your immune system. PML can result in death or severe disability. There is no known
1044 treatment, prevention, or cure for PML.

1045 Tell your doctor right away if you have any of the following symptoms or if anyone close to you
1046 notices these symptoms:

- 1047 • confusion or problems thinking
- 1048 • loss of balance
- 1049 • change in the way you walk or talk
- 1050 • decreased strength or weakness on one side of your body
- 1051 • blurred vision or loss of vision

1052 **3. Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can
1053 cause you to have:

- 1054 • kidney failure and the need for dialysis treatment
- 1055 • abnormal heart rhythm

1056 Your doctor may do blood tests to check you for TLS. Your doctor may give you medicine to
1057 help prevent TLS.

1058 **4. Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get
1059 any of these symptoms at anytime during your treatment with Rituxan:

- 1060 • painful sores or ulcers on your skin, lips or in your mouth
- 1061 • blisters
- 1062 • peeling skin
- 1063 • rash
- 1064 • pustules

1065 See “**What are possible side effects of Rituxan?**” for more information about side effects.

1066 **What is Rituxan?**

1067 Rituxan is a prescription medicine used to treat:

- 1068 • **Non-Hodgkin’s Lymphoma (NHL):** alone or with other chemotherapy medicines.
- 1069 • **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and
1070 cyclophosphamide.
- 1071 • **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce
1072 the signs and symptoms of moderate to severe active RA in adults, after treatment with at least
1073 one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not
1074 work well enough.
- 1075 • **Wegener’s Granulomatosis (WG) and Microscopic Polyangiitis (MPA):** with
1076 glucocorticoids, to treat WG and MPA.

1077 People with serious infections should not receive Rituxan.

1078 It is not known if Rituxan is safe or effective in children.

1079

1080 **What should I tell my doctor before receiving Rituxan?**

1081 Before receiving Rituxan, tell your doctor if you:

- 1082 • have had a severe infusion reaction to Rituxan in the past
- 1083 • have a history of heart problems, irregular heart beat or chest pain
- 1084 • have lung or kidney problems
- 1085 • have an infection or weakened immune system.
- 1086 • have or have had any severe infections including:
 - 1087 • Hepatitis B virus (HBV)
 - 1088 • Hepatitis C virus (HCV)
 - 1089 • Cytomegalovirus (CMV)
 - 1090 • Herpes simplex virus (HSV)
 - 1091 • Parvovirus B19
 - 1092 • Varicella zoster virus (chickenpox or shingles)
 - 1093 • West Nile Virus

- 1094 • have had a recent vaccination or are scheduled to receive vaccinations. You should not receive
1095 certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your
1096 household is scheduled to receive a vaccination. Some types of vaccines can spread to people
1097 with a weakened immune system, and cause serious problems.
- 1098 • have taken Rituxan for WG or MPA in the past.
- 1099 • have any other medical conditions
- 1100 • are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of
1101 your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.
1102 Women who are able to become pregnant should use effective birth-control (contraception)
1103 while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about
1104 effective birth control.
- 1105 • are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk.
1106 You and your doctor should decide the best way to feed your baby if you receive Rituxan.

1107 Tell your doctor about all the medicines you take, including prescription and nonprescription
1108 medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

- 1109 • a Tumor Necrosis Factor (TNF) inhibitor medicine
- 1110 • a Disease Modifying Anti-Rheumatic Drug (DMARD)

1111 If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

1112 Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you
1113 get a new medicine. Do not take any new medicine without talking with your doctor.

1114 **How will I receive Rituxan?**

- 1115 • Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in
1116 your arm. Talk to your doctor about how you will receive Rituxan.
- 1117 • Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects
1118 of infusions such as fever and chills.
- 1119 • Your doctor should do regular blood tests to check for side effects to Rituxan.

1120 Before each Rituxan treatment, your doctor or nurse will ask you questions about your general
1121 health. Tell your doctor or nurse about any new symptoms.

1122 **What are the possible side effects of Rituxan?**

1123 Rituxan can cause serious and life-threatening side effects, including:

1124 See **“What is the most important information I should know about Rituxan?”**

- 1125 • **Hepatitis B virus (HBV) reactivation.** If you have had hepatitis B or are a carrier of hepatitis B
1126 virus, receiving Rituxan could cause the virus to become an active infection again. This may
1127 cause serious liver problems including liver failure, and death. You should not receive Rituxan
1128 if you have active hepatitis B liver disease.
- 1129 • **Serious infections.** Serious infections that happen with Rituxan can lead to death. Call your
1130 doctor right away if you have any symptoms of infection:
 - 1131 ○ fever
 - 1132 ○ cold symptoms, such as runny nose or sore throat that do not go away
 - 1133 ○ flu symptoms, such as cough, tiredness, and body aches
 - 1134 ○ earache or headache

- 1135 ○ pain during urination
- 1136 ○ white patches in the mouth or throat
- 1137 ○ cuts, scrapes or incisions that are red, warm, swollen or painful
- 1138 ● **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need
1139 treatment, or your doctor may decide to stop your treatment with Rituxan.
- 1140 ● **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do
1141 blood tests to check how well your kidneys are working.
- 1142 ● **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems,
1143 including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy
1144 medicines to treat non-Hodgkin's lymphoma. Tell your doctor right away if you have any
1145 stomach area pain during treatment with Rituxan.
- 1146 ● **Low blood cell counts.** Your doctor may do blood tests during treatment with Rituxan to check
1147 your blood cell counts.
 - 1148 ○ **White blood cells.** White blood cells fight against bacterial infections. Low white
1149 blood cells can cause you to get infections, which may be serious. See "Increased
1150 risk of infections" above for a list of symptoms of infection.
 - 1151 ○ **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
 - 1152 ○ **Platelets.** Platelets are blood cells that help your blood to clot.

1153 **Common side effects during Rituxan treatment include:**

- 1154 ● infusion reactions (see What is the most important information I should know about Rituxan?)
- 1155 ● chills
- 1156 ● infections
- 1157 ● body aches
- 1158 ● tiredness
- 1159 ● low white blood cells

1160 Other side effects with Rituxan include:

- 1161 ● aching joints during or within hours of receiving an infusion
- 1162 ● more frequent upper respiratory tract infection

1163 Tell your doctor about any side effect that bothers you or that does not go away.

1164 These are not all of the possible side effects with Rituxan. For more information, ask your doctor or
1165 pharmacist.

1166 Call your doctor for medical advice about side effects. You may report side effects to FDA at
1167 1-800-FDA-1088.

1168 **General information about Rituxan**

1169 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This
1170 Medication Guide provides a summary of the most important information about Rituxan. If you
1171 would like more information, talk with your doctor. You can ask your doctor for information about
1172 Rituxan that is written for healthcare professionals.

1173 For more information, go to www.Rituxan.com or call 1-877-474-8892.

1174 **What are the ingredients in Rituxan?**

1175 Active ingredient: rituximab

1176 Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for
1177 injection.

1178 Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.

1179

RITUXAN® [rituximab]

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

10126776

Initial US Approval: November 1997

Med Guide Revision Date: April 2011

Rituxan® is a registered trademark of Biogen Idec, Inc.

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1180

1181 This Medication Guide has been approved by the U.S. Food and Drug Administration.

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50247-0511-01

1021987
50247-0511-01

**RITUXAN[®]
Rituximab**
500 mg/50 mL (10 mg/mL)
For Intravenous Use

NDC 50247-0511-01

500 mg  only

One 100 mg vial

Jointly Marketed by Regeneron Inc. and Genentech USA, Inc.

**RITUXAN[®]
Rituximab** 500 mg 

Caution: For Intravenous Use Only. Do not use if the solution is cloudy or contains a precipitate. Do not use if the vial stopper is damaged or the vial is leaking. Do not use if the vial is cracked or broken. Do not use if the vial is contaminated.

Manufactured by:
Genentech, Inc.
1 DNA Way
Sunnyvale, CA 94088
© 2008 Genentech, Inc.

**RITUXAN[®]
Rituximab**
500 mg/50 mL (10 mg/mL)
For Intravenous Use

NDC 50247-0511-02

500 mg  only

One 100 mg vial

Jointly Marketed by:
Regeneron Inc. and Genentech USA, Inc.

**RITUXAN[®]
Rituximab** 500 mg 

Caution: For Intravenous Use Only. Do not use if the solution is cloudy or contains a precipitate. Do not use if the vial stopper is damaged or the vial is leaking. Do not use if the vial is cracked or broken. Do not use if the vial is contaminated.

Manufactured by:
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1 DNA Way
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50247-0511-01

1001924
50247-0511-01

**RITUXAN[®]
Rituximab**
100 mg/10 mL (10 mg/mL)
For Intravenous Use

NDC 50247-0511-21

100 mg  only

One 100 mg vial

Jointly Marketed by Regeneron Inc. and Genentech USA, Inc.

**RITUXAN[®]
Rituximab** 100 mg 

Caution: For Intravenous Use Only. Do not use if the solution is cloudy or contains a precipitate. Do not use if the vial stopper is damaged or the vial is leaking. Do not use if the vial is cracked or broken. Do not use if the vial is contaminated.

Manufactured by:
Genentech, Inc.
1 DNA Way
Sunnyvale, CA 94088
© 2008 Genentech, Inc.

**RITUXAN[®]
Rituximab**
100 mg/10 mL (10 mg/mL)
For Intravenous Use

NDC 50247-0511-21

100 mg  only

One 100 mg vial

Jointly Marketed by:
Regeneron Inc. and Genentech USA, Inc.

**RITUXAN[®]
Rituximab** 100 mg 

Caution: For Intravenous Use Only. Do not use if the solution is cloudy or contains a precipitate. Do not use if the vial stopper is damaged or the vial is leaking. Do not use if the vial is cracked or broken. Do not use if the vial is contaminated.

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50247-0511-01

50247-0511-01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: April 19, 2011

From: Badrul A. Chowdhury, MD, PhD *Badrul A. Chowdhury*
Director, Division of Pulmonary, Allergy, and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review

BLA Number: 103-705, supplement 5344

Applicant Name: Genentech, Inc.

Date of Submission: October 15, 2010

PDUFA Goal Date: April 19, 2011

Proprietary Name: Rituxan

Established Name: Rituximab

Dosage form: Single-use vials for intravenous infusion

Strength: 100 mg/10 mL single-use vial, 500 mg/50mL single use vial

Proposed Indications: In combination with glucocorticoids for the treatment of (b) (4)
(b) (4)

Action: Approval

1. Introduction

Genentech submitted this BLA supplement seeking approval for Rituxan (rituximab) in combination with glucocorticoids for the treatment of (b) (4). On February 14, 2006, an orphan designation was granted for Rituxan for the treatment of patients with AAV. Rituxan is currently approved for treatment of Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), and Rheumatoid Arthritis (RA). The proposed dose for (b) (4) is 375 mg/m² intravenous infusion once weekly for 4 weeks, along with glucocorticoids. The application is based on a single clinical efficacy and safety study. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety study.

2. Background

Vasculitis is characterized by inflammation and necrosis of blood vessels. Patients with Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS) share the common feature of vasculitis with or without necrotizing granulomatous process with angitis. The underlying pathological link for these diseases is the presence of antineutrophil cytoplasmic antibodies (ANCA) and the finding that most patients with WG and MPA, and to a lesser extent CSS have ANCA in their serum. These diseases are termed as ANCA-associated vasculitis (AAV), even though not all patients with these diseases have detectable ANCA. There are two types of ANCA associated with AAV; those directed against proteinase-3 (PR3) and myeloperoxidase (MPO). Both of these are serine proteases and constitute the primary granules of

neutrophils and monocytes. Antibodies directed against these antigens are known, respectively, as PR3-ANCA and MPO-ANCA.

Patients with AAV present with involvement of various organs, such as ear, nose, throat, eyes, lung, kidneys, heart, and peripheral nerves, with varying organ involvement among the three diseases. There is no FDA approved treatment for AAV. In treating patients with severe AAV, the standard approach at present is to induce remission with cyclophosphamide, followed by maintenance treatment with either azathioprine or methotrexate. Corticosteroids are also used for the treatment of AAV. Even with treatment, mortality and morbidity with AAV are substantial. Disease relapse after remission is a major threat, which is more likely in WG than in MPA and CSS. One of the major causes of morbidity in patients with AAV is multiple and prolonged courses of immunosuppression, particularly the need to re-treat patients who suffer multiple relapses.

Genentech submitted results from one controlled clinical trial (Study ITN021A1 or RAVE), and supportive information from published literature. The design of the study was complicated because cyclophosphamide is standard of care for AAV, although not approved by the FDA. In design of the trial, the Agency and Genentech agreed that cyclophosphamide will be used as an active control in the trial and the trial will be of non-inferiority design. Cyclophosphamide was used as the active control because it has been used historically to treat these diseases with favorable response.¹ A non-inferiority margin of 20% was agreed upon based on analysis of historical data informing the cyclophosphamide treatment effect from a review of cases of WG published in 1958,² and from clinical trials in WG patients that included an oral cyclophosphamide treatment group.^{3, 4} The review of cases from 1958 showed that WG is rapidly progressive and fatal and only about 38% patients survived at 6 months. The later trials showed that remission at 6 months in patients with WG treated with oral cyclophosphamide is 75% with lower limit of 95% CI of 55%. The agreed upon 20% non-inferiority margin preserve over half of the estimated active control treatment effect. These trial design issues were discussed at a CDER Regulatory Briefing on February 26, 2010, where the discussion was supportive of the use of active comparator and the non-inferiority margin.

3. Chemistry, Manufacturing, and Controls

Rituxan is an approved marketed product and there are no CMC issues. While there is no change to the currently marketed drug product, CMC review of the immunogenicity assay used in the clinical program found the assay to be appropriately validated and the data can be used to support approval of this supplement.

¹ Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's Granulomatosis Prospective Clinical and Therapeutic Experience with 85 Patients for 21 Years. *Annals of Internal Medicine* 1983; 98: 76-85.

² Walton EW. Giant Cell Granuloma of the Respiratory Tract (Wegener's Granulomatosis). *British Medical Journal* 1958; Aug 2: 265-270.

³ Wegener's Granulomatosis Etanercept Trial Research Group (WGET). *NEJM* 2005; 352-351-61.

⁴ de Groot K, Harper L, Jayne DRW, et. al. Pulse versus Daily Oral Cyclophosphamide for Induction of Remission in ANCA Associated Vasculitis. *Annals of Internal Medicine* 2009; 150: 670-680.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

The Applicant performed a population PK analysis on rituximab in patients with WG and MPA based upon data obtained in RAVE. The population PK analysis showed that dose adjustment is not necessary for typical covariates, such as sex and body surface area.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

This submission is based on one study (Study ITN021A1 or RAVE), and supportive information from published literature. A limited program was acceptable because the number of patients with AAV is small, provided demonstrated efficacy was robust.

b. Design and conduct of the study

RAVE was a multicenter, multinational (USA and Netherlands), randomized, double-blind, double-dummy, active-controlled, non-inferiority study conducted in patients with WG (75% of patients) and MPA (24% of patients) diagnosed according to the Chapel Hill Consensus Conference definition and positive PR3-ANCA or MPO-ANCA. Patients had to have active disease with a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) ≥ 3 and severe disease defined by one or more major BVAS/WG items or disease severe enough to require treatment with cyclophosphamide. One hundred patients in each treatment group were planned for enrollment. The study was conducted in two phases: a 6-month remission induction phase and a 12-month remission maintenance phase. During the remission induction phase, patients were randomized 1:1 to receive either Rituxan 375mg/m² IV once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months. Patients in both treatment groups received 1000 mg pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. All patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Patients who were treatment failures or had severe flares during the remission induction phase were crossed over to the opposite treatment arm or under specific conditions treated with best medical judgment. During the maintenance phase or if remission was achieved after month 3, patients receiving cyclophosphamide were switched to oral azathioprine daily.

Efficacy was assessed with the BVAS/WG, which is a disease specific index modified for WG. The index consists of items related to major and minor criteria in the following categories: general, cutaneous, mucous membranes/eyes, ENT, cardiovascular, gastrointestinal, pulmonary, renal, nervous system, and other. The index was designed to assess active WG and only items that are attributable to active WG are scored. The

maximum possible score is 63. The BVAS/WG is considered a valid, disease specific activity index for WG.⁵ Although the BVAS/WG is specific for WG, use in patients with WG and MPA is reasonable, given that there is some overlap in disease between these vasculitides. The primary endpoint was the percentage of patients who have a BVAS/WG of 0 and have successfully completed the glucocorticoid taper at 6 months after randomization. Non-inferiority of Rituxan to cyclophosphamide was concluded if the lower bound of the CI of the treatment difference was above -20%.

c. Efficacy findings and conclusions

The submitted clinical program supports use of Rituxan in combination with glucocorticoids for the treatment of adult patients with WG and MPA. The (b) (4) claim of (b) (4) is not supported because (b) (4). Limitation of the WG and MPA indication to (b) (4) is not warranted because (b) (4).

Results for the primary efficacy endpoint are shown in Table 3. The results show that the lower bound for the 95.1% CI for the treatment difference was greater than the non-inferiority margin of -20%, thus Rituxan was non inferior to cyclophosphamide. The complete remission in the Rituxan group exceeded 50%, which suggests that Rituxan was superior to the historical control survival data from a review of cases of WG published in 1958.⁶ The efficacy data at months 12 and 18 also continued to exclude the non-inferiority margin of -20%, and other secondary efficacy measures were also supportive (data not shown in this document).

Data on the effect of retreatment is limited to only 15 patients who received a second course of Rituxan for relapsing disease. This limited data preclude any conclusions regarding the efficacy of retreatment of Rituxan in patients with WG and MPA. Genentech has agreed to conduct a post-marketing observational study to further obtain information regarding repeat courses of Rituxan and use with concomitant medications in patients with WG and MPA.

Table 1. Percentage of patients who achieved complete remission at 6 months (ITT population)

	Rituxan	Cyclophosphamide	Treatment Difference (Rituxan- Cyclophosphamide)
	N= 99	N= 98	
Rate	64%	53%	11%
95.1% CI*	(54%, 73%)	(43%, 63%)	(-3%, 24%)**
* The 95.1% confidence interval level reflects an additional 0.001 alpha to account for an interim efficacy analysis			

⁵ Stone JH, Hoffman GS, Merkel PA, et al. A Disease-Specific Activity Index for Wegener's Granulomatosis- Modification of the Birmingham Vasculitis Activity Score. *Arthritis & Rheumatism* 2001; 44(4): 912-920.

⁶ Walton EW. Giant Cell Granuloma of the Respiratory Tract (Wegener's Granulomatosis). *British Medical Journal* 1958; Aug 2: 265-270.

Rituxan	Cyclophosphamide	Treatment Difference (Rituxan- Cyclophosphamide)
N= 99	N= 98	
** Non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (-3% > -20%)		

8. Safety

a. Safety database

The safety profile of Rituxan in patients with rheumatoid arthritis and lymphoma has already been established. The safety data with Rituxan in patients with WG and MPA comes from the single trial, RAVE. Given the limited population and the known safety information from other populations, the safety database in patients with WG and MPA is acceptable.

b. Safety findings and conclusion

The safety review of the RAVE study did not identify a new safety signal for Rituxan.

c. REMS/RiskMAP

Rituximab currently has a medication guide, which is part of the approved labeling but not part of REMS. No new safety signals were identified in this submission. Therefore, no REMS is warranted.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Rituximab is an approved product with known safety profile and the safety profile in this patient population did not reveal a new safety signal. The single clinical study was somewhat unique in design because it relied on historical control, but the efficacy finding was quite robust. The design of the clinical study was discussed at a Regulatory Briefing on February 26, 2010, where the committee was supportive. Thus, this application did not raise any issues that warranted discussion at an advisory committee meeting.

10. Pediatric

Pediatric studies under PREA are not required because this application was granted an orphan designation.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit of 3 study centers involved in the RAVE study was done. These 3 centers had almost 65% of the entire study population. DSI audit showed that there were no major issues identified at 2 of the 3 study centers, however, there was an issue with regards to dosing at the third study center. Twelve patients in this center received a higher concentration of study drug or a higher infusion rate, leading to administration of a higher dose than specified. Because of concerns with data from this site and these patients, sensitivity analyses were performed for the primary endpoint removing the data

from these patients as well as the entire study center. The results showed that Rituxan remained non-inferior to cyclophosphamide.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name as the name Rituxan was previously reviewed and found to be acceptable. The product is currently marketed under the trade name Rituxan.

b. Physician Labeling

The labeling of Rituxan was reviewed previously with the original approval of the product and subsequent supplements. With this application the existing label will be updated to include the new information regarding the claim of treating patients with WG and MPA. The main changes are in the Clinical Studies section where new data from the RAVE study are described. In addition there will be changes in the Adverse Reactions and Clinical Pharmacology sections of the label.

c. Carton and Immediate Container Labels

Rituxan is a marketed product and there were no changes to the carton and immediate container labels with this application. These were reviewed previously by various disciplines of this Division, and the current version was found to be acceptable.

d. Patient Labeling and Medication Guide

There are no data that warrant major changes to the currently approved patient labeling and Medication Guide. Minor changes reflecting the new study supporting use of Rituxan in patients with WG and MPA will be included.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval for Rituxan in combination with glucocorticoids for the treatment of adult patients with WG and MPA. The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of Rituxan in combination with glucocorticoids for the treatment of patients with severely active anti-neutrophil

cytoplasmic antibody (ANCA)-associated WG and MPA. The efficacy finding was robust. Rituxan has safety concerns, including infusion reactions, infections, severe mucocutaneous reactions, and PML. The clinical program submitted to support this new indication is limited in size due to the patient population, but no unique safety signal was identified. Currently, there are no approved treatment for the treatment of WG and MPA. Although corticosteroids and cyclophosphamide are used for these conditions, these medications have potentially serious risks as well. Given the submitted efficacy data, unmet need, and the known safety findings, the overall risk benefit profile in patients with WG and MPA is acceptable.

c. Post-marketing Risk Management Activities

Rituxan has a medication guide, which is part of the approved labeling but not part of REMS. No new safety signals were identified in this submission. Therefore, no REMS is required for this application.

d. Post-marketing Study Commitments

Genentech has agreed to conduct a post-marketing observational study to further obtain information regarding repeat courses of Rituxan and use with concomitant medications in patients with WG and MPA. Since the primary goal of this study is to obtain safety information, this will be a post-marketing required study.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

OFFICER/EMPLOYEE LIST

Consent for the Officer/Employee List for sBLA 103705/5344
Rituxan® (rituximab)

1. Robin Duer
2. Badrul Chowdhury
3. Melissa Hulett
4. Roberta Szydlo
5. Sandy Barnes
6. Tejashri Purohit-Sheth
7. Mamata De
8. Philantha Montgomery Bowen
9. Yaning Wang
10. Timothy Robison
11. Suresh Doddapaneni
12. Marjorie Shapiro
13. Denise Baugh
14. Deborah Seibel
15. LaShawn Griffiths
16. Todd Bridges
17. Sally Seymour
18. Elizabeth Shang
19. Yun Xu
20. Kimberly Rains
21. Molly Topper
22. Joan Buenconsejo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 5, 2011
From	Sally Seymour, MD Deputy Director for Safety Division of Pulmonary, Allergy, and Rheumatology Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA# 103705
Supplement#	5344
Applicant	Genentech
Date of Submission	October 15, 2010
PDUFA Goal Date	April 19, 2011
Proprietary Name / Established (USAN) names	Rituxan/ Rituximab
Dosage forms / Strength	Solution for injection
Proposed Indication(s)	Wegener's Granulomatosis and Microscopic Polyangiitis
Recommended:	Approval

1. Introduction

On October 15, 2010, Genentech submitted a supplemental Biologic Licensing Application (BLA), seeking approval for rituximab in combination with glucocorticoids for the treatment of (b) (4)

(b) (4). Rituximab (RTX) is a chimeric murine/human monoclonal antibody directed against the CD20 antigen and is currently marketed under the trade name Rituxan.

Vasculitis is characterized by inflammation and necrosis of blood vessels. ANCA are autoantibodies directed against the cytoplasm of neutrophils and monocytes, primarily against proteinase 3 or myeloperoxidase. ANCA-associated vasculitis is a systemic vasculitis affecting small to medium size vessels and the presence of ANCA. Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg Strauss syndrome (CGS) are all considered ANCA-associated vasculitides (AAV).¹ Currently, there are no drugs approved for the treatment of patients with AAV.

To support the safety and efficacy of rituximab for the proposed indication, Genentech submitted the results of one controlled clinical trial in patients with WG and MPA, Study ITN021AI (RAVE), hereafter referred to as RAVE and supportive information from published literature. The focus of this review will be a somewhat detailed discussion of RAVE because of its unique design using an unapproved control group with non-inferiority design and reliance on historical control information from published literature. In addition, this review includes a discussion of the appropriateness of reliance on a single controlled clinical trial to support the efficacy and safety of RTX in this patient population.

¹ Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. *Am J Med.* 2004; 117: 39-50.

2. Background

WG is characterized by granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium sized vessels. WG is characterized by upper respiratory tract involvement, including nasal pain, congestion, epistaxis, septal erosions and perforations, nasal bridge collapse (saddle-nose deformity), and hearing loss. However, other organs can be involved including the eyes, lungs, joints, and kidneys. MPA is a necrotizing vasculitis affecting small vessels. Upper respiratory involvement is typically absent. CGS is characterized by eosinophilia, eosinophilic tissue infiltrates, nasal polyps, allergic rhinitis, and asthma.¹ Glomerulonephritis is one of the most serious effects of WG or MPA. Estimates of incidences are reported as 8.5 cases per million for WG and 3.6 cases per million for MPA, and 2.4 cases per million for CGS.² The mean age of diagnosis is 55 years and primarily caucasians are affected.

RTX was approved in 1997 for treatment of patients with CD20-positive, B-cell non-Hodgkin's lymphoma (NHL). In 2006, RTX was approved for use in combination with methotrexate for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonists therapies. RTX has also been approved for use in combination with fludarabine and cyclophosphamide (CYC) for patients with CD20-positive chronic lymphocytic leukemia. RTX is currently approved in numerous other countries and the Applicant reports that there have been no market withdrawals or suspensions.

RTX is administered by intravenous infusion. RTX has known safety issues, including infusion reactions which can be fatal. Because of the risk of infusion reactions, premedication is recommended as well as specified infusion rates. The product labeling has a Boxed Warning for infusion reactions, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML). Other known risks described in the Warnings section of the label include infections (potentially fatal) and cardiac arrhythmias during infusion, and cytopenias requiring laboratory monitoring. RTX is a Category C for pregnancy and post-marketing data shows that B-cell lymphocytopenia lasting less than 6 months can occur in infants exposed to RTX in-utero.

Regulatory History

With regards to the proposed indication, there was a lot of discussion between the Applicant and the Agency regarding the design of RAVE. Two of the key interactions are summarized below. Based upon review of the regulatory interactions, the Agency agreed with the design of RAVE, including the use of CYC as an active control and non-inferiority design. The Applicant was to provide justification for reliance on a single trial and justification of the 20% non-inferiority margin.

- April 6, 2004 teleconference
 - Generally two controlled clinical trials are expected to support efficacy.
 - CYC is an appropriate comparator since it is considered standard of care

² Watts RA, Carruthers DM, Scott DG. Epidemiology of systemic vasculitis: changing incidence or definition? *Semin Arthritis Rheum.* 1995; 25: 28-34.

- If the BVAS/WG AUC is chosen as the primary endpoint then include the percent of patients with a BVAS score of zero at 6 months as a major secondary endpoint
- The sponsor will need to provide information regarding the effects of CYC in patients with MPA; if the effect is similar in patients with WG and MPA, then (b) (4) indication may be supported.
- Perform subgroup analysis on patients who received pulse corticosteroids.
- Provide historical data regarding CYC and remission and justification of 20% NI margin.
- March 11, 2010 – pre-sBLA meeting
 - The Agency agreed that a single trial (RAVE) is acceptable for sBLA submission, but the application should provide justification for reliance on a single trial. RITUXVAS does not appear to be adequate for a supportive study.
 - An ISE and ISS are required. The ISE does not need to have pooled data but could include a discussion of RAVE and literature. The ISS can contain safety information from other patient populations.
 - The proposed application appeared to meet the criteria for priority review.
 - An advisory committee is likely.

On February 14, 2006, orphan drug designation was granted for RTX for the treatment of patients with AAV (WG, MPA, and CSS).³ On February 26, 2010, the trial design and use of historical control were presented at a CDER Regulatory Briefing where the discussion was supportive of the trial design.

3. CMC/Device

RTX is produced by Chinese Hamster Ovary suspension culture in a nutrient medium containing gentamycin. The drug product is a sterile, clear, colorless, preservative-free liquid concentrate marketed in 100mg/10mL and 500mg/50mL single use vials. There is no change to the currently marketed drug product. The CMC reviewer, Dr. Marjorie Shapiro, reviewed the immunogenicity assay used in the clinical trial, RAVE, and found the assay to be appropriately validated and the data can be used to support approval of this supplement.

4. Nonclinical Pharmacology/Toxicology

Since RTX is already marketed for other indications, no additional pharmacology/toxicology studies were required for this application. According to the product label, no long term animal studies have been performed to establish the carcinogenic or mutagenic potential of RTX or to determine potential effects on fertility in males or females. The pharmacology/toxicology reviewer, Dr. Mamata De, recommended some minor labeling revisions.

5. Clinical Pharmacology/Biopharmaceutics

Since RTX is already marketed for other indications, the general clinical pharmacology is already described in the Rituximab product label and a full clinical pharmacology program was not required for this application. However, the Applicant performed a population PK

³ FDA Orphan Drug Designation Search

(http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm) accessed on January 21, 2011

analysis of RTX in patients with WG and MPA based upon data obtained in RAVE. The population PK analysis showed that the terminal half life was 23 days. Although sex, human anti-chimeric antibodies (HACA) and body surface area are important covariates for clearance, dose adjustment is not necessary. The primary clinical pharmacology reviewer, Dr. Elizabeth Shang, found the application acceptable.

6. Clinical Microbiology

Clinical microbiology is not applicable for the proposed application.

7. Clinical/Statistical- Efficacy

To support the safety and efficacy of RTX for the proposed indication, Genentech submitted the results of one controlled clinical trial in patients with WG and MPA, Study ITN021AI (RAVE). The table below shows the basic elements of the RAVE trial. This trial relied on historical control data; therefore, literature reports will be included in the discussion accordingly.

Table 1 Summary of Clinical Program					
Study No.	Description	Subjects	Treatments	Duration	Endpoints
ITN021AI/ RAVE United States, Netherlands Dec 2004 - ongoing	R, DB, AC, DD, 2-phase, non- inferiority efficacy and safety trial	197 pts with WG or MPA 15 years and older (6 pts ≤ 18 yrs)	Rituximab IV 375mg/m ² per wk x 4 + IV corticosteroids (CS) and oral CS taper OR Cyclophosphamide (oral) 2mg/kg/day for 3-6 months + IV corticosteroids (CS) and oral CS taper; azathioprine administered in remission maintenance phase	6 mo – remission induction phase then 12 mo remission maintenance phase	Complete remission BVAS/WG = 0 and successful taper of CS at 6 months
R=randomized, DB = double-blind, AC – active controlled, DD – double dummy					

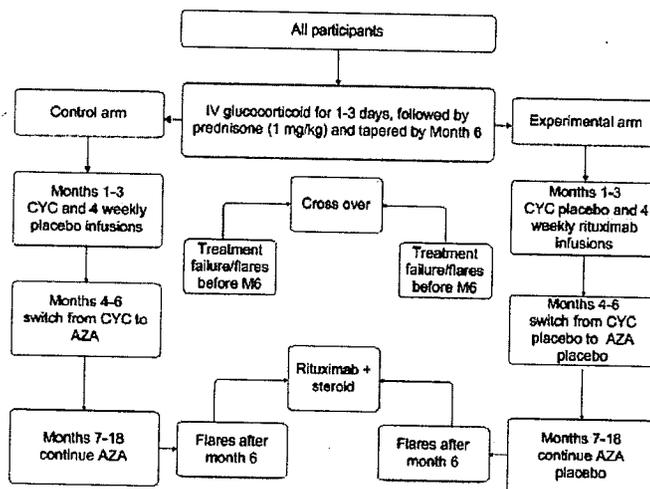
RAVE Trial Design

RAVE was a multicenter, randomized, double-blind, double-dummy, active-controlled, non-inferiority clinical trial in patients with WG and MPA, which was conducted by the Immune Tolerance Network (sponsored by the National Institute of Allergy and Infectious Diseases). The trial was conducted in two phases: a 6 month remission induction phase and a 12 month remission maintenance phase. During the remission phase, eligible patients were randomized 1:1 to receive either rituximab (RTX) 375mg/m² IV once weekly for 4 weeks or oral cyclophosphamide (CYC) 2 mg/kg daily for 3 to 6 months. RTX placebo and CYC placebo were administered in a blinded fashion. Both treatment groups received pulse glucocorticoid therapy (1 g methylprednisolone or equivalent up to 3 days) the last dose of which was required to have occurred within 14 days of initiation of RTX/RTX placebo infusion, followed by an oral prednisone taper starting at 1mg/kg/day.

Patients who were treatment failures or had severe flares during the remission induction phase were crossed over to the opposite treatment arm or under specific conditions treated with best medical judgment (BMJ). During the maintenance phase or if remission was achieved after Month 3, patients receiving CYC were switched to oral azathioprine (AZA) daily. Patients in the RTX group did not receive additional therapy (AZA) for maintenance of remission.

Patients who had flares after Month 6 received RTX and corticosteroids. The study scheme is shown in the figure below.

Figure 1 RAVE Study Scheme



Eligible patients had to have a diagnosis of WG or MPA according to the Chapel Hill Consensus Conference definition and positive PR3-ANCA or MPO-ANCA. Patients had to have active disease with a BVAS/WG ≥ 3 and severe disease defined by one or more major BVAS/WG items or disease severe enough to require treatment with CYC. One hundred patients in each treatment group were planned for enrollment.

Patients were assessed once a week for the first 4 weeks and then every one to two months for the first 6 months. For the remission maintenance phase, patients were assessed every 3 months.

Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG)

Efficacy was assessed with the BVAS/WG, which is a disease specific index modified for WG. The index consists of items related to major and minor criteria in the following categories: general, cutaneous, mucous membranes/eyes, ENT, cardiovascular, gastrointestinal, pulmonary, renal, nervous system, and other. Disease status/flares are assessed as well as the physician's global assessment (PGA). Signs and symptoms are scored as persistent, new/worse, or none. The index was designed to assess active WG and only items that are attributable to active WG are scored. The maximum possible score is 63. The BVAS/WG is considered a valid, disease specific activity index for WG.⁴ Although the BVAS/WG is specific for WG, use in patients with WG and MPA is reasonable, given that there is some overlap in disease between these vasculitides. Subgroup analysis based upon disease (WG vs. MPA) is warranted.

Additional efficacy variables included the Vasculitis Damage Index (VDI) and the SF-36 for health related quality of life. Safety assessments included adverse events, vital signs, physical

⁴ Stone JH, Hoffman GS, Merkel PA, et al. A Disease-Specific Activity Index for Wegener's Granulomatosis-Modification of the Birmingham Vasculitis Activity Score. *Arthritis & Rheumatism* 2001; 44(4): 912-920.

examination, chest x-ray, and laboratories. A Data Safety Monitoring Board (DSMB) monitored the safety data.

Statistical

The statistical analysis plan was dated January 12, 2009. The primary endpoint, the non-inferiority margin, and the criteria for superiority over CYC were included in the original 2004 protocol.

The primary endpoint was the percentage of patients who have a BVAS/WG of 0 and have successfully completed the glucocorticoid taper at 6 months after randomization.

A two-sided 95.1% CI of the difference in the primary efficacy endpoint between RTX and CYC groups was determined. *Non-inferiority of RTX to CYC* was concluded:

- if lower bound of the CI of the treatment difference was above -20%
- if the % of patients with remission in the RTX group is lower than that of the CYC group, the % of patients with remission in the CYC group must be at least 40%

Secondary endpoints included:

- 1) AE rate during 6 months for specified list of events including death, leucopenia, thrombocytopenia, infections, hemorrhagic cystitis, malignancy, venous thromboembolic event, hospitalization, infusion reactions, and CVA.
- 2) Superiority of RTX to CYC for percentage of patients who have a BVAS/WG of 0 and have successfully completed the glucocorticoid taper at 6 months after randomization (two sided 95.1% CI).

Superiority of RTX to CYC was concluded:

- if lower bound of the CI for the treatment group difference is greater than 0 **and**
- lower bound of two-sided 95.1% CI of the primary efficacy endpoint for the RTX group is greater than or equal to 50%, a conclusion that RTX is superior to CYC can be made.

A detailed discussion of the rationale for use of non-inferiority (NI) design and proposed margins is warranted. NI trial design is typically proposed when a placebo controlled trial or other trial designed to show a difference between two treatments is considered unethical. NI trials can show that any difference between two treatments is small enough to allow a conclusion that the new drug has at least some effect or an effect that is not too much smaller than the active control.⁵ Currently, there are no medications approved for WG and MPA, and because of the serious course of the disease, a placebo controlled trial would not be ethical. Thus, the use of a NI design is reasonable. Since CYC has been used historically to treat these diseases, CYC was chosen as the active comparator.⁶

When using a NI design, it is important to have evidence of efficacy in placebo-controlled trials for the comparator product (historical evidence of sensitivity to drug effects) and to

⁵ FDA Draft Guidance for Industry: Non-Inferiority Clinical Trials. March 2010.

⁶ Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's Granulomatosis Prospective Clinical and Therapeutic Experience with 85 Patients for 21 Years. *Annals of Internal Medicine* 1983; 98: 76-85.

determine an effect size for the active comparator to ensure that the NI trial has assay sensitivity. Using the terminology in the FDA Draft Guidance on Non-Inferiority Clinical Trials, this is termed M1 - the effect of the active control. It is also important to determine the largest clinically acceptable difference of the test drug compared to the active control (M2), i.e. non-inferiority margin.⁵ The rationale for the M1 and M2 chosen for RAVE is discussed below. It is important to note that one of the limitations of NI trials is that variability in trial conduct that “bias towards the null” can obscure lack of a difference, so issues with trial conduct (compliance, patient population, etc) need to be considered in the efficacy analysis.

Historical control information for CYC compared to placebo (M1) is not available and M1 was based upon data from several clinical trials in WG patients that included an oral CYC treatment group. Based upon published data, remission at 6 months in patients with WG treated with oral CYC is 75% with lower limit of the 95% CI of 55%.^{7,8} The Applicant estimated that based upon historical data and the differences in trial design, 55% of patients treated with oral CYC in RAVE would be in remission at 6 months (M1).

In addition to the historical data informing the CYC treatment effect, criteria to assess the efficacy of RTX were also specified based upon historical data. In the Walton paper from 1958, a retrospective review of cases of Wegener’s Granulomatosis was performed and the clinical features, course and treatment (if applicable) were described.⁹ The Applicant analyzed the data in the Walton paper and determined that at 6 months, only 38% of patients survived as shown in the table below.

Table 2 Clinical Course of Patients with WG derived from Walton⁹ Review			
	Patients who died N=56	Surviving patients N=56	95% CI of % of surviving patients
6 months	63%	38%	24.9, 51.5
9 months	75%	25%	14.4, 38.4
12 months	82%	18%	8.9, 30.4

The historical data shows that if WG is not treated, it is rapidly progressive and fatal. Since only 38% of patients survived at 6 months, it is likely that few patients, if any, would have been in complete remission at 6 months. This historical information was used as one of the criteria to assess the efficacy of RTX. If survival with complete remission with RTX at 6 months was greater than 50% (lower bound of 95% CI > 50%), RTX would be superior to untreated WG patients at 6 months based upon historical control. This measure for superiority for RTX is conservative because of the comparison between remission in RAVE versus survival from historical control data. This is reasonable given that the historical control data is quite old and standards of care and supportive care have improved.

⁷ Wegener’s Granulomatosis Etanercept Trial Research Group (WGET). *NEJM* 2005; 352-351-61.

⁸ de Groot K, Harper L, Jayne DRW, et. al. Pulse versus Daily Oral Cyclophosphamide for Induction of Remission in ANCA Associated Vasculitis. *Annals of Internal Medicine* 2009; 150: 670-680.

⁹ Walton EW. Giant Cell Granuloma of the Respiratory Tract (Wegener’s Granulomatosis). *British Medical Journal* 1958; Aug 2: 265-270.

The Applicant proposed the following rationale to support the NI margin (M2) of 20%. As stated above, based upon published data, remission at 6 months in patients with WG treated with oral CYC is 75% (M1) with lower bound 95% CI of 55%. The NI margin of 20% preserves over half of the estimated active control treatment effect. In addition, feasibility played into determination of the margin as well, because of the limited patient population. According to the Applicant, a margin of 10% would have required a similarly powered trial to have a sample size of 792 patients.

An interim analysis was performed when half the patients completed the 6 month evaluation. The purpose of the interim analysis was to stop the trial for inferior efficacy in the RTX group compared to CYC.

Dose Selection

Given the limited patient population, the Applicant did not conduct formal dose ranging studies. The dose of RTX for the pivotal clinical trial was consistent with earlier literature reports with RTX in patients with WG in which RTX was dosed at 375mg/m² once weekly for 4 weeks to achieve B cell depletion.^{10,11} This is also the approved dose for non-Hodgkins lymphoma.

Phase 3 Results

Demographics and Baseline Disease Characteristics

The treatment groups were balanced in terms of baseline demographics. The mean age of patients was 53 years of age. As the protocol allowed adolescents age 15 and older, there were 4 patients that were 15 to ≤ 18 years of age. Patients were primarily caucasian with an even distribution of males and females, which is consistent with the expected population for WG and MPA.

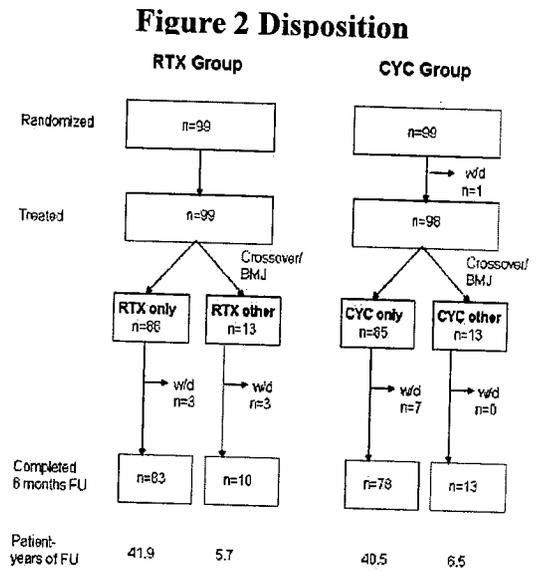
More patients had a diagnosis of WG, 147 (75%), compared to a diagnosis of MPA, 48 (24%). Two patients did not have their AAV type characterized due to missing information or indeterminate diagnosis. Forty-nine percent of patients were newly diagnosed at the time of enrollment. The most common organ system involvement included renal (66%), pulmonary (53%), systemic – fevers, arthralgias (61%), ENT (58%), mucous membranes/eyes (26%), nervous system (20%), cutaneous (18%), with GI and cardiovascular involvement <2%. The mean baseline BVAS/WG score was 8 and similar between groups. In terms of antibody status, 67% of patients had positive ELISA for PR3 and 33% for MPO. Pulse corticosteroid use was balanced between treatment groups.

¹⁰ Specks U, Fervenza FC, McDonald TJ, Hogan MCE. Response to Wegener's Granulomatosis to Anti-CD20 Chimeric Monoclonal Antibody Therapy. *Arthritis & Rheumatism* 2001; 44(12): 2836-2840.

¹¹ Keogh KA, Wylam ME, Stone JH, Specks U. Induction of B Lymphocyte Depletion in Eleven Patients with Refractory Antineutrophil Cytoplasmic Antibody. *Arthritis & Rheumatism* 2005; 52(1): 262-268.

Patient Disposition

There were 13 patients who discontinued by 6 months: 6 in the RTX group and 7 in the CYC group. The majority of patients (2 RTX, 5 CYC) discontinued due to “voluntary withdrawal”, 3 patients died (2 CYC, 1 RTX - discussed in Section 8), 2 patients in the RTX group withdrew due to adverse events (osteomyelitis of ankle requiring debridement and pneumonia), and 1 patient in the RTX group discontinued due to persistent and progressive disease. Dr. Seibel reviewed the CRFs for patients who voluntarily withdrew and determined that many of the patients had experienced AEs or worsening of disease that may have influenced the decision to withdrawal. Thirteen patients in each group received cross over or BMJ therapy. Disposition is shown in Figure 2.



There were nine sites that participated in RAVE and the number of patients enrolled per site is shown in Table 3. The sites were primarily in the US, with one international site in The Netherlands.

Study Center	Number Patients Enrolled
Mayo Clinic	53
Boston University	43
Johns Hopkins	35
Cleveland Clinic	18
Hospital for Special Surgery, New York, NY	17
University Hospital Groningen, The Netherlands	16
Duke University	7
University of Alabama at Birmingham	7
UCSF	1

Compliance, Exposure

With regards to compliance for patients treated with RTX, 97% of patients received $\geq 75\%$ of doses of RTX. With regards to CYC compliance, the data provided has limitations. The CYC dose was adjusted based upon renal function, leucopenia, and other tolerability criteria. Compliance was monitored as patients brought in their pill boxes at each clinic visit to have the number of remaining CYC pills counted. However, the adjusted dose was only recorded in the source documents and not the case report forms and thus not included in the clinical database. When queried about CYC compliance, the Applicant determined that on average, based upon mean dose, patients received 77% of the initial CYC dose at baseline, which was adjusted for renal function and weight. The Applicant noted that this may underestimate compliance given that CYC use was later adjusted by other factors not accounted for in the initial dose (e.g., WBC count). The Applicant evaluated efficacy (complete remission) based upon the percentage of initial CYC dose and found that 54%, 58%, and 48% patients with > 80 , 65-80%, and $<65\%$ of initial CYC dose had complete remission, respectively.

Efficacy Results

The primary analysis population was the ITT population, which included all patients randomized who received study medication. As discussed above, the primary endpoint was the percentage of patients who have a BVAS/WG of 0 and have successfully completed the glucocorticoid taper at 6 months after randomization. Table 4 displays the results for the

primary endpoint for the ITT population with worst observation carried forward for missing data. The results are very similar for the observed data and other analysis sets.

Table 4 Complete Remission (ITT Population)			
	Rituximab N=99 n (%) [95% CI]	Cyclophosphamide N=98 n (%) [95% CI]	Treatment Difference (Two sided 95.1% CI)
Month 6 (primary EP)	63 (64%) [54, 73]	52 (53%) [43, 63]	10.6% (-3.2, 24.3)
Month 12	44 (44%) [34, 54]	37 (38%) [28, 47]	6.7% (-7.0, 20.4)
Month 18	38 (38%) [29, 48]	30 (31%) [22, 41]	7.8% (-5.5, 21.0)
† BVAS/WG of 0 and prednisone dose of 0, worst observation carried forward data imputation			

The results show that the lower bound for the 95.1% CI for the treatment difference was greater than the non-inferiority margin of -20%, thus RTX is not inferior to CYC. One of the secondary efficacy variables included the assessment of superiority of RTX based upon two criteria (lower bound of CI for treatment difference >0 and lower bound of CI for RTX > 50%). While the CI for complete remission in the RTX group excludes 50%, as shown in the above table, the CI for the treatment difference includes the null, thus RTX is not superior to CYC. However, the fact that complete remission in the RTX group exceeded 50% is important and confirms that RTX is superior to historical control survival data from the Walton cohort (Table 2), which supports the efficacy of RTX.

While the main efficacy endpoint was at 6 months, the Applicant provided data on complete remission at Months 12 and 18 as shown in Table 4. The percentage of patients with complete remission decreased over time in both treatment groups; however, the RTX group continued to have a numerically greater proportion of patients with complete remission compared to the CYC group, despite the fact that the CYC group was treated with azathioprine. The CI for the treatment difference at Months 12 and 18 continued to exclude the non-inferiority margin of -20%.

DSI inspection indicated a dosing problem for the infusion of RTX/RTX placebo in 12 patients at the Boston University site. The problems included patients receiving a higher concentration of RTX/RTX placebo or a higher infusion rate, leading to administration of a higher dose of RTX/RTX placebo than specified. Because of the issue at this site, sensitivity analyses were performed removing these patients and excluding all the patients at Boston University. Analyses showed that excluding the patients with dosing issues and excluding all the patients at Boston University, RTX remains non-inferior to CYC as shown in the table below.

Table 5 Complete Remission[†] at Month 6 Sensitivity Analyses - Boston University			
	Rituximab N=99 n (%) [95% CI]	Cyclophosphamide N=98 n (%) [95% CI]	Treatment Difference (Two sided 95.1% CI)
Exclusion of patients with dosing issue	N=93 60 (65%) [55, 74]	N=92 48 (52%) [42, 62]	12.3 (-1.8, 26.5)
Exclusion of Boston University data	N=78 52 (67%) [56, 77]	N=76 40 (53%) [41, 64]	14% (-1.4, 29.4)

[†] BVAS/WG of 0 and prednisone dose of 0, worst observation carried forward data imputation

Flares

The secondary efficacy variables included severe and limited flares. A severe flare was defined as a BVAS/WG ≥ 3 or the occurrence of a new major sign/symptom (pre-specified in the protocol) following a period in which the BVAS/WG had improved or if the investigator decided that CYC would be indicated by standard clinical practice. A limited flare was defined as a new occurrence or worsening of a minor sign/symptom (pre-specified in the protocol) following a period of improvement. The number of severe (6 RTX, 10 CYC) and limited flares (14 RTX, 14 CYC) during the first 6 months were similar between treatment groups. At 18 months, the number of severe (8 RTX and 4 CYC) was higher in the RTX group. Severe flares included the general, mucous membranes/eyes, ENT, pulmonary and renal systems.

Subgroup and sensitivity analyses

One treatment center (Mayo) enrolled the most number of patients and had the largest treatment difference (92% RTX, 59% CYC) of 33% compared to the other treatment centers. A sensitivity analysis was performed without this center and it showed that the treatment difference was 2.7% (-14%, 19%) with the lower bound of the CI that was above the non-inferiority margin of -20%. The Applicant explored gender and there was no notable difference. With regards to age subgroups (< 18 years, 18-65 years, ≥ 65 years), there were few patients < 18 years and > 65 years so data is limited, but a lower percentage of patients > 65 years had complete remission compared to younger patients.

Subgroup analysis based upon AAV disease type is shown in Table 6. There was a numerically greater proportion of patients in the RTX group with WG and MPA with complete remission compared to the CYC group. The treatment group difference was greatest for the WG group and consistent with the primary endpoint results. The treatment group difference was less for patients with MPA; however, it should be noted that there were only 48 patients with MPA and thus the study was not powered for this subgroup. The Applicant provided the subgroup analyses for Months 12 and 18. The percentage of patients with complete remission was smaller at the later timepoints.

Table 6 Complete Remission at 6 months† - Subgroup Analyses (ITT Population)			
	Rituximab N=99	Cyclophosphamide N=98	Treatment Difference (Two sided 95.1% CI)
Wegener's Granulomatosis	46/73 (63%)	37/74 (50%)	13.0 % (-2.9, 29.0)
Microscopic Polyangiitis	16/24 (67%)	15/24 (63%)	4.2% (-23.0, 31.3)
New disease at baseline	29/48 (60%)	31/48 (65%)	-4.2% (-23.6, 15.3)
Relapsing disease	34/51 (67%)	21/50 (42%)	25% (5.8, 43.6)

† BVAS/WG of 0 and prednisone dose of 0, worst observation carried forward data imputation
Based upon non-missing data

The Applicant proposed a labeling claim regarding the efficacy of (b) (4). This claim is not supported. First, this is an exploratory subgroup analysis that was not pre-specified. Second, the definition of (b) (4)

(b) (4)

Given the issues described above a specific labeling claim is not supported, but the (b) (4)

Because of the issues with the (b) (4) definition, a subgroup analysis based upon previous CYC use was requested and is shown in the table below. Overall 45% of patients received treatment with CYC prior to randomization ((b) (4)). There were fewer patients previously treated with CYC that had complete remission in the CYC group compared to the RTX group. The proportion of patients treated with RTX who had complete remission in both subgroups was similar.

Table 7 Complete Remission at 6 months† Subgroup Analysis Prior Use of Cyclophosphamide			
	Rituximab N=99	Cyclophosphamide N=98	Treatment Difference (Two sided 95.1% CI)
Prior use of CYC	29/47 (62%)	19/42 (45%)	16.5% (-4.0, 37.0)
No prior use of CYC	34/52 (65%)	33/56 (59%)	6.5% (-11.8, 24.7)

† BVAS/WG of 0 and prednisone dose of 0, worst observation carried forward data imputation

The effect of RTX in patients with baseline renal disease is important given that renal involvement occurs in the majority of patients with WG and MPA. Analyses were performed for baseline renal disease as shown in the table below. The analyses show that in patients with baseline renal disease, a greater proportion of patients treated with CYC achieved remission compared to patients treated with RTX, although the results were quite similar in patients with at least one major renal item on the BVAS/WG (61-63%). For higher baseline renal function,

the results trended the opposite direction – a greater proportion of patients in the RTX group achieved remission compared to the CYC group.

Table 8 Complete Remission at 6 months[†]			
Subgroup Analyses – Baseline Renal Disease			
	Rituximab N=99	Cyclophosphamide N=98	Treatment Difference (Two sided 95.1% CI)
Baseline Renal Disease			
≥ 1 major renal item on BVAS/WG – RBC casts + ↑Cr >30% or ↓CrCl >25%	31/51 (61%)	32/51 (63%)	-2.0 (-20.1, 17.0)
No major renal item on BVAS/WG	32/48 (67%)	20/47 (43%)	24.1 (4.6, 43.6)
CrCl < 60 mL/min	25/45 (56%)	18/28 (64%)	-8.7 (-31.8, 14.3)
CrCl ≥ 60 mL/min	38/54 (70%)	34/70 (49%)	21.8 (4.8, 38.8)
Creatinine > 1.2 mg/dL	24/47 (57%)	31/45 (69%)	-11.4 (-31.1, 8.2)
Creatinine ≤ 1.2 mg/dL	36/52 (69%)	21/53 (40%)	29.6 (11.3, 47.9)

[†] BVAS/WG of 0 and prednisone dose of 0, worst observation carried forward data imputation

In the discussion of remission in patients with renal disease, it is important to note the recent publication of results of a clinical trial with RTX in patients with renal vasculitis, RITUXVAS.¹² RITUXVAS was an open-label, randomized trial in 44 patients with AAV with renal involvement (necrotizing granulonephritis on biopsy, red cell casts, or hematuria). Patients received IV corticosteroids followed by an oral glucocorticoid regimen and either RTX 375 mg/m² weekly for 4 weeks and IV CYC with the 1st and 3rd dose OR IV CYC for 3 to 6 months followed by azathioprine. The primary outcome was sustained remission (BVAS 0 for 6 months) achieved in 76% (25/33) of patients in the RTX group and 82% (9/11) in the CYC group with a treatment difference of -6% (p=0.68). RITUXVAS was a different trial design (open label and IV CYC) and the RTX group also received CYC so cross study comparison with RAVE is limited.

Retreatment

Only one 4-week course of RTX was specified in RAVE; however, patients could receive an additional course of RTX based upon BMJ. In addition, in the maintenance phase, additional courses of RTX were allowed. Information on retreatment was requested during the review period. Of the 99 patients randomized to RTX, 15 patients received open-label RTX ranging from 32 to 79 weeks (mean 54 weeks) after the first dose of study medication. Ten of the 15 patients had complete remission at 6 months and 5 did not. One additional patient received a second course of RTX therapy but they also received cross over treatment. This limited data does not establish the efficacy of retreatment with subsequent course of RTX and a post-marketing study to evaluate retreatment is recommended.

Efficacy Conclusions

The Applicant submitted the results of a single trial to support this application. The Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biologic

¹² Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *NEJM* 2010; 363:211-220.

Products outlines situations in which reliance on a single study can be considered, e.g. a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds. The results of RAVE demonstrated that RTX is non-inferior but not superior to CYC for the induction of complete remission in patients with WG and MPA. Also supportive of efficacy is that remission in patients treated with RTX exceeded the survival of untreated patients based upon historical data. The results of RAVE are reliable and statistically persuasive and the statistical reviewer, Dr. Yongman Kim agrees. The endpoint (complete remission) is of important clinical benefit; thus, reliance on a single clinical trial is acceptable. The primary clinical reviewer, Dr. Deborah Seibel agrees with this conclusion.

8. Safety

The safety profile of RTX in patients with rheumatoid arthritis and lymphoma has already been established. The safety data with RTX in patients with WG and MPA comes from the single trial, RAVE. Given the limited population and the known safety information from other populations, the safety database in patients with WG and MPA is acceptable. Overall, the safety review did not identify a new safety signal for RTX. The safety data presented below are primarily from the 6 month remission induction phase, unless otherwise noted. The safety data are presented for the RTX and CYC group overall, but it should be noted that 13 patients in each treatment group received cross over or BMJ therapy (Figure 2), which complicates interpretation of the safety data. The subgroups of RTX only, RTX other (other treatment) and CYC only and CYC other (other treatment) will be noted as needed.

Deaths

In the remission induction phase, there were 2 deaths in the CYC group (infection) and 1 in the RTX group (multi-organ failure and infection). There was an additional death in the RTX group (pulmonary hemorrhage) in the remission maintenance phase. Overall, the deaths were balanced and the causes of death (infection and worsening of disease) are not unexpected in this patient population.

Serious Adverse Events (SAEs)

Serious adverse events at 6 months were generally balanced between treatment groups (33-34% of patients); however, there were some differences that should be noted. There were more diarrhea (2%), leucopenia (3%), and pyrexia (2%) SAEs in the RTX group compared to none in the CYC group. There were more vascular disorder SAEs in the CYC group (8%) compared to the RTX group (2%), primarily due to deep venous thrombosis. The general pattern of SAEs was similar at 18 months; however, there were more patients with SAEs in the RTX group (47%) compared to the CYC group (42%).

There were more hospitalizations in the RTX group (10%) at 6 months compared to the CYC group (4%). The hospitalizations were reviewed and are primarily due to leucopenia and infection and various other isolated events, such as pulmonary embolism, renal failure, and hypersensitivity. In addition, some of the patients who were hospitalized in the RTX group also received cross over or BMJ therapy as shown in the table below. Due to the small number of events for each cause of hospitalization and the additional therapy some patients received, a clear pattern was not identified other than infection and leucopenia, which are known risks with RTX.

Table 9 Cause of Hospitalizations at 6 Months			
	RTX N=99		CYC Only N=98
6 months	10 (10%)		4 (4%)
	RTX only n=5	RTX other [†] n=5	
leucopenia and pneumonia	2		
leucopenia and pyrexia		1	
pneumonia	1		2
pulmonary embolism		1	
pulmonary hemorrhage		1	
bronchitis	1		
renal failure		1	
hypersensitivity	1		
osteomyelitis		1	
ARDS			1
URTI			1
[†] Patients who received cross over or BMJ therapy in addition to RTX			

Discontinuations

Withdrawals due to adverse events were similar between treatment groups. Eight (8%) of patients withdrew due to adverse events in the RTX group compared to 13 (13%) of patients in the CYC group. Leukopenia, hypersensitivity, and renal failure were the most common AEs leading to discontinuation.

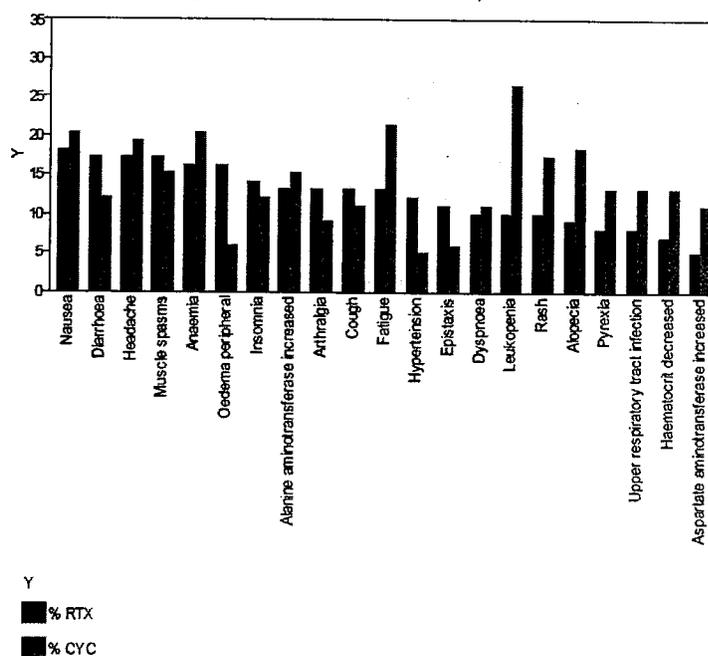
Common AEs

At 6 months, the total number of AEs and the number of patients with AEs were similar between treatment groups. A table of common AEs is shown below and a version of the table is recommended for the product label. The dataset for adverse events was reviewed and a random sample of verbatim terms (1/10th of AEs) was compared to preferred terms and coding appeared appropriate. An analysis of AEs (figure below) was consistent with the table of common AEs provided in the study report. Overall, infection was one of the most common AE categories and will be discussed in more detail. Some of the preferred terms could be combined, such as leucopenia and decreased WBC count, anemia and decreased HCT, and increased ALT and AST, but combining these groups does not substantially change the pattern.

Table 10 Adverse Events in >10% of Patients in Either Treatment Group at 6 Months

Preferred Term	RTX N=99	CYC N=98
Nausea	18 (18%)	20 (20%)
Anemia	16 (16%)	20 (20%)
Headache	17 (17%)	19 (19%)
Leukopenia	10 (10%)	26 (27%)
Fatigue	13 (13%)	21 (21%)
Muscle spasms	17 (17%)	15 (15%)
Diarrhea	17 (17%)	12 (12%)
Increased ALT	13 (13%)	15 (15%)
Alopecia	9 (9%)	18 (18%)
Rash	10 (10%)	17 (17%)
Insomnia	14 (14%)	12 (12%)
Cough	13 (13%)	11 (11%)
Decreased WBC	4 (4%)	19 (19%)
Arthralgia	13 (13%)	9 (9%)
Peripheral edema	16 (16%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Pyrexia	8 (8%)	13 (13%)
URTI	8 (8%)	13 (13%)
Decreased HCT	7 (7%)	13 (13%)
Epistaxis	11 (11%)	6 (6%)
Hypertension	12 (12%)	5 (5%)
Increased AST	5 (5%)	11 (11%)

Figure 3 Common AEs at 6 Months
(generated from dataset)



Selected AEs of Interest

Given the known safety profile of rituximab, several categories of AEs are of interest, including infusion reaction, infection, immunogenicity, and malignancy. In addition, as described above, the Applicant included a secondary endpoint of safety events of interest. These will be discussed below.

Infusion Reaction

Infusion reactions, including fatal reactions, are a known risk of RTX. Infusion related reactions were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. In the remission induction phase, these reactions were balanced between treatment groups (RTX 12%, CYC 11%) and included cytokine release syndrome (RTX 5%, CYC 2%), flushing (RTX 4%, CYC 4%), throat irritation (RTX 2%, CYC 1%), and tremor (RTX 2%, CYC 1%). Infusion reactions decreased with each RTX infusion from 12% with the 1st infusion to 1% with the 4th infusion. Two patients in the RTX group had dose modification or interruption, but no patient was discontinued due to infusion related reaction. It is important to note that patients were pre-medicated with antihistamine and acetaminophen before each infusion and were on background oral corticosteroids which may have mitigated or masked an infusion reaction.

Infection

Infection is a known adverse event associated with both RTX and CYC. In the remission induction phase, there were more patients with infection AEs in the RTX group (62%)

compared to 47% in the CYC group. The most common infections in the RTX group were upper respiratory tract infections, urinary tract infections, and herpes zoster. Overall infection SAEs were balanced between groups (10-11%). The most common serious infection was pneumonia (4% in each group).

Safety Secondary Endpoint

The Applicant included a secondary endpoint of safety events of interest at 6 months - death, leucopenia, thrombocytopenia, infections, hemorrhagic cystitis, malignancy, venous thromboembolic event, hospitalization, infusion reactions, and CVA. Overall, there were fewer patients treated with RTX (22%) and total number of selected AEs (37) compared to the CYC group (35%, 45, respectively). Grade ≥ 3 infections were balanced. Of the individual categories, the largest imbalances were grade ≥ 2 leukopenia (CYC 17%, RTX 5%), venous thromboembolic events (CYC 8%, RTX 5%), and hospitalizations (RTX 10%, CYC 4%). Leukopenia is a known AE and the imbalance in DVT and hospitalizations was discussed previously. Thus, there is no new information gleaned from this composite safety endpoint.

Malignancy

Given the size and duration of RAVE, the data on malignancy are limited, but of interest. During the 6 month remission induction period, 3 malignancies were reported: 2 in the CYC group and 1 in the RTX group. Including the additional remission maintenance period, there were 6 malignancies (prostate, uterine, colon, bladder and colon, lung) in 5 patients in the RTX group and 2 malignancies (prostate and thyroid) in 2 patients in the CYC group. The majority of patients with malignancies had received methotrexate or CYC prior to the start of the study, including 2 patients in the RTX group. Due to the previous medication use and the short term duration of RAVE, it is difficult to draw any conclusions regarding malignancy.

Immunogenicity

Rituximab is a chimeric murine/human monoclonal antibody and is known to be associated with antibody formation in other patient populations. In patients with WG and MPA, 23% of RTX treated patients tested positive for anti-human anti-chimeric antibodies (HACA) by 18 months. The percentage of patients testing positive for antibodies increased during the study, which is likely related to the decrease in RTX serum concentration over time as RTX in the serum may interfere with the assay. The Applicant evaluated the safety profile of patients who were HACA positive vs. HACA negative and the rates of AEs and patients with infusion related reactions were similar between the subgroups. At least 4 patients who tested positive for HACA received a second open-label course of RTX without an infusion reaction. While the presence of HACA is notable and will be described in the label, the clinical relevance is unclear.

Retreatment

As discussed in Section 7, of the 99 patients randomized to RTX, 15 patients received open-label RTX ranging from 32 to 79 weeks (mean 54 weeks) after first dose of study medication. One additional patient received a second course of RTX therapy but they also received cross over treatment. The safety profile of the 1st versus 2nd course of RTX in the 15 patients was evaluated and there was no increase in AEs following the 2nd course of RTX. This limited

data does not establish the safety of retreatment with subsequent course of RTX and a post-marketing study to evaluate retreatment will be required.

Safety Summary

The safety data submitted in this program is limited due to the limited patient population, but is acceptable given that the safety profile of RTX in patients with rheumatoid arthritis and lymphoma has already been established. The safety review did not identify a new safety signal for RTX in this population. Additional long term safety will be requested in a post-marketing study.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application for the following reasons. Rituximab is an approved product with known safety profile and the safety profile in this patient population did not reveal a new safety signal. Although the pivotal trial design relied on historical control, the design of the clinical trial was discussed at a Regulatory Briefing on February 26, 2010, where the committee was supportive. The study met the pre-specified primary endpoint to establish efficacy. Thus, this application did not raise any issues that warranted discussion at an advisory committee meeting.

10. Pediatrics

Because this application was given orphan designation, pediatric studies under PREA are not required. There were 6 patients 18 years and younger included in the clinical trial, RAVE, and given the limited number of patients, no conclusions can be drawn in this patient population.

11. Other Relevant Regulatory Issues

A DSI consult was requested for this application because only a single pivotal study was submitted for this indication for which there are no FDA-approved therapies. Three US centers (Boston University, Johns Hopkins, Mayo Clinic) were chosen based upon the largest enrollment. In addition, once center (Mayo Clinic) reported higher complete remission rate for rituximab compared to the overall population. These 3 centers had 65% of the entire study population. At the time of finalization of this review, a clinical inspection summary from the DSI inspection is available. Preliminary findings showed that there were no major issues identified at the Johns Hopkins or Mayo Clinic sites. However, there was an issue with regards to dosing identified at the Boston University site. Twelve patients received a higher concentration of RTX or RTX placebo or a higher infusion rate, leading to administration of a higher dose of RTX or RTX placebo than specified. Because of concerns with data from this site and these patients, sensitivity analyses were performed for the primary endpoint removing the data from these 12 patients as well as the entire Boston University site. The results showed that RTX remained non-inferior to CYC.

12. Labeling

At the time of finalization of this review, labeling negotiations are ongoing with the Applicant. The following are the main issues with regards to labeling.

- The proposed indication of treatment of [REDACTED] (b) (4) patients with WG and MPA were

included in this program. The recommended indication is for the treatment of patients with WG and MPA.

- A new Warning was added regarding limited information with retreatment.
- The Applicant proposed a claim regarding (b) (4), but this language was removed because of the issues discussed in Section 7.
- The current labeling for rituximab includes a Medication Guide and minor modifications regarding the new indication were incorporated

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is **Approval**. The Applicant has provided the results of a single adequate and well-controlled clinical trial that demonstrated that RTX is non-inferior but not superior to CYC for the induction of complete remission in patients with WG and MPA. Also supportive of efficacy is that at 6 months, remission in patients treated with RTX exceeded the survival of untreated patients based upon historical data. Although the Applicant submitted the results of a single trial to support this application, based upon criteria outlined in the Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, reliance on a single trial is appropriate in this situation because RAVE is a single multicenter trial of excellent design and provided highly reliable and statistically strong evidence of an important clinical benefit, complete remission.

- Risk Benefit Assessment

The risk benefit profile of RTX is favorable for patients with WG and MPA. The efficacy of RTX for the induction of remission in patients with WG and MPA was established in RAVE. RTX does have known safety concerns, including infusion reactions, infections, severe mucocutaneous reactions, and PML. The clinical program submitted was limited in size due to the patient population, but no unique safety signal was identified in this patient population. Currently, there are no approved therapies for the treatment of WG and MPA. There is an unmet need for treatments for these serious diseases that have significant morbidity and are potentially life-threatening. Although therapies, such as corticosteroids and CYC are used off-label for these conditions, these medications have potentially serious risks as well. Given the submitted efficacy data and the unmet need, the risk benefit profile in patients with WG and MPA is acceptable.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A Risk Evaluation and Mitigation Strategy is not required for this application. Rituximab has a Medication Guide for patients, which is part of the approved labeling but is not part of a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

To further obtain information regarding repeat courses of rituximab and use with concomitant medications in patients with WG and MPA, the Applicant has agreed to conduct a post-marketing study. The details of the study are under discussion at the time of finalization of this review. Since this supplemental BLA is for an orphan indication, PREA is not triggered.

- Recommended Comments to Applicant

None.

 4/5/11

Sally Seymour, M.D.
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
Division of Pulmonary, Allergy and Rheumatology Products (HFD-570)

Application:	sBLA 103705	Proprietary Name:	Rituxan
Applicant:	Genentech Inc,	USAN Name:	rituximab
Medical Officer:	Deborah Seibel, M.D.	Category:	biologic
Team Leader:	Sally Seymour, M.D.	Route of Administration:	intravenous
Review Date:	November 18, 2010		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
October 15, 2010	October 18, 2010	sBLA 103705/5344	Electronic

RELATED APPLICATIONS :

Document Date	Application Type	Comments
7/20/2004	IND 11831 Submitted by DAIT NIAID	part of a joint development project between Genentech, Biogen Idec Inc, and F.Hoffman La Roche Ltd

REVIEW SUMMARY: This is a filing and planning review of a supplemental BLA for rituximab, an approved medication for a new indication. The proposed indication is (b) (4) in combination with glucocorticoids. There are currently no approved treatments for this indication that has been granted Orphan status. The proposed dose is 375 mg/m² once a wk for 4 weeks. The dose was based upon investigator studies, and is similar to the dose approved for lymphoma. Notably, the proposed duration is shorter (4 weeks) and used in combination with glucocorticoids.

The Sponsor has submitted a single pivotal trial, RAVE, which is a multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international study in 197 patients with Wegener's Granulomatosis or Microscopic Polyangiitis. Patients received pulse steroids and were randomized 1:1 to either rituximab (RTX) for 4 weeks or oral cyclophosphamide (CYC) for 4 to 6 months. The development program is somewhat unusual in that it consists of a single clinical trial that compares rituximab to an active control (CYC) that is not approved for the proposed indication. The Sponsor has also provided some supportive information from other studies of (b) (4), and from other indications for RTX, but this is limited to summary information.

The application contains the elements required for filing, including an ISE and ISS and datasets. The application is electronic and is organized in eCTD format. The application contains material supporting the stated primary endpoint but does not include the additional 12 month remission maintenance phase data. Nonetheless, the submission is adequate to allow clinical review and is fileable. The Sponsor has requested priority status for the application. Because of the serious nature of (b) (4) and the unmet need, a priority review is appropriate. Comments will be conveyed requesting some of the additional analyses.

OUTSTANDING ISSUES: comments will be conveyed

RECOMMENDED REGULATORY ACTION: Fileable

Medical Reviewer: Deborah Seibel, MD

Medical Team Leader: Sally Seymour, MD

[Handwritten signatures and dates]
 12/3/10
 12/3/10

General Information

ANCA-associated vasculitis refers to a group of rare vascular inflammatory diseases with a common serologic finding, a positive anti-neutrophilic cytoplasmic antibody. Two of these disorders share some common features: Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA). WG and MPA affect similar size vessels, similar organs, similar patient populations, have similar prognosis, and appear to respond to similar therapy. These diseases were fatal until the advent of steroids but proved to be even more responsive to steroids in combination with additional immunosuppressive therapy. While corticosteroids and cyclophosphamide (CYC) are the standard of care, there are, however, no approved therapies for ANCA-associated vasculitis.

Genentech has submitted an application for its antiCD-20 antibody, rituximab (Rituxan) for the proposed indication (b) (4) in combination with glucocorticoids. The therapy was developed in partnership with the National Institute of Allergy and Infectious Diseases. The application includes a pivotal study comparing patients with Wegener's Granulomatosis and Microscopic Polyangiitis treated with rituximab to those treated with the unapproved standard of care, cyclophosphamide. The proposed rituximab dosing follows the dose already approved for lymphoma. The cyclophosphamide and steroid doses are taken from the literature. This sBLA application includes unusual features in trial design, using noninferiority to an unapproved therapy, a historical control. It provides some interesting questions regarding choice of patient population and substantial evidence in the case of rare diseases. The submission is provided in eCTD format.

I. Regulatory and Foreign Marketing History

A. Regulatory History

The original Rituxan BLA was approved November 26, 1997 for the treatment of lymphoma. Subsequent approvals were for treatment of non-Hodgkins Lymphoma in 2001, for treatment of Rheumatoid Arthritis starting in 2006, and for treatment of CD20-positive chronic lymphocytic leukemia in 2010.

The following is a brief summary of the regulatory history for the (b) (4) (b) (4) development program.

- **April 2004** PIND/EOP2 meeting discussion on proposal for single trial with CYC as comparator with non-inferiority design
 - two controlled clinical trials are generally expected to support efficacy
 - regarding (b) (4) indication - the sponsor will need to provide information regarding the effects of CYC in patients with MPA. If the effect is similar in patients with WG and MPA, then (b) (4) indication may be supported.
 - CYC is an appropriate comparator since it is considered standard of care
 - perform subgroup analysis on patients who received pulse corticosteroids

- provide historical data regarding CYC and remission and justification of 20% NI margin
- **July 2004** IND 11831 for Rituxan in (b) (4) (the pivotal study in this submission) was submitted
- **July 2006** – orphan drug designation (b) (4)
- **February 2010** the trial design and use of a historical control presented at a CDER Regulatory Briefing where the discussion was supportive of the trial design.
- **March 2010** type B pre-sBLA meeting to discuss the data from the pivotal Phase II/III Study ITN201AI(RAVE) contained in this sBLA application. Points discussed included:
 - a single trial (RAVE) is acceptable for sBLA submission, but the application should provide justification for reliance on a single trial. RITUXVAS does not appear to be adequate for a supportive study.
 - ISE and ISS are required
 - the proposed application appeared to meet the criteria for priority review
 - an advisory committee is likely

B. Foreign Marketing History

The Sponsor provided a summary of significant foreign marketing developments (such as approvals) that occurred for rituximab between May 14, 2008 and September 13, 2010. An appendix "Current Registration Status Report" covered the time period from initial FDA approval of Rituxan for Rheumatoid Arthritis on February 28, 2006 through May 31, 2008. Rituximab does not currently have the proposed (b) (4) indication in any other country.

II. Items required for Filing

A. Necessary Elements (21 CFR 314.50)

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			

	Content Parameter	Yes	No	NA	Comment
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1) efficacy supplement
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Location in submission: Study U2639s/ITN021A1		X		The study uses a dose already approved for NHL, & submitted a PK study to demonstrate the medication in this new indication
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: _____ Indication: _____ Pivotal Study #2 _____ Indication _____				Rituximab Therapy for the Induction of Remission & Tolerance in ANCA-associated vasculitis (b) (4) N/A. The Sponsor submitted a single pivotal study.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Discussed at EOP2 meeting
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Primarily US population
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Orphan indication
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			Acceptable for orphan indication
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? Granted Orphan Drug Status 2/14/2006 letter attached	X			Also qualifies for an exemption from the Pediatrics Research Equity Act as orphan drug
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Primarily US population
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				Deferred to stats
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Deferred to stats

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				Deferred to stats
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

B. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

Reviewer's Comment: Although the Sponsor did submit the material pertaining to the primary endpoint, additional subgroup analyses may be needed as well as the 12 month period following induction would be informative and will be requested. .

III. Clinical Studies

This sBLA submission consists of 1 controlled study as described below. There is some additional information from RITUXVAS, an open label study in a different population, with a different treatment regimen, that was not successful. The Sponsor also provided 12 additional uncontrolled or case studies cited, each w/ approx 10 patients, published 2005-2009.

Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
ITN021AI/RAVE United States	P3 efficacy and safety trial	197 patients with WG and MPA	R, DB, AC	Rituximab IV 375mg/m ² per wk x 4 +oral corticosteroids OR Cyclophosphamide + oral corticosteroids	6 months – remission induction then 12 month remission maintenance period	Complete remission BVAS/WG = 0 and successful taper of CS at 6 months

A. Pivotal Study

Study ITN201AI(RAVE) is a multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international non-inferiority study. In the 6 month remission phase, 197 patients with Wegener's Granulomatosis or Microscopic Polyangiitis received pulse steroids then were randomized 1:1 to either rituximab (RTX) or oral cyclophosphamide (CYC), both with oral steroid therapy tapered off by 6 months. The 6 month remission phase was followed by a 12 month maintenance phase. Patients who got CYC received oral azathioprine to maintain remission off steroids. Patients who received RTX did not receive azathioprine.

The primary endpoint was complete remission off steroids at 6 months defined as a BVAS=0 (Birmingham Vasculitis Activity Score) and no corticosteroids. The study was non-inferiority design with a NI margin of -20% comparing rituximab to cyclophosphamide. In addition, superiority of rituximab to historical control (>50% remission) was also specified. The following table shows the results for the primary endpoint from the proposed product label.

(b) (4)



B. Dose Selection

The proposed dose for rituximab of 375 mg/m² per week for 4 weeks was based upon the approved dose for rituximab for lymphoma and published reports of investigator studies that suggested efficacy with the proposed dose.

C. Supportive Studies

Also submitted was Study U2639s/ITN021AI, population pharmacokinetics of rituximab in patients with severe ANCA-associated vasculitis. This population pharmacokinetic (PK) analysis characterizes the pharmacokinetics of rituximab based upon analysis at 6 months in 97 AAV patients in the rituximab arm of the pivotal Study ITN201AI(RAVE).

A supportive study entitled RITUXVAS was supplied in support of the pivotal study, but the information provided was limited and the study report was not included.

IV. DSI Review / Audit

A DSI consult has been requested for this application because only a single pivotal study was submitted for this indication for which there are no FDA-approved therapies. The study had a multicenter design with eight U.S. centers and one European center enrolling a total of 197 patients. The sites requested for inspection are the three centers with the highest enrollment, Boston U (n=45), Johns Hopkins U (n=35), and Mayo Clinic (n=53). These 3 centers had 65% of the entire study population. In addition, efficacy results could be driven by one of these 3 centers; Mayo Clinic reported a higher complete remission rate for RTX (92.3%) compared to that of CYC (61.5%) considering rates in the overall population (64.3% for RTX vs. 54.7% for CYC with total n=193).

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects
Peter Merkel, M.D. Boston University School of Medicine, Vasculitis Center, E-533, 715 Albany Street Boston, MA 02118 Phone 617 414 2501, fax 617 414 2510	Study ITN201A1 (RAVE)	43
Philip Seo, M.D. The Johns Hopkins Vasculitis Center, 5501 Hopkins Bayview Circle, Room 1B.1A The Johns Hopkins Asthma and Allergy Center, Baltimore, MD 21224 Phone 410 550-6813, fax 410 550 6830	Study ITN201A1 (RAVE)	35
Ulrich Specks, M.D. Mayo Clinic 200 First Street SW Rochester, MN 55905 Phone 507 284 2301, fax 507 284 4521	Study ITN201A1 (RAVE)	53

V. Brief Review of Proposed Labeling

The proposed labeling provided in the application is based on the currently approved labeling with additional information:

- Indications and Usage, Dosage and Administration
 - (b) (4): Rituxan (rituximab), in combination with glucocorticoids, is indicated for the treatment of (b) (4)
 - administer Rituxan as 375 mg/m² intravenous infusion once weekly for 4 weeks
- Section 6 - Adverse Reactions
 - new table of AR, paragraphs regarding infusion reactions, infection, malignancies
- Section 14 – Clinical Trials
 - description of clinical trial, table of primary efficacy results
 - (b) (4)

Reviewer's Comment: Although the indication of (b) (4) preliminary review of that term and the (b) (4) qualification of the proposed indication (i.e. (b) (4)) or specification that the product is indicated for (b) (4)

VI. Timeline for Review

<u>Milestone</u>	<u>Target Date for Completion</u>
<u>Filing Planning Meeting</u>	<u>November 18, 2010</u>
<u>Filing Date</u>	<u>November 18, 2010</u>
<u>74th Day Letter</u>	<u>November 18, 2010</u>
<u>Mid-Cycle Meeting</u>	<u>January 28, 2011</u>
<u>Full Labeling Meeting</u>	<u>March 2, 2011</u>
<u>Wrap-up Meeting</u>	<u>March 7, 2011</u>
<u>Primary Reviews</u>	<u>March 26, 2011</u>
<u>CDTL Memo</u>	<u>April 5, 2011</u>
<u>Secondary Reviews</u>	<u>March 29, 2011</u>
<u>PDUFA Due Date</u>	<u>April 19, 2011</u>

VII. Summary

This is a medical officer Filing Review of supplemental BLA 103705 for rituximab, an approved medication for a new indication. The proposed indication is (b) (4) (b) (4) in combination with glucocorticoids. There are currently no approved treatments for this indication (b) (4). The proposed dose is 375 mg/m² once a wk for 4 weeks. The dose was based upon investigator studies, and is similar to the dose approved for lymphoma. Notably, the proposed duration is shorter (4 weeks) and used in combination with glucocorticoids.

The Sponsor has submitted a single pivotal trial, RAVE, a multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international study in 197 patients with Wegener's Granulomatosis or Microscopic Polyangiitis. Patients received pulse steroids and were randomized 1:1 to either rituximab (RTX) for 4 weeks or oral cyclophosphamide (CYC) for 4 to 6 months. The development program is somewhat unusual in that it consists of a single clinical trial that compares rituximab to an active control (CYC) that is not approved for the proposed indication. The Sponsor has also provided some supportive information from other studies of (b) (4), and from other indications for RTX, but this is limited to summary information.

The application contains the elements required for filing, including an ISE and ISS and datasets. The application is electronic and is organized in eCTD format. The application contains material supporting the stated primary endpoint but does not include the additional 12 month remission maintenance phase data. Nonetheless, the submission is adequate to allow clinical review and is fileable. The Sponsor has requested priority status for the application. Because of the serious nature of (b) (4) and the unmet need, a priority review is appropriate. Comments will be conveyed requesting some of the additional analyses.

VIII. Comments to the Sponsor

Study ITN201AI included a 6 month remission phase and an additional 12 month remission maintenance phase. Your submission did not include the data from the additional 12 month remission maintenance phase, which provides information on duration of treatment effect and long term safety. Without the remission maintenance phase data, the adequacy of your application to support the proposed indication will be a review issue.

CLINICAL REVIEW

Application Type Supplemental BLA
Application Number(s) sBLA 103705/5344
Priority or Standard Priority

Submit Date(s) October 15, 2010
Received Date(s) October 18, 2010
PDUFA Goal Date April 19, 2011
Division / Office Division of Pulmonary, Allergy,
and Rheumatology Products

Reviewer Name(s) Deborah Seibel, M.D.  3/25/11
Clinical Team Leader Sally Seymour, M.D.  3/25/11
Review Completion Date March 25, 2011

Established Name Rituximab
(Proposed) Trade Name Rituxan
Therapeutic Class CD20-directed cytolytic antibody
Applicant Genentech Inc

Formulation(s) Injection
Dosing Regimen 375 mg/m² Q wk for 4 weeks
Indication(s) Wegener's Granulomatosis (WG)
and Microscopic Polyangiitis
(MPA)
Intended Population(s) Patients with
Wegener's Granulomatosis and
with Microscopic Polyangiitis

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation is for approval of this supplemental biological licensing application for rituximab for the treatment of patients with Wegener's Granulomatosis and Microscopic Polyangiitis who are also receiving glucocorticoid therapy. The data contained in this application is sufficient to support a finding of efficacy and safety for rituximab for Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) when administered as a dosing regimen of 375mg/m² by intravenous infusion once weekly for 4 weeks along with glucocorticoid therapy for induction of remission. The recommendation for approval is assuming a satisfactory report on the DSI audit, which is pending at the time of finalization of this review.

It should be noted that the Applicant proposed an indication for (b) (4) patients with WG and MPA (b) (4). Therefore, the recommendation is to (b) (4) patients with WG and MPA.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The clinical program is based upon a single, active controlled, non-inferiority design clinical study comparing rituximab to cyclophosphamide in patients with WG and MPA (Study ITN021AI - RAVE). To understand the rationale for the study design, a brief discussion of WG and MPA is warranted.

Two major forms of systemic vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA) are Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA). WG and MPA share many overlapping features including the necrotizing small vessel vasculitis found in the lungs, skin, vaso nervorum, and other organs, and pauci-immune, segmental, necrotizing (crescentic) glomerulonephritis found in the kidney. The prognosis for untreated disease was poor with a low likelihood of survival, until use of glucocorticoids that slowed disease progression, and extended survival. In the 1970's, the use of cyclophosphamide with glucocorticoids was shown to extend survival and induce a remission in some patients. Because of this information, cyclophosphamide has been the standard of care, but it is also associated with serious toxicities. Promising results from open label investigator studies suggested rituximab

might offer another treatment option for patients with Wegener's Granulomatosis and Microscopic Polyangiitis.

To evaluate the efficacy and safety of rituximab in patients with WG and MPA, a placebo-control would be unethical and there are no approved treatments to provide an active control for which there would be historical evidence of sensitivity to drug effects. Specifically, there were no placebo-controlled studies with cyclophosphamide to provide reproducible evidence of efficacy, and no data to establish an effect size. The Applicant's solution was a novel design demonstrating efficacy using both superiority to a historical control and non-inferiority to the unapproved standard of care, cyclophosphamide.

Summary of Efficacy

The efficacy of rituximab as a treatment for two forms of ANCA-associated vasculitis, WG and MPA, was assessed in a single controlled study, ITN021AI(RAVE), a randomized, double-blind, double-dummy, active-controlled study that was conducted in two phases, a 6 month remission induction phase and a 12 month remission maintenance phase. Efficacy data was derived from the 6-month remission induction phase, in which 197 patients with WG and MPA were randomized to either rituximab 375 mg/ m² once weekly for 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily plus glucocorticoids to induce remission. The primary endpoint was remission assessed at 6 months and defined as a BVAS/WG score of 0 (Birmingham Vasculitis Activity Score for Wegener's Granulomatosis) with steroids tapered off completely. If, during the study, a patient had a severe flare or had disease uncontrolled by the assigned treatment, that patient was allowed to switch over to the opposite treatment arm or receive treatment according to best medical judgment (BMJ). This allowed the patient to be followed for purposes of safety, but the patient was considered a treatment failure for the primary efficacy endpoint. In the remission maintenance phase, patients treated with cyclophosphamide switched to azathioprine to maintain remission and the rituximab group did not receive additional therapy to maintain remission.

The non-inferiority margin was pre-specified at 20% based upon literature information regarding treatment with cyclophosphamide in patients with WG. The Applicant referenced data that approximately 70% of WG patients treated with cyclophosphamide will show a response. A non-inferiority margin of 20% would retain over half the treatment effect of cyclophosphamide. Details regarding justification of the non-inferiority are discussed in Section 6.1.4. In addition, the point estimate for the cyclophosphamide arm complete remission rate had to be at least 40% to meet the claim of non-inferiority for rituximab.

In addition to the non-inferiority criteria, to support the efficacy of rituximab, superiority of rituximab over historical control was pre-specified. Because complete remission data in untreated patients at 6 months is not available, survival data in untreated

patients was used. Based upon a historical database from a retrospective case report study by Walton, the Applicant determined that survival in untreated patients with WG was 38% (95% CI: 25-52%). Assuming a very conservative best case scenario that patients who survived would meet the definition of complete remission, in order to conclude efficacy for rituximab, the lower limit of the 95% CI of the complete remission rate for rituximab at 6 months would have to exceed 50% (upper bound of the 95% CI of the survival rate of the Walton cohort).

In RAVE, for the primary endpoint of complete remission at six months, 63 (64.3%, 95% CI 54.8, 73.8) of the rituximab patients attained complete remission, compared to 52 (54.7%, 95% CI 44.7, 64.8) of the cyclophosphamide patients. The treatment difference was 9.5%, with a 95% CI (-4.3, 23.4). These results satisfy the pre-specified non-inferiority margin of 20% so that rituximab was shown to be non-inferior to cyclophosphamide. The secondary endpoint of superiority to historical control was also achieved with the 95% CI of the rituximab complete remission exceeding the pre-specified threshold of 50%, the survival rate in the untreated historical control. These data are statistically persuasive and provide the clinically meaningful result of treated patients in complete remission.

Additional data related to remission at 12 months and at 18 months was provided during the review period. Complete remission in the RTX group continued to be higher at 12 and at 18 months compared to the CYC group. The treatment difference was 6.7% (-7.0, 20.4) at 12 months and 7.8% (-5.5, 21.0) at 18 months, excluding the non-inferiority margin of -20% at 12 and 18 months. This data is complicated by the use of azathioprine to maintain remission in the cyclophosphamide group.

Several subgroups are of interest. With regards to WG vs. MPA patients, both patient populations treated with rituximab had a similar proportion of patients with complete remission at 6 months (63%, 67%), which was numerically higher than complete remission with cyclophosphamide (50%, 63%). The Applicant categorized patients as having either new disease or relapsing disease at baseline. Both populations treated with rituximab had a similar proportion of patients with complete remission, 60%, 67%, respectively. In comparison to cyclophosphamide, it was notable that there were less patients with new disease who had remission (42%). Patients with renal disease at baseline treated with rituximab had numerically fewer patients with complete remission compared to cyclophosphamide, while patients without renal involvement treated with rituximab had numerically greater number of patients with complete remission compared to cyclophosphamide. Refer to Table 13 for details.

One of the limitations of the program is lack of information regarding retreatment with rituximab as this was not an objective of the clinical program. This is important information that will be useful for practitioners to better understand how and when to use repeat courses of rituximab in patients with WG and MPA. The lack of this

information should be noted in the product label. Additional information regarding retreatment can be obtained in a post-marketing commitment study.

The Applicant submitted a single study to support this application. The Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products outlines situations in which reliance on a single study can be considered. Reliance on a single study is generally limited to cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds. The results of RAVE are reliable and statistically persuasive and the endpoint (complete remission) is of important clinical benefit. Given the unmet medical need and the seriousness of the disease, the results of the submitted single study support the efficacy of rituximab in patients with WG and MPA.

Summary of Safety

Rituximab is an approved product with a known safety profile in rheumatoid arthritis patients and patients with lymphoma or leukemia. In Study ITN021AI(RAVE), safety of rituximab was assessed in patients with severe and active Wegener's Granulomatosis or Microscopic Polyangiitis. Safety data from the 6 month remission induction portion of the study which includes the 4 weeks of active rituximab treatment reflects a total of 47.6 patient-years of observation in the 99 WG and MPA patients randomized to the rituximab treatment arm of Study ITN021AI(RAVE). The main safety issues identified in RAVE are consistent with the known adverse reaction profile for rituximab described in the current product label.

Deaths across the treatment groups were balanced and do not suggest a safety signal for rituximab. At 6 months, there was one death in the rituximab group (multiorgan failure) and 2 deaths in the cyclophosphamide group (infection). At 18 months, there was one additional death in the rituximab group (pulmonary alveolar hemorrhage). Both deaths in the rituximab group were associated with vasculitis disease manifestations.

Serious adverse events (SAEs) were reported in a similar number of patients in each treatment group (33-34%). SAE system organ classes were generally similar between treatment groups except there were more vascular disorders in the CYC group 8 (8.2%) vs. 2 (2.0%) in the rituximab group, which was due to deep venous thrombosis. The most frequent SAE reported by 6 months in patients treated with rituximab was pneumonia (4%), which was reported in a similar number of patients in the cyclophosphamide group. Leukopenia (3%), diarrhea (2%), and pyrexia (2%) were reported more frequently in the patients initially treated with rituximab than in patients in the cyclophosphamide group.

Of concern was a greater number of hospitalizations in the rituximab group compared to the cyclophosphamide group. At 6 months there were 10 and 4 hospitalizations in the rituximab and cyclophosphamide groups, respectively. The hospitalization data was reviewed, and because patients were allowed to cross over and receive additional treatment with BMJ, half of the rituximab cases of hospitalization received additional therapy, which complicates interpretation of the findings. The majority of hospitalizations in both groups were related to infection, or other problems often associated with WG and MPA. There did not appear to be a consistent pattern.

During the first 6 months of the study, infection was the most common category of adverse events reported with 62% (61/99) of patients in the rituximab group having an infection of any type, the most common being upper respiratory tract infections, urinary tract infections, and herpes zoster. Infusion-related reactions are a known safety issue with rituximab and all patients received pre-medication with antihistamine and acetaminophen prior to rituximab infusion. In RAVE, infusion reactions were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with rituximab, 12% experienced at least one infusion related reaction. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor.

As with all therapeutic proteins, there is a potential for immunogenicity. Development of anti-human anti-chimeric antibody (HACA) has been noted in patients treated with rituximab for other indications. In Study ITN021AI(RAVE), a total of 3/99 (3%) of rituximab-treated patients with WG and MPA tested positive for HACA by 6 months. The number of HACA positive patients in the RTX group increased to 15/99 (15%) at 12 months and 23/99 (23%) at 18 months. HACA positivity was not associated with increased infusion reactions or other adverse reactions but did increase clearance rate of the drug. However dose adjustment is not recommended and the clinical relevance of HACA formation in rituximab-treated patients is unclear.

The safety data available at 18 months, from the additional 12 months remission maintenance phase of the study do not show any new or different safety concerns from the initial 6 month remission induction phase.

Although safety data is available for the patients throughout the 18 month study, these data have been analyzed in the context of a single 4 week course of rituximab treatment, as this was the pre-specified treatment regimen. However, in actual use, it is likely that patients with WG and MPA, both chronic diseases, may need retreatment, for recrudescence disease after the first remission. Fifteen patients in RAVE received a second 4 week course of rituximab, but no conclusions can be drawn from this data.

In summary, the review of the safety data from Study ITN021AI(RAVE) did not identify new safety signals for rituximab. For the indication of WG and MPA, the safety profile of rituximab is no less favorable than the profile of cyclophosphamide, the unapproved

standard of care. Most major rituximab-related safety issues have been addressed in labeling for other approved indications. The major exception is the safety of rituximab retreatment in WG and MPA. Retreatment information can be addressed with a post-marketing commitment.

Risk Benefit Assessment

The current submission provides evidence of rituximab's clinical efficacy in treatment of patients with WG and MPA, two forms of systemic, ANCA positive vasculitis. In this study efficacy was demonstrated when rituximab was used in conjunction with oral glucocorticoids for induction of remission, a BVAS of 0 and glucocorticoid tapered off, which was a stringent endpoint.

The clinical safety data of rituximab for treatment of WG and MPA is consistent with the known safety profile of rituximab. A new safety signal was not identified, although the known risks for infection, infusion related reactions, and immunogenicity, remain a concern. However, these concerns are offset by the severe morbidity and high mortality of WG and MPA without treatment, as seen in the era before immunosuppressive therapy. The overall risk-to-benefit profile of rituximab is favorable in the population of patients with WG and MPA, especially given that there is currently no approved treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant submitted an updated Medication Guide to inform patients about the serious risks, e.g., risk for death, infections including Progressive Multifocal Leukoencephalopathy (PML), infusion reactions, severe skin and mouth reactions, associated with the use of rituximab intravenous infusion. Although Rituxan currently has a Medication Guide, it does not have a REMS and this is acceptable and consistent with the February 2011 Draft Guidance for Industry: Medication Guides –Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS). No additional post-marketing risk management activities should be required for rituximab at the present time.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant should be required to perform a postmarketing study to provide additional efficacy and safety data related to retreatment of patients who require additional therapy for recrudescence disease. This would include optimum time for retreatment, dosing and monitoring for retreatment. Also desirable is more long term safety data on use of concomitant medications for maintenance of remission, as azathioprine was used for the cyclophosphamide group in Study ITN021AI(RAVE). Wegener's Granulomatosis

and Microscopic Polyangiitis are relatively rare diseases, and it would be acceptable for these data to be generated from an observational study.

The Pediatric Research Equity Act (PREA) is not triggered with this application as this application has Orphan designation. In addition, Wegener's Granulomatosis and Microscopic Polyangiitis are not diseases that occur in the pediatric population. Therefore, no pediatric studies are required.

2 Introduction and Regulatory Background

2.1 Product Information

Rituxan (rituximab) is a chimeric murine/human monoclonal antibody specific for the CD20 antigen on the surface of B cells. It is licensed and approved in the United States and in many other countries for the treatment of relapsed or refractory, low-grade or follicular, CD20+, B-cell non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia, and Rheumatoid Arthritis.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no products approved for treatment of the proposed indication. Corticosteroids, azathioprine and cyclophosphamide are commonly used for the treatment of WG and MPA, but neither has been approved for these patient populations.

2.3 Availability of Proposed Active Ingredient in the United States

Rituxan (rituximab) is approved and is marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The approved rituximab labeling includes a Boxed Warning with the following important safety issues:

- infusion reactions, especially associated with the first infusion, with death possible during the first 24 hours
- tumor lysis syndrome causing acute renal failure, some with fatal outcome, in the setting of treatment of non-Hodgkin's lymphoma with rituximab monotherapy.
- severe mucocutaneous reactions, including fatal, mucocutaneous reactions
- progressive multifocal leukoencephalopathy (PML)

Other safety considerations include hepatitis B reactivation, serious bacterial, fungal, and new or reactivated viral infections, during, and up to 1 year following rituximab treatment. Also listed are potential serious adverse reactions associated with rituximab treatment include cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

The most common adverse events associated with the use of cyclophosphamide are nausea, vomiting, abdominal pain, diarrhea, skin rash, alopecia, amenorrhea, leukopenia, thrombocytopenia, hepatitis, pneumonitis, infertility, hemorrhagic cystitis, infections, delayed wound healing, and malignancies (i.e., bladder cancer and leukemia).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original Rituxan BLA was approved November 26, 1997, for the treatment of lymphoma. Subsequent approvals were for treatment of non-Hodgkins Lymphoma in 2001, for treatment of Rheumatoid Arthritis in 2006, and for treatment of CD20-positive chronic lymphocytic leukemia in 2010.

There were numerous interactions between the Applicant and Agency regarding the (b) (4) development program. The following is a brief summary of the regulatory history for the (b) (4) development program.

- **April 2004** - PIND/EOP2 meeting discussion on proposal for single trial with CYC as comparator with non-inferiority design
 - two controlled clinical trials are generally expected to support efficacy
 - regarding (b) (4) indication - the sponsor will need to provide information regarding the effects of CYC in patients with MPA. If the effect is similar in patients with WG and MPA, then (b) (4) indication may be supported.
 - CYC is an appropriate comparator since it is considered standard of care
 - perform subgroup analysis on patients who received pulse corticosteroids
 - provide historical data regarding CYC and remission and justification of 20% NI margin
- **July 2004** - IND 11831 for Rituxan (b) (4) was submitted with the protocol for the pivotal study (RAVE)
- **August 2004** - the Agency had further discussion with involved representatives of the Division of Allergy, Immunology and Transplantation National Institute of Allergy and Infectious Diseases (DAIT/NAID). The question was what kind of control could be used for statistical purposes. On August 27, 2004, DAIT/NAID provided published data on the natural history of Wegener's Granulomatosis. In the 1958 Walton database, none of the patients would have met the remission endpoint proposed for the new study.
- **July 2006** – orphan drug designation (b) (4)
- **February 26, 2010** - the trial design and use of a historical control presented at a CDER Regulatory Briefing where the discussion was supportive of the trial design.

- **March 2010** - type B pre-sBLA meeting to discuss the data from the pivotal Phase II/III Study ITN201A1(RAVE) contained in this sBLA application. Points discussed included:
 - a single trial (RAVE) is acceptable for sBLA submission, but the application should provide justification for reliance on a single trial. RITUXVAS does not appear to be adequate for a supportive study.
 - ISE and ISS are required
 - the proposed application appeared to meet the criteria for priority review
 - an advisory committee is likely
- **October 18, 2010** – sBLA submitted for (b) (4) and granted priority status

2.6 Other Relevant Background Information

While rituximab is approved many other countries, rituximab does not currently have the proposed (b) (4) indication in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This supplemental BLA submission was in electronic common technical document (eCTD) format and was adequately organized. Additional information for minor omissions and for purposes of clarification was provided in response to our information requests.

Because this was a single study, and because the site with the highest enrollment, Mayo Clinic, also had the highest rituximab remission rate, inspections by the Division of Scientific Investigations (DSI) were requested for 3 of 9 sites with the highest enrollment, Mayo Clinic (n=52), Boston University (n=42), and Johns Hopkins University (n=35). At the time of this review, the final DSI report is pending. However, there is evidence that protocol deviations at Boston University were not reported to the Sponsor. Reportedly, these deviations did not result in any AEs, and exclusion of the patients with deviations does not change the overall study conclusion, per the Statistical review team. Final report is pending at the time of this review. No other protocol deviations have been reported from the other 2 sites.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in the supplemental BLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in

the US were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

Study ITN201AI was a collaborative study sponsored by NIH's Division of Allergy, Immunology, and Transplantation of the National Institute of Allergy and Infectious Diseases (DAIT NIAID). The submission includes a list of 62 investigators, subinvestigators, site and research coordinators who reported No Disclosable Interests. Two subinvestigators, (b) (6), and (b) (6) both from the (b) (6) reported Disclosable Interests. Both had on their behalf, the requisite form 3455 submitted by the Applicant in accordance with 21 CFR part 54. The Applicant was unable to obtain financial disclosure from a principle investigator, also from the (b) (6) site, and from twenty-two scattered subinvestigators. The Applicant did provide certification on FDA form 3454 that none of the investigators participated in any financial arrangement with the Sponsor, and also had no proprietary interest in the studied product.

Reviewer Comment: The (b) (6) was the only site from which there were disclosed financial interests, and the only site where a principle investigator did not file a financial disclosure. This site had (b) (6) patients, the (b) (6) enrollment, and the results from that center are not statistically dissimilar to results from other centers or from the overall study results. Therefore, this reviewer does not believe the irregularities in financial disclosure from the single center could adversely affect the study integrity.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No significant efficacy/safety issues have been identified by the other review disciplines.

4.1 Chemistry Manufacturing and Controls

Because there is no change to the approved drug product, no new manufacturing information was required for this application. The following is CMC information from the approved rituximab labeling. Rituxan is genetically engineered chimeric murine/human monoclonal IgG₁ kappa antibody directed against the CD20 antigen. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous infusion. Rituxan 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 in

polysorbate 80 (0.7 mg/mL), sodium citrate dehydrate (7.35 mg/mL), sodium chloride and Water for Injection. The pH is 6.5.

4.2 Clinical Microbiology

No clinical microbiology data were submitted with this supplement for review.

4.3 Preclinical Pharmacology/Toxicology

Because this is an approved product, no new pharmacology/toxicology data were submitted with this supplement for review.

4.4 Clinical Pharmacology

Because rituximab is an approved product, a full clinical pharmacology program was not required. The clinical pharmacology data submitted with this supplement included both PK measurements and the assessment of peripheral blood CD19 B-cell depletion following rituximab treatment through 18 months of Study ITN021AI(RAVE). The applicant also submitted a population PK study to test covariates (e.g., age, race, ethnicity, albumin, body surface area, sex, and HACA) effect on PK. The results did not demonstrate any clear effect of these covariates on PK. The pharmacometrics data was reviewed by Clinical Pharmacology review team and summarized below.

4.4.1 Mechanism of Action

Rituximab is a chimeric murine/human monoclonal antibody specific for the CD20 antigen on the surface of B cells. Rituximab has been shown to effectively eliminate CD20-positive B lymphocytes for 6 to 12 months in patients with non-Hodgkin's lymphoma. Potential mechanisms of action for rituximab include both complement-mediated and antibody-dependent cell-mediated cytotoxicity, as well as inhibition of B-cell proliferation and induction of apoptosis. In Wegener's Granulomatosis and in Microscopic Polyangiitis, rituximab may be used to disrupt critical B-cell contributions to disease and suppress autoantibody production by the short-lived plasma cells, the terminally differentiated progeny of antigen-specific B-cell precursors that are thought to be the primary source of pathogenic autoantibodies such as ANCA (anti-neutrophilic cytoplasmic antibody).

4.4.2 Pharmacodynamics

In Wegener's Granulomatosis and Microscopic Polyangiitis patients, peripheral blood CD19 B-cells depleted to less than 10 cells/ μ L following the first two infusions of Rituxan, and remained at that level in most patients through Month 6. By Month 12, the majority of patients (81%) showed signs of B cell return with counts > 10 cells/ μ L. By Month 18, most patients (87%) had counts > 10 cells/ μ L.

4.4.3 Pharmacokinetics

Based on the population pharmacokinetic analysis of data in 97 rituximab treated patients with Wegener's Granulomatosis or Microscopic Polyangiitis, the estimated median terminal elimination half-life was 23 days. Rituximab mean clearance and volume of distribution were 0.312 L/day and 4.50 L, respectively. Male patients and patients with higher BSA or positive HACA have higher clearance. However, further dose adjustment based on gender and HACA status is not necessary.

5 Sources of Clinical Data

This submission is comprised of a single pivotal trial, Study ITN021AI (RAVE), a multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international, non-inferiority trial, which the Applicant conducted to compare the efficacy of rituximab vs. cyclophosphamide in patients with Wegener's Granulomatosis (WG) or Microscopic Polyangiitis (MPA). In addition to the controlled clinical trial, the Applicant referenced several key literature reports that are essential to establish the clinical course of WG and MPA and historical control.

The most important are:

- Walton E. Giant cell granuloma of the respiratory tract (Wegener's Granulomatosis). Br Med J. 1958;2(5091):265-70 documents the natural course of Wegener's Granulomatosis without treatment and is the source of the data on which the historical control is based.
- Keogh KA, Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial, Am J Respir Crit Care Med. 2006 Jan 15;173(2):180-7.

To support efficacy results, the applicant also referenced information from RITUXVAS, an open-label, two group, parallel arm, randomized trial in 44 patients with newly diagnosed AAV with renal involvement; however, no study report or data was submitted:
Jones R, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS). N Engl J Med 2010;363:211-220

These literature reports and other relevant publications will be included in the review as appropriate.

5.1 Tables of Studies/Clinical Trials

The following table shows the general study design for the single controlled trial submitted in this application.

Table 1 Summary of Clinical Program

Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
ITN021AI/RAVE United States	P3 efficacy and safety trial	197 patients with WG and MPA 15 years and older	R, DB, AC	Rituximab IV 375mg/m ² per wk x 4 + oral corticosteroids OR Cyclophosphamide + oral corticosteroids	6 months – remission induction then 12 month remission maintenance period	Complete remission BVAS/WG = 0 and successful taper of CS at 6 months

5.2 Review Strategy

Because this submission contains a single pivotal trial, the study design is presented in Section 5.3 below. The efficacy results will be presented and discussed in Section 6 along with relevant published literature, when appropriate. The safety results and safety data from other indications for this approved product will be included in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

As the submission relies on a single pivotal trial, the following is a detailed summary of the protocol. Study ITN021AI was originally proposed in July 1, 2004. The protocol was amended 6 times with the final version of the protocol dated July 15, 2009. The summary below is based upon the final version of the protocol dated July 15, 2009. A list of the versions of the protocols with pertinent changes is located at the end of this section. The statistical analysis plan was dated January 9, 2009.

Study ITN021AI/RAVE -

"Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-Associated Vasculitis"

Objectives

Primary:

- To determine the efficacy of rituximab (375 mg/m², four weekly infusions) and glucocorticoids in the induction of complete remission, defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0 and off glucocorticoid therapy in patients with severe ANCA-associated vasculitis.

Secondary (assessed at 6 months along with the primary):

- To compare the safety profile of rituximab with that of conventional therapy (cyclophosphamide)
- To assess the superiority of rituximab compared with conventional therapy (cyclophosphamide)
- To determine duration of complete remission induced by four infusions of rituximab (375 mg/m²) – assessed at 18 months

- To determine whether patients with severe anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) who are treated with rituximab can achieve clinical tolerance defined as remission for more than 6 months without immunosuppressive therapy, normal immune function, and absence of markers of autoimmunity (e.g., serum ANCA, elimination of ANCA-reactive B cells, normalization of T-cell activity, and down-regulation of Th1 responses).

Tertiary:

- To determine the percentage of patients in complete remission at 12 and 18 months after randomization
- To assess other measures of efficacy and safety of rituximab in patients with severe AAV.
- To determine the effect of rituximab on markers of inflammation.
- To determine specific immune parameters through a series of detailed mechanistic studies

Study Design:

ITN021AI/RAVE was a randomized, multicenter, double-blinded, double-dummy, active controlled, non-inferiority trial conducted in 2 sequential phases:

- a 6-month remission induction phase (Day 1 through Month 6) during which patients are randomized to rituximab or cyclophosphamide in addition to corticosteroids and the corticosteroids are subsequently tapered off as described below.
- a 12-month remission maintenance phase (Month 7 through Month 18) during which patients are treated with AZA or placebo as described below.

Reviewer's Comment: The Applicant only submitted the initial 6 month data in the original sBLA submission. The remission maintenance phase data was submitted in the safety update on January 12, 2011. Additionally, the submission lists Study ITN021AI(RAVE) as being placebo controlled. However, in both the proposed protocol and the final trial report, placebos are involved, but not as the control; the control in this trial is active, cyclophosphamide, and the placebos are used only for blinding.

Remission Induction Phase

After screening, eligible patients were randomized 1:1, stratified for both study site and type of ANCA (PR3 or MPO), to the rituximab group or to the control group as shown below.

- Rituximab:
 - IV rituximab infusion (375 mg/ m²) once weekly for 4 weeks
 - daily oral cyclophosphamide placebo for 3-6 months
 - One gram of IV methylprednisolone/day for 1-3 days followed by daily oral prednisone 1mg/kg/day, (<80 mg/day) with the aim that all steroids would be completely tapered off by the 6-Month study visit
- Cyclophosphamide (control):
 - Oral cyclophosphamide (2mg/kg/day) for 3-6 months (minimum of 3 months)

- IV rituximab placebo infusions once a week for 4 weeks
- One gram of methylprednisolone/day for 1-3 days followed by daily oral prednisone 1mg/kg/day, (<80 mg/day) with the aim that all steroids would be completely tapered off by the 6-Month study visit

Reviewer's Comment

Because WG and MPA are serious diseases with potentially fatal outcomes without any treatment, a placebo controlled trial would not be ethical and an active controlled trial is appropriate. CYC and corticosteroids are considered standard of care but neither product has an indication for WG or MPA. As discussed later in this review, literature reports support that CYC has clinical benefit in patients with WG and MPA, thus, CYC is an acceptable active comparator.

During the initial remission induction phase of the trial, all patients (in both arms of the trial) were initially treated with 1g pulsed IV methylprednisolone or its dose equivalent for 1-3 days {within 14 days of randomization?}. Duration of the pulse was determined on a case by case basis by the investigators. Following the IV corticosteroid, all patients (in both arms of the study), were treated with a tapering course of oral prednisone at 1mg/kg/day, (<80 mg/day) with the aim that all steroids would be completely tapered off by the 6-Month study visit. In addition to the course of tapering steroids, patients received the treatment to which they had been randomized.

Once patients entered clinical remission (BVAS/WG = 0), the patient was switched to maintenance therapy (described below). Subjects who failed the assigned treatment in the first 6 months, were crossed over to the opposite treatment arm or were treated with best medical judgment (BMJ). For blinded crossover, treatment failure (between week 5 and month 6) was defined as a severe flare or a limited flare with a BVAS/WG > 3 that would normally require treatment with CYC.

Reviewer Comment: A patient who crosses over will be considered a treatment failure, which is appropriate because once the patient has received more than 1 treatment, assessment of efficacy and safety would be difficult to attribute to one particular treatment.

Remission Maintenance Phase

In the remission maintenance phase, months 7-18, patients in the control arm were switched from cyclophosphamide to azathioprine. If a patient achieved remission earlier than the 6 month point (but after treatment for at least 3 months), the patient was switched earlier, at the time of clinical remission. In the rituximab arm, patients in remission were switched to azathioprine placebo as shown below.

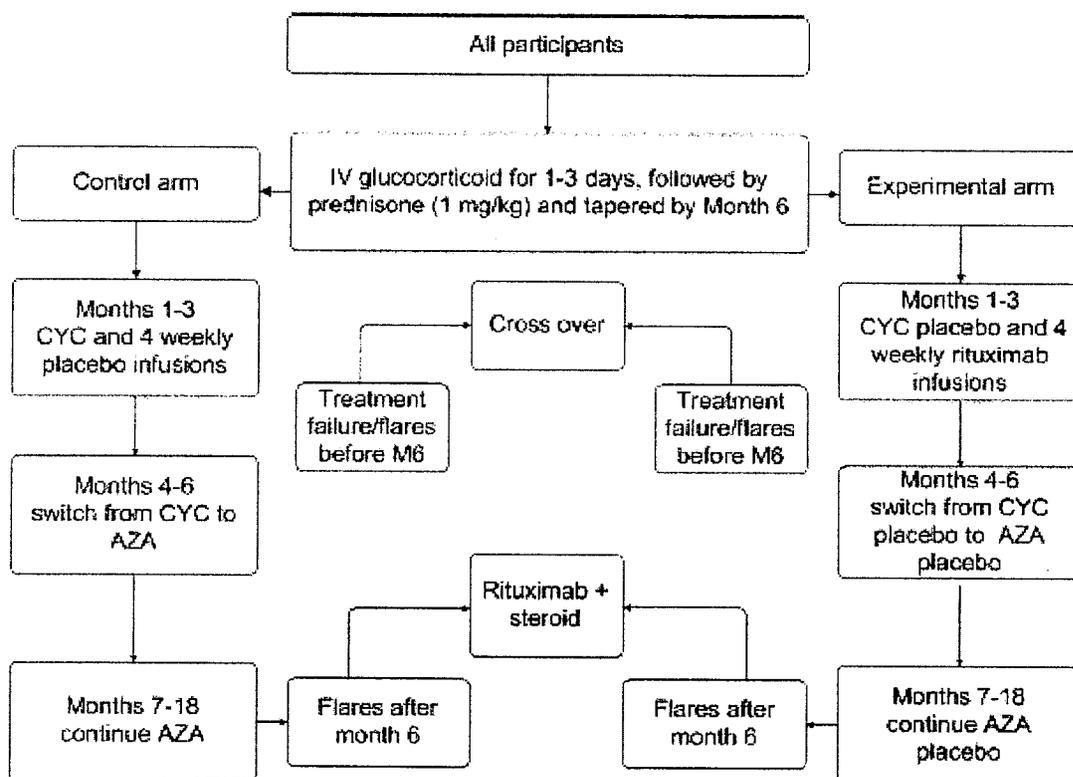
- Rituximab:
 - azathioprine placebo
- Cyclophosphamide (control):

- azathioprine 50 mg/day by mouth for first week, with dose increase of 50mg/day each week up to a dose of 2mg/kg/day, rounded to next closest multiple of 25, as tolerated.

If the patient experiences a new severe flare or limited flare requiring CYC after month 6, the patient will be treated with open-label rituximab and glucocorticoids unless contraindicated.

A schematic of the study design is shown in Figure 1.

Figure 1 ITN021AI Study Design



An important aspect of this study design is the crossover. A patient who experienced a severe flare while on one treatment regimen could be crossed over to receive the opposite treatment regimen. In this case, a severe flare is defined as a BVAS/WG > 3 or the occurrence of at least one major item listed in Table 2 (shown below) following a period in which the BVAS/WG had improved. This crossover was permitted if the flare occurred between Visit V5 (1 week after the last rituximab/rituximab placebo infusion) and Visit V8 (Month 6 Visit). Crossover to the opposite treatment arm included remission induction treatment of that arm followed by remission maintenance treatment of that arm. Treatment blinding was maintained. Additional provisions were made for

patients who either could not be switched to the other arm, or who failed treatment in the opposite arm; these patients were treated according to Best Medical Judgment (BMJ). BMJ means that the study therapies have been discontinued but the participant has agreed to continue to be followed. The treatment a patient would receive as BMJ would be at the discretion of the investigator and could include any number of treatments including rituximab, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, and glucocorticoids. As blinding would be maintained, BMJ could even include the treatment that was discontinued.

Reviewer's Comment: For the crossover criteria, the protocol specified a severe flare following a period in which the BVAS/WG had improved, but the protocol did not specify how much or for what duration the BVAS/WG had to improve to consider crossover treatment.

Table 2 Major and Minor Criteria for Disease Activity or Flare

Severe (major) BVAS/WG items ¹	Limited (minor) BVAS/WG items ⁴
Cutaneous gangrene	Arthralgias/arthritis
Scleritis	Fever (>38 °C)
Retinal exudates/hemorrhage	Purpura
Sensorineural hearing loss	Skin ulcer
Mesenteric ischemia	Mouth ulcers
Alveolar hemorrhage	Conjunctivitis/episcleritis
Red blood cell urinary casts	Orbital mass/proptosis
Rise in serum creatinine 30% over baseline	Uveitis
Aseptic meningitis	Bloody nasal discharge/nasal crusting
Spinal cord lesions	Sinus involvement
Cerebrovascular accident caused by vasculitis	Swollen salivary gland
Cranial nerve palsy	Subglottic inflammation
Sensory peripheral neuropathy	Conductive deafness ³
Motor mononeuritis multiplex	Pericarditis
	Pleurisy
	Pulmonary nodules or cavities
	Other pulmonary infiltrates secondary to vasculitis
	Endobronchial lesions
	Hematuria

The cross over and BMJ treatments serve to allow patients who have ongoing disease activity because of lack of response to the initially assigned treatment to have the possibility of a better response in the opposite treatment arm. Additionally, ongoing participation in active treatment allows for accumulation of data, especially if the patients remain in blinded treatment. However, if a patient received crossover or BMJ treatment, prior to Visit 8 at Month 6, that patient was considered to have failed to achieve remission, the primary endpoint.

Dosing Schedule/Materials

After screening, and within 14 days of starting randomized treatment, all patients received pulsed IV glucocorticoids, 1g methylprednisolone or its dose equivalent, for 1-3 days with duration determined on a case by case basis by the investigators.

The dose of rituximab was 375mg/m² for the 4 weekly infusions in the remission induction phase. For patients who crossed over from the control group to the rituximab group, the dose was recalculated using a more current body weight and height.

The dose of cyclophosphamide was 2mg/kg/day for 3-6 months (minimum of 3 months), rounded to the closest multiple of 25. The dose was adjusted for renal dysfunction.

Reviewer Comment: Because the duration of the pulsed IV glucocorticoid is determined on a case by case basis, the total dose of the pulsed glucocorticoid is also determined based on investigator judgment. This introduces a potential for investigator bias. At the 2004 teleconference, the Agency recommended inclusion of a subset analysis to determine if the variability in pulse corticosteroid treatment influences the study outcome.

Study Population

Approximately 200 patients with active ANCA-associated vasculitis were planned to be enrolled in this study. The following are pertinent inclusion/exclusion criteria:

Inclusion criteria

1. Age 15 years or older,
2. Diagnosis: WG (Wegener's Granulomatosis) or MPA (Microscopic Polyangiitis) according to the Chapel Hill Consensus Conference Definitions. The percentage of participants with MPA should not exceed 50% of total participants.

Reviewers Note: the Sponsor provides the Chapel Hill Consensus Conference Definitions for MPA, but gives the ACR criteria for WG. ACR criteria for MPA do not exist. The 2 sets of definitions/diagnostic criteria were constructed many years apart, Chapel Hill in 1944 and ACR in 1990. The diagnostic tools available at the time of the ACR criteria were not available at the time of the Chapel Hill Consensus. This may make diagnosis of especially MPA less precise than diagnosis of WG. Although it is generally accepted that there is a disease continuum, in this study MPA is distinguished from WG. The inconsistency of the diagnostic criteria may eventually play a role in the subgroup analyses where response is related to diagnosis at screening.

3. Newly diagnosed with WG or MPA, or disease flare that fulfills inclusion criteria 4, 5, and 6.
4. active disease with a BVAS/WG ≥ 3 that would normally require treatment with CYC.
5. severe disease, i.e., one or more of the major BVAS/WG items listed in Table 2 (above), or disease severe enough to require treatment with CYC.
6. positive for either PR3-ANCA or MPO-ANCA at screening

7. Participants must practice medically acceptable contraception (e.g., combination barrier method and spermicide, hormonal therapy) until one full menstrual cycle (women) or 3 months (men) have passed after the discontinuation of AZA/AZA placebo and at least 1 year after the first rituximab/rituximab placebo infusion.

Exclusion Criteria

1. Diagnosis of Churg Strauss syndrome as defined by the Chapel Hill Consensus Conference.
2. Disease severity:
 - a. Limited disease that would not normally be treated with CYC.
 - b. Severe disease - mechanical ventilation because of alveolar hemorrhage.
3. Co-morbidities:
 - a. history of severe allergic reactions to human or chimeric monoclonal antibodies or murine protein.
 - b. active systemic infection or deep space infection within 6 months of randomization.
 - c. active hepatitis B or active hepatitis C or a documented history of HIV, hepatitis B, or hepatitis C.
 - d. acute or chronic liver disease that is deemed sufficiently severe to impair their ability to participate in the trial.
 - e. history of documented anti-GBM disease.
 - f. Active or history of malignancy in the last Malignancy: Active or history of malignancy in the last 5 years. Individuals with squamous cell or basal cell skin carcinomas and individuals with cervical carcinoma in situ may be enrolled if they have received curative surgical treatment.
4. Diagnostics:
 - a. WBCs less than 4,000/mm³.
 - b. Platelet count that is less than 120,000/mm³.
 - c. ALT or AST level that cannot be attributed to underlying AAV disease.
 - d. serum creatinine level greater than 4.0 mg/dL that is attributed to renal failure from a current flare. Individuals with stable renal failure from the previous episode of active disease may be included in the study if the flare involves other organ systems.
 - e. history of HACA formation
 - f. Pregnancy test: positive
5. Treatments
 - a. CYC (adverse effects): They are intolerant to CYC
 - b. CYC (recent use): They have used CYC, oral or IV, within the past 4 months unless they started oral CYC not more than 1 week prior to enrollment
 - c. Monoclonal antibodies: They have had any previous treatment with rituximab or Campath-1H.
 - d. Prohibited medications listed in the protocol, which are primarily other concomitant immunosuppressive therapy

- e. Plasma exchange: They have been treated with plasma exchange within the 3 months preceding the screening visit.
- f. Vaccines: They have had a live vaccine fewer than 4 weeks before randomization.

Assessments

Patients were evaluated at baseline, weeks 1-3 and then months 1, 2, 4, and 6. Thereafter they were evaluated every 3 months until month 18. Safety monitoring included PPD (screening), vital signs, physical examinations, adverse events (AEs), CXR, and laboratories. All patients received pneumocystis prophylaxis therapy. AEs were recorded and classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Diphenhydramine 50mg and acetaminophen 650mg were administered as premedication in both the rituximab and control treatment groups one hour prior to infusion. A Data Safety Monitoring Board (DSMB) was chartered to review the safety data every 6 months.

Efficacy assessments included the BVAS/WG, Physician Global Assessment Form, glucocorticoid log, SF-36, Vasculitis Damage Index (months 6, 12, and 18) and AVID (months 6, 12, and 18).

Reviewer's comment: The BVAS/WG is the primary efficacy assessment and will be discussed in further detail below. The Vasculitis Damage Index (VDI) was used to assess and separate damage, as an irreversible process or scarring, from active inflammation or persistent disease. The ANCA-associated Vasculitis Instrument of Damage (AVID) is a tool that has yet to be validated and in this trial, is being compared with the VDI.

Procedures to minimize bias or unblinding included the use of concomitant glucocorticoid therapy to minimize infusion reactions, patients wore hats to conceal thinning of hair associated with CYC, evaluation by a safety officer and an investigator to separate safety assessments from BVAS/WG assessment, and use of blinded cross-over for treatment failures.

Primary Endpoint

The primary efficacy endpoint was the percentage of patients who achieved complete remission at 6 months, as defined by a BVAS/WG of 0 and successful completion of the glucocorticoid taper at 6 months after randomization (glucocorticoid dose of 0 at Month 6).

The Birmingham Vasculitis Activity Score (BVAS) is the current standard for assessing disease activity in vasculitis. The score is based on evidence of active disease in nine organ systems. The overall range of possible scores for the BVAS is 0 to 63, with the higher the score the more active the disease. In this tool, positive findings are recorded only if directly attributable to active vasculitis rather than to a secondary cause. For example, fever could be related to vasculitis or to infection, or to drug toxicity. This

requires investigator judgment, as it may not be possible at the time of scoring to know if an element is secondary to vasculitis or to some other cause. BVAS/WG has been adapted by North American investigators for trials in WG. Remission is defined as the complete absence of disease activity attributable to vasculitis, usually measured by BVAS= 0, and only if prednisone dose is ≤ 7.5 mg/d.

Reviewer Comments: The BVAS/WG has only been validated in patients with WG, but has been shown to correlate with the BVAS (old and new) in cases of WG and MPA in the literature.¹² However, it has not been validated in current patients with MPA, other ANCA vasculitis, or any other types of vasculitis. While use of the BVAS/WG for assessment in diseases other than WG has not been validated, the limitations of the patient population and validated efficacy variables in MPA and similarity of diseases makes use of the BVAS/WG acceptable in this clinical trial. However, subgroup analysis should be evaluated based upon disease – WG and MPA- to evaluate the response in the different population.

For the purposes of the primary endpoint remission is defined as a BVAS/WG=0 off steroids. However, in a clinical sense, duration of any remission is also important. The additional information provided in the 18 month data will provide data on the duration of remission.

Secondary Endpoints

1. The adverse event rate during the 6 months after randomization for the following adverse events combined:
 - Death (all causes)
 - Grade ≥ 2 leukopenia or thrombocytopenia
 - Grade ≥ 3 infections
 - Hemorrhagic cystitis (grade 2 or lower needs cystoscopy confirmation)
 - Malignancy
 - Venous thromboembolic event (deep venous thrombosis or pulmonary embolism)
 - Hospitalization resulting either from the disease or from a complication due to study treatment
 - Infusion reactions that resulted in the cessation of further infusions
 - Cerebrovascular accident (CVA)
2. The two-sided 95.1% CI of the percentage of patients who achieve complete remission at Month 6 and the two-sided 95.1% CI of the difference between the two arms for assessing the superiority of RTX to CYC/AZA.
3. The duration of complete remission, the time to limited and/or severe flare after remission in the two treatment groups.
 - limited flare – new occurrence or worsening of one or more minor BVAS/WG items (Table 2)

- severe flare – BVAS/WG ≥ 3 or occurrence of at least one major item (Table 2) following a period in which the BVAS/WG had improved; if the BVAS/WG is < 3 and/or the investigator decides CYC is indicated, the flare is considered severe

4. The percentage of patients who meet the criteria for clinical tolerance at 12 and 18 months after randomization

Reviewer Comment: The Applicant's hypothesis is that elimination of PR3- or MPO-specific memory B cells with anti-CD20 rituximab therapy would reset the patient's immune response restoring tolerance to the self antigens PR3 and MPO. In theory, this would permit a distinction between immunosuppressive effects of treatment and the restoration of tolerance.

In addition, there were 10 additional tertiary endpoints not listed here.

Statistical Analysis

The statistical analysis plan was dated January 9, 2009.

Analysis populations

The primary analysis population is the intent to treat (ITT) population, which includes all randomized patients except those who withdrew consent before study treatment. The per-protocol population (PP) is a subset of the ITT population and includes all enrolled patients except the following: patients without any BVAS/WG observation post randomization, patients with less than 75% of the 4 planned infusions, and patients with major protocol violations.

Interim Analysis

One formal interim analysis was planned when half of the patients completed 6 months evaluation. This was primarily done to stop the trial for inferior efficacy. An alpha adjustment of 0.003 was applied resulting in an alpha of 0.049 for the final analysis.

Primary Analysis

Noninferiority

With regards to efficacy and the primary efficacy variable, patients who discontinued the trial early or received cross-over treatment were considered treatment failures. The non-inferiority margin was set at -20% and the justification for this margin will be discussed in Section 6 with the efficacy results. Two sided 95.1% confidence intervals were determined for the treatment difference between rituximab and cyclophosphamide. The lower bound in the confidence interval around the difference in proportion of patients who attain complete remission was used to assess non-inferiority and superiority. If the lower bound is below -20%, non-inferiority will be rejected and if the lower bound is above -20%, non-inferiority will be concluded. If the point estimate for the complete remission rate in the rituximab arm is lower than that of the CYC arm, the

point estimate for the CYC arm complete remission rate must be at least 40% to meet the claim of noninferiority for rituximab.

Superiority

If the lower bound of the difference in complete remission rate at 6 months is above zero, superiority will be concluded conditioning on that the lower bound of the two-sided 95% confidence interval of the complete remission rate at 6 months in the rituximab is greater than or equal to 50%. Since the evaluation of noninferiority and superiority is based on the same analysis no multiplicity adjustment was made.

Reviewer's Comment: The margins reflect advice from the agency during numerous regulatory interactions detailed above in 2.5 Summary of Presubmission Regulatory Activity Related to Submission. Using the observation that WG and MPA patients did not achieve complete remission without immunosuppressive treatment such as CYC, the NI trial giving the rate of complete remission uses the rate of historical control placebo, or remission without treatment. The non-inferiority margin of 20% was to preserve 60% of the treatment effect of CYC that was conservatively estimated from the literature. Refer to the detailed discussion of the non-inferiority margin in Section 6 with the efficacy results.

Protocol Amendments

The original protocol, Version 1, is dated July 1, 2004. The following is a list of the protocol amendments with pertinent changes from the original protocol:

- April 27, 2005 (Version 2)
 - added secondary objectives to demonstrate superiority of rituximab to conventional therapy and to determine the duration of remission induced by four infusions of rituximab
 - added secondary endpoints
 - 2-sided 95% CI of % of patients with BVAS/WG of 0 and completed CS taper by 6 months
 - duration of remission, time to limited and/or severe flare after remission
 - % patients who meet criteria for clinical tolerance
 - added tertiary objectives/endpoints to determine % participants in complete remission at 12 and 18 months
 - maximum # patients with MPA won't exceed 50% of participants
 - worst score method to be used as primary imputation method for AUC BVAS/WG
 - if the lower bound of the difference in complete remission rate at 6 months is above zero, superiority will be concluded as long as the lower bound of the two-sided 95% CI of the complete remission rate at 6 months in the experimental arm is \geq to 50%
- September 12, 2006 (Version 3)
 - administrative changes and clarifications
 - deleted tertiary endpoint related to cumulative BVAS/WG AUC during months 6, 12, & 18
- April 7, 2008 (Version 4)
 - administrative changes and clarifications
 - changed terminology from prednisone to include all glucocorticoids.
- October 2, 2008 (Version 5)
 - administrative changes and clarifications
- May 19, 2009 (Version 6)

- o administrative changes
- July 15, 2009 (Version 7)
 - o administrative changes and clarifications
 - o further description of best medical judgment (BMJ) including the addition of rituximab to treatments available under BMJ

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The Applicant proposes the following new indication for rituximab:

- Rituximab, in combination with glucocorticoids, for the treatment of (b) (4)

Reviewer Comment: The proposed indication warrants two comments:

- The (b) (4) Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), (b) (4) (b) (4) but also includes some patients with syndromes that do not neatly fit into these disease categories. The proposed indication is intended to (b) (4)
- The issue of how to determine (b) (4) is worth noting because the proposed indication is for (b) (4)

6.1.1 Methods

Clinical efficacy data to provide evidence for regulatory approval of the proposed indication was derived from a single study, Study ITN021AI(RAVE). The study enrolled adult patients with ANCA positive vasculitis, WG and MPA. This efficacy review focuses on the single pivotal trial, with incorporation of relevant literature as appropriate.

Reviewer's comment: As noted previously, the Applicant only included results from the first 6 month phase – remission induction in the original sBLA submission. The additional 12 month data regarding remission maintenance was submitted January 12, 2011, and will be included in this review.

6.1.2 Demographics

Demographic characteristics were similar between the treatment arms in terms of age at screening, primary race, and ethnicity. The median age of patients was 52.0 years, with a range of 15 to 92 years. Baseline characteristics (age, race, sex) of patients enrolled in each treatment arm reflected the typically affected populations, i.e. more prevalent in older caucasian adults, with both males and females affected equally. Baseline demographics are shown below in Table 3.

Table 3 Baseline Demographics of Study ITN021AI(RAVE)

Age	RTX N=99	CYC N=98	Total N=197
Mean(SD)	54.0 (17)	51.5 (14)	52.8 (15)
Median	55	52	52
Min, Max	16, 92	15, 80	15, 92
Age categories			
15-20	4 (4%)	5 (5%)	9 (5%)
21-30	7 (7%)	1 (1%)	8 (4%)
31-40	11 (11%)	11 (11%)	22 (11%)
41-50	17 (17%)	29 (29%)	46 (23%)
51-60	22 (22%)	28 (28%)	50 (25%)
>60	38 (38%)	24 (24%)	62 (32%)
Sex			
Male	46 (47%)	53 (54%)	99 (50%)
Female	53 (54%)	45 (46%)	98 (50%)
Race (Primary)			
White	91 (92%)	93 (95%)	184 (93%)
Black or African American	3 (3%)	3 (3%)	6 (4%)
Asian	1 (1%)	0	1 (<1%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	4 (4%)	2 (2%)	6 (3%)
Ethnicity			
Not Hispanic or Latino	91 (92%)	93 (95%)	184 (93%)
Hispanic or Latino	6 (6%)	3 (3%)	9 (5%)
Unknown	2 (2%)	2 (2%)	4 (2%)

Baseline disease characteristics are shown below in Table 4. The majority of patients had WG (74%) compared to MPA (24%), but this was balanced between treatment groups. About half of all patients had newly diagnosed disease, and the proportion of patients with newly diagnosed vs. relapsing disease was the same in each arm. The distribution of organ involvement was not completely balanced; more patients in the RTX arm had nervous system, cutaneous, ENT, and gastrointestinal involvement. Slightly more patients in the CYC arm had systemic and pulmonary involvement. This unbalanced distribution is not surprising given the array of disease manifestations, and is acceptable given that the majority of organ manifestations are generally balanced between study arms.

Table 4 Baseline Disease Characteristics (ITT population)

	Rituximab N=99	Cyclophosphamide N=98	All Patients N=197
ANCA-associated vasculitis type (%)	%	%	%
Wegener's Granulomatosis	74	75	75
Microscopic Polyangiitis	24	24	24
Indeterminate	1	0	0.5
Missing	1	0	0.5
Newly diagnosed at enrollment	48	49	49
BVAS/WG score (mean [SD])	8 (2.8)	8 (3.4)	8 (3.1)
Organ involvement (%)			
Renal	66	66	66
Pulmonary	52	54	53
Systemic	56	66	61
Ear/Nose/Throat	61	56	58
Mucous Membranes/Eyes	27	26	26
Nervous System	25	15	20
Cutaneous	20	16	18
Gastrointestinal	2	0	1

Baseline ANCA status is shown below in Table 5. Antibody status was similar between treatment groups.

Table 5 Baseline Anti-Neutrophil Cytoplasmic Antibody Status (ITT population)

	Rituximab N=99 n(%)	Cyclophosphamide N=98 n(%)	All Patients N=197 n(%)
Positive immunofluorescence assay	97 (100)	94 (100)	191 (100)
C-ANCA	65 (67)	61 (65)	126 (66)
P-ANCA	33 (34)	33 (35)	66 (35)
Positive ELISA results for ANCA	97 (98)	98 (100)	195 (99)
PR3	66 (68)	65 (66)	131 (67)
MPO	32 (33)	33 (34)	65 (33)
Percentage is based on number of subjects with non-missing values.			

Table 6 shows the demographics by diagnosis and disease duration. The study population was generally balanced between newly diagnosed patients (96) and patients

with relapsing disease (101). Most patients with relapsing disease had WG (90%) but the newly diagnosed patients were more evenly distributed with 58% WG and 41% MPA.

Reviewer Comment: This may not be a result of enrollment or randomization, but rather could reflect the nature and prevalence of the diseases.

Table 6 Demographics by Diagnosis and Disease Duration (ITT population)

AAV Type	New Disease N=96	Relapsing Disease N=101	Total N=197
Microscopic Polyangiitis (MPA)	39 (41%)	9 (9%)	48 (24%)
Wegener's Granulomatosis (WG)	56 (58%)	91 (90%)	147 (75%)
Indeterminate	1 (1%)	0	1 (<1%)
Missing diagnosis	0	1 (1%)	1 (<1%)

6.1.3 Subject Disposition

Patient disposition is shown below in Table 7. The majority of patients (>80%) completed the 6 month treatment period without crossing over. Patients who crossed over are of interest and there were different scenarios for patients who crossed over during the 6 month remission induction phase. Patients who failed the assigned treatment in the first 6 months were crossed over to the opposite treatment arm or could receive treatment per Best Medical Judgment (BMJ). Approximately 11-12% of patients crossed over or received BMJ treatment and this was similar between treatment groups. For purposes of the primary endpoint, any patient crossed over or treated with BMJ, was considered a treatment failure, even if the patient improved on the alternate treatment.

Table 7 Patient Disposition at 6 Months

	Rituximab N=99	Cyclophosphamide N=98
Randomized and treated	99 (100%)	98 (100%)
Completed 6 months on any treatment	93 (94%)	91 (93%)
On assigned treatment at 6 months	82 (83%)	79 (81%)
Crossed over by 6 months	5 (5%)	7 (7%)
BMJ by 6 months	6 (6%)	5 (5%)
Discontinued by 6 months	6 (6%)	7 (7%)
Without crossover or BMJ	3 (3%)	5 (5%)
Crossed over without BMJ by 6 months	1 (1%)	0 (0%)
BMJ by 6 months, no crossover	2 (2%)	2 (2%)
Primary reason for discontinuation by 6 months		
voluntary withdrawal	2 (2%)	5 (5%)
death	1 (1%)	2 (2%)
adverse event	2 (2%)	0 (0%)
other	1 (1%)	0 (0%)

Few patients discontinued and the main reason for discontinuation was listed as voluntary withdrawal. The Case Report Forms for patients who withdrew were reviewed and the main reasons for withdrawal were either adverse events associated with treatment or with disease activity, or both (e.g. pneumonia and hemoptysis). Disease progression was the reason for two patients in each arm. The reason for 2 withdrawals in the CYC arm, listed as voluntary withdrawal, were unclear and appeared unrelated to AAV or to treatment. By Month 6, there were 3 deaths, one patient in the RTX arm, and two patients in the CYC arm. These are discussed in Safety Section 7.3.1 Deaths.

6.1.4 Analysis of Primary Endpoint(s)

Primary endpoint selection and validation: The primary endpoint was the percentage of patients who achieved complete remission at 6 months, defined by a BVAS/WG of 0 and successful completion of the glucocorticoid taper at 6 months after randomization (glucocorticoid dose of 0 at Month 6). This endpoint represents remission as defined by the Birmingham Vasculitis Activity Score (BVAS), a clinical tool specifically developed to assess vasculitis disease activity because it incorporates the multi-organ nature of vasculitis^{1,2}. Achievement of remission was chosen as a marker of effective induction treatment in a disease whose natural history does not include remission. Maintenance therapy determines whether a patient stays in remission beyond 6 months, but this is not included in the primary endpoint.

The BVAS was developed and validated in 1994. The BVAS has undergone further refinements in version 2 and version 3, the latter validated in 2009³. Although the BVAS has been used to assess disease activity in ANCA-associated vasculitis⁴, the BVAS/WG was further refined in North America for trials involving patients with WG. The BVAS/WG is categorized into 10 groups: general, cutaneous, mucous membranes/eyes, ENT, cardiovascular, GI, pulmonary, renal, nervous system, and other. Responses regarding signs/symptoms are: persistent, new/worse, none. The BVAS/WG also includes a disease status category and Physicians Global Assessment (PGA). The BVAS/WG is shown in the Appendix, Section 9.4. The BVAS/WG has been validated only in patients with WG, but has been shown to correlate with the BVAS in cases of WG and MPA in the literature.⁵

Non-inferiority Margin

A discussion of the rationale for the non-inferiority margin of 20% is warranted. To understand the basis for the non-inferiority margin, it is important to understand the expected effect of the active control, CYC. Although CYC is not approved for use in treatment of AAV, it has been the standard of care because in clinical experience a large proportion of AAV patients treated with CYC experienced remission. The applicant states that research studies demonstrate that approximately 70% of this patient population will show a positive response if treated with CYC^{8,9,15}. The applicant

also references unpublished data from a completed trial in Wegener's Granulomatosis on 180 participants (WGET trial)⁷ that suggests approximately 70% of participants who receive CYC as induction regimen, will have a BVAS/MWG of 0 by month 6.

Reviewer Comment: The Guidance for Industry, Non-Inferiority Clinical Trials describes the margin (M1) that is determined using the historical treatment effect of the active control drug versus placebo that was demonstrated in the statistical analysis of a prior clinical trial. The "clinical margin" (M2) is "the largest clinically acceptable difference (degree of inferiority) of the test drug compared to the active control." M2 is a subjective clinical judgment about how much of M1 should be preserved, how much of the effectiveness of the active control is permitted to be lost in the performance of the test drug. While we do not have placebo controlled studies with CYC, the Applicant has estimated the treatment effect of CYC to be 70% based upon literature (M1). The proposed M2 is 20% "Success" would mean that there is reasonable assurance that rituximab treatment preserves 70% of the effectiveness of cyclophosphamide, the active control drug, but that as much as 30% of its benefit may be lost. It would not mean that the effectiveness of rituximab is "equivalent" or the "same" as cyclophosphamide.

The non-inferiority margin of -20% represents a potential loss of approximately 29% (20% margin of difference / 70% expected remission rate with CYC) = 28.6%) of the therapeutic effect of the CYC. In addition, the observed complete remission of the CYC group must be at least 40% to assure assay sensitivity and conclude noninferiority of Rituximab.

Since there were no placebo-controlled studies to provide historical evidence of sensitivity to drug effects or reproducible evidence of efficacy, the applicant needed to demonstrate that treatment with RTX, and hence treatment with CYC, is better than no treatment at all. In the absence of data on the complete remission rates in untreated patients at 6 months, a historical database from a retrospective case report study by Walton⁶ was used to provide data on survival of 56 untreated patients. The Applicant analyzed the Walton data for survival rates at 6, 9, and 12 months as shown in Table 8.

Table 8 Applicant's Analysis of Survival Based upon Walton Review

Timepoint	% of patients who died	% of patients who survived	95% CI of the % of surviving patients
6 months	63%	21/56= 38%	24.9%, 51.5%
9 months	75%	14/56= 25%	14.4%, 38.4%
12 months	82%	10/56= 18%	8.9%, 30.4%

Assuming a very conservative best case scenario that patients who survived would meet the current definition of complete remission, in order to conclude efficacy for RTX in Study ITN021AI(RAVE), the lower limit of the 95% CI of the complete remission rate for RTX at 6 months would have to exceed 50%, which was the upper bound of the 95% CI of the survival rate of the Walton cohort at 6 months.

Primary endpoint limitations:

In Study ITN021AI(RAVE), the primary endpoint is limited in several respects:

- it assesses only achievement of remission, not the duration or maintenance of remission, an important aspect of treatment efficacy
- it measures remission in patients diagnosed with WG and MPA with a tool validated only in WG patients
- the complicated study design uses the noninferiority to standard of care for the primary endpoint, and a secondary endpoint, which is based upon a historic control from a retrospective case report study by Walton⁶ published in 1958 as the validated standard against which to compare RTX treatment regimen, and by extension, the CYC regimen, as well.

Reviewer Comment: Although the BVAS/WG has been validated only in Wegener's Granulomatosis, MPA and WG are often thought to represent a continuum of the same disease spectrum as they share many overlapping features. Because use of the BVAS/WG is more specific for evaluation of these types of vasculitis, and because there is no tool specific to MPA, it is acceptable to use the BVAS/WG for both types of vasculitis.

Efficacy Findings

The single Phase 3 study, Study ITN021AI(RAVE), provides the primary efficacy support for the proposed indication, the treatment of (b) (4). Study ITN021AI(RAVE) was randomized, controlled, and used appropriate inclusion/exclusion criteria. The efficacy endpoint was reasonable, and had Agency support during review of the protocol. The primary results of Study ITN021AI(RAVE) are summarized in Table 9.

Table 9 Primary Efficacy Endpoint- Complete Remission at Month 6 (ITT Population)

	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)	Treatment Difference % (95.1% CI)	p-Value
N	98	95		
Complete Remission	63 (64.3)	52 (54.7)	9.5 (-4.3, 23.4)	0.177
95.1% CI	54.8, 73.8	44.7, 64.8		

Note: Percentages are based on the number of patients with non-missing results for complete remission at month 6.

Based on the primary endpoint of BVAS=0 off steroids at 6 months and the pre-specified non-inferiority margin of -20%, the margin of -20% was excluded and treatment with rituximab is not inferior to treatment with cyclophosphamide.

{consider a couple sentences about the 12 and 18 month data here. I realize it may be discussed later as well, but it would fit nicely here}

Efficacy findings in select subpopulations

The tables below show comparisons of remission rates in each treatment arm in different subpopulations. Although the results are considered exploratory, the breakdown of remission rates also may help characterize the nature of the diseases, by grouping together the clinical features (apart from diagnoses) that respond preferentially to a certain treatment.

In Table 10 remission at 6 months is shown related to the type of disease a patient had, (WG or MPA). The diagnosis was based on accepted, pre-specified diagnostic criteria. At 6 month, both patients with WG and with MPA in the RTX group had a higher rate of remission than the patients in the CYC group. However, the treatment difference in the WG patients was numerically higher for the WG patients in favor of the RTX group than the treatment difference in the group of patients with MPA (13.0 compared to 4.2).

Table 10 Remission at 6m by Baseline AAV type

AAV Diagnosis	RTX N=99	CYC N=98	Difference 95% CI	p-value
Wegener's Granulomatosis	46/73 (63.0%)	37/74 (50.0%)	13.0 (-2.9, 29.0)	0.112
Microscopic Polyangiitis	16/24 (66.7%)	15/24 (62.5%)	4.2 (-23.0, 31.3)	0.763

(worst case imputation)

Table 11 shows that patients positive for PR3 antibody at baseline had a higher remission rate in the RTX arm (65.2%) compared to the CYC arm (47.7%). PR3 is considered highly specific for Wegener's Granulomatosis, and the results are consistent with subgroup analysis of remission in patients diagnosed with Wegener's Granulomatosis (Table 10).

Table 11 Remission at 6m by Baseline ANCA

Baseline ANCA	RTX N=99	CYC N=98	Difference 95% CI	p-value
PR3	43/66 (65.2%)	31/65 (47.7%)	17.5 (0.6, 34.3)	0.044
MPO	20/33 (60.6%)	21/33 (63.6%)	-3.0 (-26.5, 20.5)	0.800

(worst case imputation)

Reviewer Comment: It would appear that patients positive for PR3 at baseline had a higher rate of remission at 6m if treated with RTX than the PR3 positive patients in the CYC arm. For the patients positive for MPO at baseline, the rates of remission in the RTX and CYC treatment arms was similar. Since PR3 is specific for WG, this is consistent with the results shown in Table 10 above where the difference between treatment arms appeared greater for the WG patients than for the MPA patients. This is

also consistent with data related to renal disease below in which patients with less severe renal disease appeared to respond at a higher rate to RTX than the patients with more severe renal disease. Glomerulonephritis is the most common feature of Microscopic Polyangiitis, present in 80% of MPA patients. MPA is not associated with PR3 antibodies. Therefore better RTX remission rates in less severe renal disease is consistent with a better performance in WG and with PR3 antibodies

Table 12 shows the subgroup analysis for patients with new disease and relapsing disease. The results show that patients with new disease had similar response in both treatment groups. However, in patients with relapsing disease, the percentage of patients with remission in the RTX arm was greater than in the CYC group 66.7% vs. 42.0%, respectively.

Table 12 Remission at 6m by New or Relapsing Disease at Baseline

Baseline	RTX N=99	CYC N=98	Difference 95% CI	p-value
New disease	29/48 (60.4%)	31/48 (64.6%)	-4.2% (-23.6, 15.3)	0.673
Relapsing disease	34/51 (66.7%)	21/50 (42.0%)	24.7% (5.8, 43.6)	0.013

(worst case imputation)

Reviewer Comment: The data suggest that patients in the CYC group with relapsing disease did not have as great a response as patients with new disease in the CYC group. This may be explained by the fact that many patients previously diagnosed had been previously treated with CYC. Of the 101 (51.3% of total) patients classified as previously diagnosed 79 (78.2%) had been previously treated with CYC. Therefore the decreased response in the previously treated patients may reflect the patients' history rather than the current treatment.

We note that the use of terms "new" and "relapsing" have limitations. In response to an information request, the Sponsor clarified that these terms referred to a question asked at screening, and did not imply any specific disease duration for application of the term "new" disease. In addition, the term "new disease" did not correlate with lack of previous treatment, since some patients with new disease had received treatment for their disease prior to study entry. These limitations are one of the reasons that the Applicant's proposal to (b) (4) are not acceptable. See Table 19 for additional comparison of subgroups broken down by previous treatment with cyclophosphamide.

In the following Table 13, are remission rates for patients with renal involvement. The sub-populations are broken down by baseline presence of factors that connote serious renal disease and/or poor renal function at baseline: 1 or more renal item on BVAS/WG (see Section 9.4) creatinine clearance < 60mL/min, and serum creatinine >1.2 mg/dL.

In each category, the RTX arm showed a greater response compared to the CYC arm, for the categories related to less serious renal involvement at baseline (no renal item on BVAS at baseline, creatinine clearance ≥60 mL/min, serum creatinine of < 1.2 mg/dL).

Patients with 1 or more renal item on BVAS at baseline, or patients with poorer renal function at baseline had a numerically greater proportion of patients with remission on the CYC regimen compared to the RTX regimen.

Table 13 Remission at 6m by Presence of Renal Disease at Baseline

Baseline	RTX N=99	CYC N=98	Difference 95% CI	p-value
≥ 1 major renal item on BVAS/WG	31/51 (60.8%)	32/51 (62.7%)	-2.0% (-20.9, 17.0)	0.839
No major renal item on BVAS/WG	32/48 (66.7%)	20/47 (42.6%)	24.1% (4.6, 43.6)	0.018
CCI < 60 mL/min	25/45 (55.6%)	18/28 (64.3%)	-8.7% (-31.8, 14.3)	0.461
CCI ≥ 60 mL/min	38/54 (70.4%)	34/70 (48.6%)	21.8% (4.8, 38.8)	0.015
Creatinine >1.2mg/dL	27/47 (57.4%)	31/45 (68.9%)	-11.4% (-31.1, 8.2)	0.256
Creatinine ≤1.2mg/dL	36/52 (69.2%)	21/53 (39.6%)	29.6% (11.3, 47.9)	0.002

(worst case imputation)

Reviewer Comment: It would be appropriate at this point to discuss renal disease in ANCA-associated vasculitis. Renal involvement occurs in 70% of ANCA-associated vasculitis affected patients and is manifested as rapidly progressive glomerulonephritis with pauci-immune necrotizing, crescentic glomerulonephritis on biopsy. The Applicant cites RITUXVAS¹³, a recent study using rituximab and cyclophosphamide in the treatment of ANCA-associated renal vasculitis as supportive evidence for the efficacy of rituximab in the treatment of (b)(4). There were major differences between RITUXVAS and Study ITN021AI(RAVE).

- *The RITUXVAS treatment regimen was IV rituximab 375 mg/m²/week for 4 weeks and IV cyclophosphamide with the 1st and 3rd rituximab infusions vs IV CYC for 3-6 months followed by azathioprine (rather than oral CYC and IV RTX without CYC in RAVE)*
- *The RITUXVAS population was only newly diagnosed patients with only renal ANCA-associated vasculitis (rather than in RAVE which included relapsing disease in patients with an array of AAV symptoms, some patients had no renal involvement at all)*
- *RITUXVAS efficacy was calculated using the BVAS, not the BVAS/WG used in Study ITN021AI(RAVE). The elements assessed are slightly different, so the resulting scores are not comparable and the remissions defined by those scores are not precisely equal.*

Results from RITUXVAS did not demonstrate superiority of the rituximab regimen

- *Sustained remission occurred in 25/33 patients in the rituximab group (76%) and 9/11 patients in the control group (82%).*
- *The absolute difference in sustained remission with rituximab as compared with cyclophosphamide was -6 % (95% CI, -33,21; P=0.68)*
- *Six patients in the rituximab group and 1 patient in the CYC control group died within the first 12 months in RITUXVAS (in RAVE 3 patients died during the first*

6 months of treatment, 2 patients in the CYC arm and 1 patient in the rituximab arm died)

These results are not inconsistent with the results from Study ITN021AI(RAVE): for remission of AAV with renal features, rituximab led to fewer remissions compared to cyclophosphamide. RITUXVAS would appear to support CYC as an appropriate comparator in Study ITN021AI(RAVE).

6.1.5 Analysis of Secondary Endpoints(s).

The pre-specified secondary endpoints included both efficacy and safety variables and additional secondary analyses were included in the 18 month data submitted in the 120 day safety update. The secondary endpoints related to adverse event rates (adverse event rate during the 6, 12, and 18 months after randomization) will be discussed in Section 7, below. However, it should be noted that efficacy is intimately related to safety, in that patients who were treatment failures for the efficacy endpoints, often failed treatment because of adverse events, which included pre-specified secondary safety endpoints.

- Superiority of RTX to CYC (secondary endpoint)

Two criteria were necessary to conclude the superiority of RTX to CYC. First, the treatment difference between RTX and CYC had to be above 0 and the lower bound of the two-sided 95% CI of the primary efficacy endpoint for Rituximab group had to be greater than or equal to 50% based upon the historical survival data for untreated patients.

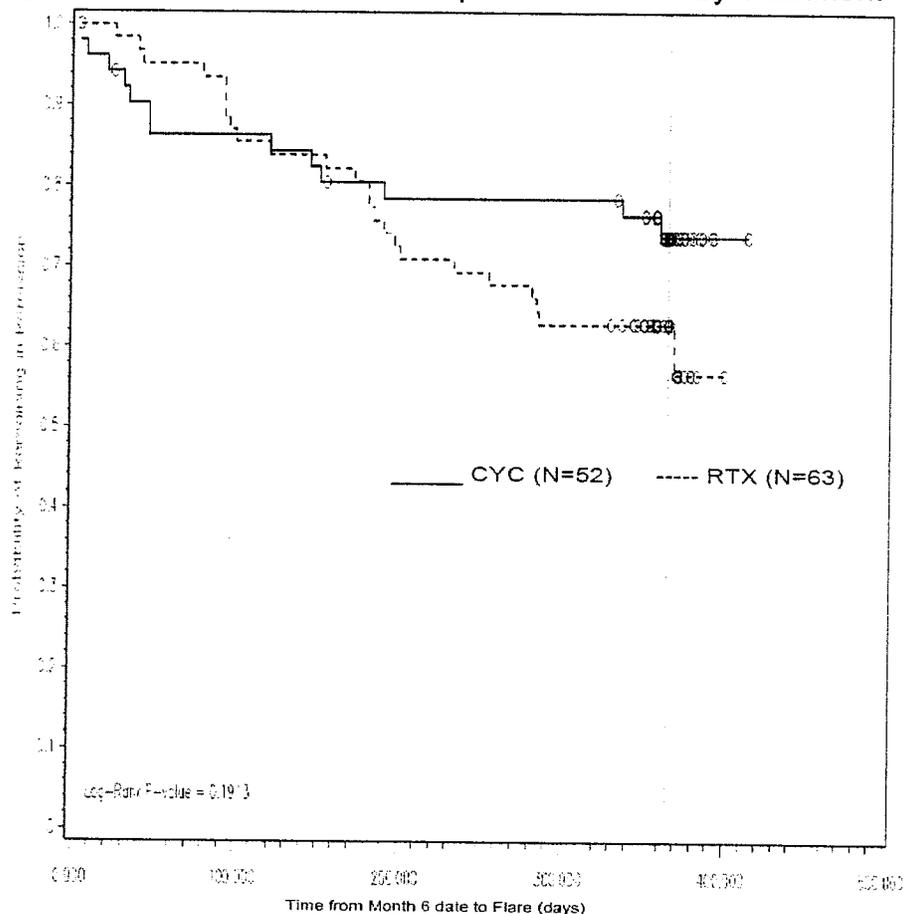
As shown in Table 9, the 95% CI (54.8, 73.8) for complete remission in the RTX group was greater than 50%. Therefore, the rate of remission achieved with the RTX treatment regimen was superior to the rate of survival in the historical control.

Although there was a greater percentage of RTX patients with CR (63%) compared to CYC patients (52%), the 9.5% difference between the groups did not exclude zero, 95%CI (-4.40, 23.40). Therefore, complete remission achieved with the RTX treatment regimen was not superior to remission achieved with the CYC treatment regimen.

- The duration of complete remission and time to limited and/or severe flare after complete remission in each treatment group. (secondary endpoint)

These secondary efficacy endpoint results were presented with the 18 month data and 120 day safety update.

Figure 2 Time to Flare from Complete Remission by Treatment



In Figure 2 the Kaplan-Meier plot of time to flare, the probability of remaining in remission as a function of number of days to flare, starting at the Month 6 point at which the primary endpoint of complete remission was assessed. We see that the probability of flare is approximately balanced between groups until about 6 months later (day 180). At this point, the rate of flare in the CYC group remains constant, while the probability of flare continues to rise for the RTX group.

Although pre-specified as a secondary endpoint, intended to show duration of efficacy of the remission induction treatment, these result show only time to flare and it is difficult to draw conclusions about the treatment for several reasons.

- The difference may be associated with the use of AZA in the CYC group although that was considered a part of the CYC treatment regimen
- The difference may reflect variability in glucocorticoid use that was allowed after the 6 month point
- Some patients in each group may have been exposed to more than simply the treatment to which they were assigned. Unlike in the evaluation of the primary endpoint where treatment failures were not included, in this

evaluation, patients who were switched over (based on failure of the initially assigned treatment) were included if they did achieve remission on the second treatment regimen.

For purposes of this review, it can be concluded that a certain proportion of patients in this study continued to do well for (diminishing) time after achieving remission. Although not what this secondary endpoint was designed to show, it does, in fact, demonstrate an ongoing benefit of both treatment arms in Study ITN021AI(RAVE) compared to the original Walton database for survival at 12 months shown in Table 8. At 12 months, only 18% of the patients in the Walton database had survived.

- The percentage of patients who met the all criteria for clinical tolerance (secondary endpoint)

The intent of this prespecified secondary endpoint is to assess the extent to which rituximab induced B-cell elimination will result in tolerance to, or recognition of PR3 and MPO self-antigens. The criteria would indirectly indicate that tolerance has been restored. These criteria are

- Complete remission (BVAS/WG=0, off glucocorticoids)
- Normalized B-cell count
- Absence of ANCA
- Normal response of the adaptive immune system

This is an exploratory endpoint based on the Applicant's hypothesis that B-cell depletion with rituximab resets the immune system. As such, the results are interesting, but not necessary for the conclusion of efficacy. The data related to the prespecified endpoint, the percentage of patients who met the above criteria, were reviewed, but the results are not presented in this review, because of the exploratory nature of these variables.

6.1.6 Other Endpoints

There were 10 tertiary endpoints:

1. The percentage of participants in complete remission at 12 and 18 months after randomization.
2. The cumulative BVAS/WG AUC during the 6, 12, and 18 months after randomization.
3. The percentage of participants who achieve and maintain partial remission at months 6, 12, 18.
4. The percentage of participants who achieve BVAS=0 on prednisone<10 mg/day at 6, 12, 18 m.
5. The percentage of participants who achieve complete remission after blinded crossover.
6. The cumulative steroid dose between groups for participants at 6, 12, and 18 months.
7. The number of severe flares in participants at 6, 12, and 18 months.
8. The number of limited flares in participants at 6, 12, and 18 months.

9. The percentage of participants who withdraw from the study or treatment because of drug intolerance (e.g., emesis, infusion reactions).
10. Laboratory markers of inflammation (ESR and CRP).

These endpoints were reviewed but are not presented here as many of the tertiary endpoints are related to endpoints already discussed. The results of these tertiary endpoints were reviewed and were generally consistent with the endpoints already discussed. Some of the endpoints are addressed in related areas. For example tertiary endpoints 1, 3, 4, 7,8 are related to maintenance of remission, and tertiary endpoint 9 is related to safety. Endpoint 6 related to cumulative glucocorticoid dose is discussed below in 6.1.10 Additional Efficacy Issues/Analyses.

6.1.7 Subpopulations

Evaluation of subpopulations was done related to the primary endpoint. The results related to some subpopulations are presented above in Efficacy findings in select subpopulations and in Table 10 -Table 13 above. Below are additional subgroup analyses that were pre-specified.

Table 14 shows that presence of alveolar hemorrhage at baseline did not affect the numerically greater proportion of patients that had remission in the RTX group compared to the CYC group

Table 14 Remission at 6m by Presence of Alveolar Hemorrhage at Baseline

Baseline	RTX N=99	CYC N=98	Difference 95% CI
Alveolar Hemorrhage	16/27 (59.3%)	11/23 (47.8%)	11.4 (-16.3, 39.1)
No Alveolar Hemorrhage	47/72 (65.3%)	41/75 (54.7%)	10.6 (-5.2,26.4)

(worst case imputation)

Table 15 shows that presence of systemic disease (fever, arthralgias) at baseline at baseline did not affect the numerically greater proportion of patients that had remission in the RTX group compared to the CYC group.

Table 15 Remission at 6m by Presence of Systemic Disease at Baseline

Baseline	RTX N=99	CYC N=98	Difference 95% CI
Systemic Disease	36/55 (65.5%)	35/65 (53.8%)	11.6 (-5.9, 29.1)
No Systemic Disease	27/44 (61.4%)	17/33 (51.5%)	9.8 (-12.6,32.3)

(worst case imputation)

Table 16 shows that with regards to age and gender subgroup analysis, patients in the RTX arm had a numerically higher proportion of patients with remission compared to patients in the CYC arm.

Table 16 Remission at 6m by Age and by Gender

Baseline Age	RTX N=99	CYC N=98	Difference 95% CI
Age <52	28/43 (65.1%)	25/48 (52.1%)	13 (-7.1,33.2)
Age ≥52	35/56 (62.5%)	27/50 (54.0%)	8.5 (-10.3,27.3)
Gender			
Male	28/46 (60.9%)	27/53 (50.9%)	9.9 (-9.7,29.5)
Female	35/53 (66.0%)	25/45 (55.6%)	10.5 (-8.9,29.9)

(worst case imputation)

Reviewer Comment: The age of 52 years is used as a cutoff here, and elsewhere in the submission as it is the median age of the safety population. Later, and with additional information obtained from the Applicant, safety results are presented with a more commonly accepted breakdown at age 65, to differentiate the older population.

This study demonstrated benefits of each of the treatment arms for specific subpopulations, but efficacy was limited to achieving remission at 6 months. Duration of remission was presented in the 120day safety update. Additional information from the Applicant provided data on the numbers of patients in remission at 12m and at 18m broken down by the prespecified subgroup. In general, the 12 and 18 month data is complicated by the use of azathioprine in the cyclophosphamide group, but no new patterns emerged.

Remission	Primary Endpoint		Durability of Remission	
	@ 6months		@ 12 months	@18 months
	Difference 95% CI	P-value	Difference 95% CI	Difference 95% CI
All patients	9.5 (-4.3, 23.40)	0.177	6.7(-7.0, 20.4)	7.8 (-5.5, 21.0)
Wegener's Granulomatosis	13.0 (-2.9, 29.0)	0.112	6.0(-9.7,21.6)	7.2 (-7.8, 22.3)
Microscopic Polyangiitis	4.2 (-23.0, 31.3)	0.763	12.5 (-15.5,40.5)	12.5(-15.3, 40.3)
PR3	17.5 (0.6, 34.3)	0.044	13.2 (-3.2,29.6)	10.2 (-5.6, 26.0)
MPO	-3.0 (-26.5,20.5)	0.800	-6.1 (-30.1,18.0)	3.0 (-20.7, 26.7)
New disease	-4.2 (-23.6, 15.3)	0.673	-8.3 (-28.3,11.6)	0 (-19.7, 19.7)
Relapsing disease	24.7 (5.8, 43.6)	0.013	21.1(3.0, 39.2)	15.3(-1.9, 32.5)
Renal disease at baseline				
≥ 1 BVAS renal item	-2.0 (-20.9, 17.0)	0.839	0.0 (-19.3, 19.3)	0 (-19.1, 19.1)
CCI ≤60 mL/min	-8.7(-31.8, 14.3)	0.461	-4.2(-28,19)	-4.2(27.6,19.2)
Creatinine >1.2mg/dL	-11.4 (-31.1, 8.2)	0.256	2.3(-18.1, 22.7)	-1.9 (22.2,18.4)
No Baseline Renal disease				
No BVAS renal item	24.1 (4.6, 43.6)	0.018	14.0 (-5.2, 33.1)	16.3 (-1.3, 33.9)
CCI ≥60 mL/min	21.8 (4.8, 38.8)	0.015	10.2 (-7.1, 27.5)	10.9(-5.3,27.1)
Creatinine ≤1.2mg/dL	29.6 (11.3, 47.9)	0.002	10.2 (-8.0, 28.4)	15.7 (-0.9,32.4)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There was only one dose of rituximab used: 375 mg/m²/week IV for 4 consecutive weeks, starting at baseline. This dose was used for patients initially assigned to RTX and also for patients who crossed over to the RTX arm. This is the dose used in published studies in AAV. The studied dose is exactly the same as approved for relapsed or refractory, low-grade or follicular, CD20 positive B-cell NHL, for initial course or for retreatment. As such, there is no information on other dosing in the WG and MPA populations in this study. This is acceptable given the limited patient population and the fact that the safety profile of rituximab at the proposed dose is well-described.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study ITN021A(RAVE), persistence of efficacy is the persistence of the complete remission beyond the primary endpoint at 6 months. The proportions of patients who achieved complete remission (BVAS/WG of 0 on a prednisone dose of 0) at 6, 12, and 18 months was numerically higher in the RTX group. Although the difference in remission rates was not significant at 6, 12, and 18 months, the non-inferiority margin was still excluded at each timepoint.

	RTX (N=99)	CYC (N=98)	Difference %(two-sided 95%CI)	p-value
6 months Worst Case	63/99(63.6%)	52/98 (53.1%)	10.6 (-3.1,24.3)	0.132
12 months Worst Case	44/99(44.4%)	37/98(37.8%)	6.7 (-7.0, 20.4)	0.340
18 months Worst Case	38/99(38.4%)	30/98(30.6%)	7.8 (-5.5, 21.0)	0.251

Complete remission is defined as BVAS/WG=0 and prednisone dose=0

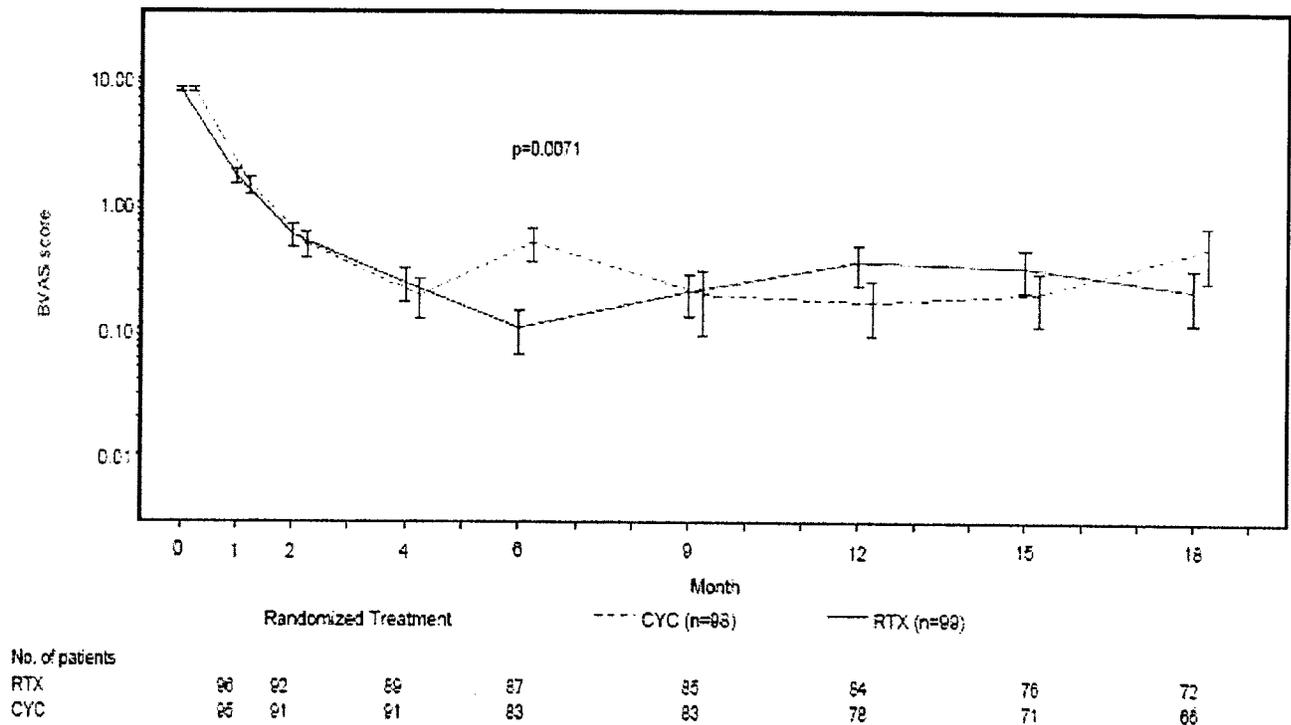
Reviewer Comment: Although the differences were not significant there are several points to consider.

- *The 6 month point is the primary endpoint when RTX was shown to be non-inferior to CYC with a noninferiority margin of 20% and better than the historical control with a remission rate of >50%. In fact, at 6 months the remission rates for both arms were better than the historical control survival rate.*
- *At 12 and 18 months the treatment difference continued to exceed the noninferiority margin of -20. However, at 12 and at 18 months, the remission rate in neither arm exceeded the 50% historical control/survival rate.*
- *Although efficacy was defined by the same criteria (BVAS=0 and off steroids) at 12 and 18 months as at 6 months, remissions at the 12 month and 18 month timepoints were "snapshots" of each time point, and may not reflect, for example, any steroid use between 6, 12, or 18 months. Therefore it may be misleading to consider this actually persistence of remission, since "persistence" suggests the same conditions are persistent throughout the whole time period.*
- *It does appear that there is some persistence of effect because at 18 months, 38% of patients treated with rituximab were in complete remission.*

Additional data demonstrating persistence of efficacy includes

- No significant difference in percentage of patients achieving a BVAS=0 on prednisone <10mg/day by worst case imputation in the ITT population at 6, 12, and 18 months.
- The mean BVAS/WG of each treatment group was similar at all timepoints during the maintenance period. The mean score was lower in the RTX group at Month 6.

Figure 3 Mean (\pm SEM) BVAS/WG Total Score by Month



6.1.10 Additional Efficacy Issues/Analyses

Prior treatment with cyclophosphamide

Because Wegener's Granulomatosis and Microscopic Polyangiitis are chronic diseases, a proportion of the study population had treatment prior to the study. Given the disease severity required for inclusion, the most likely previous treatment would have been cyclophosphamide as other possible treatments, such as azathioprine or methotrexate, would not have been considered strong enough for active disease. Review of the study subpopulations suggest that the major difference between relapsing and new disease was previous treatment, but information from the Applicant revealed that that previous treatment was not limited to the relapsing disease group. This is important in a real life setting as well, since the population that might get treatment with rituximab may also have received previous

cyclophosphamide treatment. Below, in Table 19, is remission at 6 months by treatment group in RAVE in the groups previously treatment with cyclophosphamide or without previous cyclophosphamide treatment. These data show that in patients treated with rituximab, remission was similar whether or not they had received prior treatment with cyclophosphamide. However, fewer patients in the cyclophosphamide group with prior cyclophosphamide treatment achieved complete remission at 6m compared to those without any prior cyclophosphamide treatment.

Table 19 Complete Remission at 6 months [†] - Prior Use of Cyclophosphamide (ITT Population)			
	Rituximab N=99	Cyclophosphamide N=98	Treatment Difference (Two sided 95.1% CI)
Prior use of CYC	29/47 (62%)	19/42 (45%)	16.5% (-4.0, 37.0)
No prior use of CYC	34/52 (65%)	33/56 (59%)	6.5% (-11.8, 24.7)

[†] BVAS/WG of 0 and prednisone dose of 0, worst observation carried forward data imputation

Cumulative glucocorticoid exposure

The overall mean cumulative dose of IV and oral glucocorticoids administered as a study drug was a tertiary efficacy endpoint. In Table 20 below is the glucocorticoid use by treatment arm.

The Applicant maintains there was a was a numerically lower cumulative steroid dose in the RTX group compared to the CYC group. Given the wide range of use, and the large standard deviations, the differences may not be significant.

Table 20 Glucocorticoid Use by Initial Treatment		
	Rituximab N=99	Cyclophosphamide N=98
Randomization-6 month		
Methylprednisone (IV, mg)		
Number (%) with any dose	59 (60%)	61 (62%)
Mean (SD)	1316.6 (825.6)	1348.1 (1329.7)
Prednisone (PO, mg)		
Number (%) with any dose	99 (100%)	98 (100%)
Mean (SD)	3326.9 (981.5)	3684.4 (1249.0)
6 month-18month		
Methylprednisone (IV, mg)		
Number (%) with any dose	13 (13%)	13 (13%)
Mean (SD)	1205.3 (558.8)	1558.5 (864.5)
Prednisone (PO, mg)		
Number (%) with any dose	40 (40%)	43 (44%)
Mean (SD)	2942.8 (2555.0)	3187.0 (4974.3)

From Applicant Table 32 in 120day Safety Update

Retreatment with rituximab

Wegener's Granulomatosis and Microscopic Polyangiitis are chronic diseases. Although a majority of rituximab treated patients achieved remission, the likelihood of a recrudescence of disease activity increased with time (Time to Flare from Complete Remission by Treatment). Thus, the possibility of retreatment for recurrent disease activity must be considered, along with any new safety issues that could be associated with retreatment. Although rituximab retreatment was not pre-specified in Study ITN021AI(RAVE), the applicant did provide limited data on rituximab retreatment. In Table 21 is a list of 15 patients who had a second course of rituximab treatment (4 infusions) during Study ITN021AI(RAVE). The reasons for retreatment were likely an increase in disease activity but the criteria for retreatment were not pre-specified, and not all retreated patients had achieved complete remission at Month 6.

Table 21 Patients who Received a Second Course of Rituximab Treatment during Study ITN021AI (RAVE)

Patient ID	Date of First Rituximab Dose	Date of Open-Label Rituximab	Time (days) from First Dose of Rituximab to Open-Label Rituximab	Status of Complete Remission at Month 6
001006	03 MAR 2005	20 FEB 2006	354	Success
002007	06 SEP 2005	04 DEC 2006	454	Success
002009	19 DEC 2005	27 JUN 2007	555	Success
002023	25 JAN 2007	21 APR 2008	452	Success
002029	22 JUN 2007	19 JUN 2008	363	Success
004001	22 MAR 2005	30 MAR 2006	373	Success
004008	13 OCT 2005	14 JUL 2006	274	Failure
004017	20 SEP 2006	02 MAY 2007	224	Failure
004018	02 OCT 2007	17 SEP 2008	351	Failure
006018	01 DEC 2006	13 MAR 2008	468	Success
006113	01 NOV 2006	05 JUL 2007	246	Failure
008005	17 OCT 2006	03 JAN 2008	443	Failure
009011	15 DEC 2006	17 JAN 2008	398	Success
009102	26 JUL 2006	20 APR 2007	268	Success
009104	05 OCT 2007	26 JAN 2009	479	Success

Reviewer Comment: The important points in the retreatment data are:

- *As in other rituximab indications, retreatment is a possibility in WG and MPA*
- *In the 15 retreated patients, the second course was 32-68 weeks after the first dose of the initial course. This gives a suggestion of the durability of the initial course, although some of the retreated patients did not fulfill criteria for remission at 6m either because of inability to taper off steroids or because of inability to achieve a BVAS=0.*
- *These data provide a base for additional postmarketing observation of rituximab in clinical use.*

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety assessment of rituximab in patient's with Wegener's Granulomatosis and Microscopic Polyangiitis is based on the patients enrolled in Study ITN021AI(RAVE), the single pivotal trial contained in this submission. As outlined above, this study was a multicenter, randomized, double-blind, active-controlled study with the primary endpoint assessed at month 6 in a total study duration of 18 months. The applicant has provided safety data to 18 months, although only one single course of rituximab dosing (4 weekly infusions) was specified prior to the 6 month primary endpoint. However, the profound B-cell depletion generated by rituximab treatment opens the possibility for treatment associated AE's long after direct exposure to medication, even extending to the 18 month end of the study. The 18 month safety data were reviewed, but the emphasis in this review will be the safety data from the first 6 months, the primary time period for efficacy measurement.

Safety assessments were performed on the safety population that includes all patients who received any form of study therapy. However a patient could have had exposure to more than one treatment after randomization. The patient could have crossed over to the other treatment arm or received treatment per Best Medical Judgment (BMJ), meaning open label treatment, whichever treatment judged appropriate by the investigator, possibly even the same blinded treatment that was discontinued. Safety data will be presented based upon the initially received treatment. To address the potential for cross over treatment, the Applicant also presented data in 4 groups: rituximab only (only received RTX), CYC only (only received CYC/AZA), rituximab all others (initially received RTX and received other treatment), CYC all others (initially received CYC and received other treatment). Although this additional breakdown may have been intended to highlight issues that could be associated only with exposure to a single medication, the 2 additional groups with exposure to more than one treatment regimen are complicated and the results cannot be attributed to a single treatment. This is further complicated by prior treatment since some patients had a history of cyclophosphamide exposure before randomization.

Baseline demographics and disease activity suggest that Study ITN021AI(RAVE) enrolled patients representative of those seen in clinical practice with +ANCA vasculitis

including patients already on glucocorticoid therapy, and a proportion of patients who had been previously treated, either with full courses of cytotoxic therapy for relapsing disease or with short treatment as a temporizing measure for newly diagnosed disease.

Overall, this study provides a reasonable safety assessment of one course of rituximab. However, because of the chronic nature of this disease, it is also likely that in practice, many patients with AAV may require immunosuppressive medication to maintain remission (as azathioprine was used after CYC in this study) or even another full course of therapy if unable to sustain permanent complete remission. The issues of maintenance of remission treatment after rituximab therapy and repeat courses of rituximab therapy were not evaluated because of the design of Study ITN021AI(RAVE). Rituximab is used with other immunosuppressive medications and also is given in repeat course for other approved indications. This review will reference data from other indications for this approved product as well as information from supportive studies cited by the applicant when appropriate.

7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as any occurrence or worsening of an undesirable or unintended symptom, sign, laboratory result, radiological finding, or disease state that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Individual investigators routinely monitored patients for clinical and laboratory evidence of AEs at each of 12 study visits. After baseline, safety assessments were scheduled weekly for the first 4 weeks, then at months 2, 4, 6. After the remission induction phase, assessments were scheduled every 3 months, from month 6 until month 18. The investigators recorded any AE providing an assessment that included the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "probably related" to study drug, final diagnosis (if known), and any action(s) taken. All AEs were recorded. All AEs were followed to their conclusion or for a maximum of 30 days after early discontinuation from study.

Serious adverse events (SAE), defined as any AE occurring at any dose that suggests a significant hazard, contraindication, side effect or precaution included the following:

- Death, occurring during the study or in the protocol defined follow-up period
- Life-threatening
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Important medical event requiring medical or surgical intervention to prevent a serious outcome

SAE's were reported to (b) (4), within 24 hours of occurrence or notification to the site. (b) (4) was responsible for notifying the IND Sponsor (DAIT, NIAID) and the Immune Tolerance Network (ITN) of all SAE's. The NIAID medical monitor or the ITN clinical trial physician notified the protocol chairs, and the Applicant. Genentech received copies of all expedited SAE reports. The DSMB was also informed as was the IRB of the individual study center.

All adverse events were reported, classified by body system, and preferred term according to a standardized thesaurus (MedDRA v5.1), and graded for severity using Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

The following major events were thought to represent the most important toxicities resulting in significant morbidity in this patient population and were pre-specified as the basis for a secondary endpoint of safety:

- Death
- \geq Grade 2 leukopenia or thrombocytopenia
- \geq Grade 3 infections
- Hemorrhagic cystitis
- Malignancy
- Venous thrombotic event
- Hospitalization (from disease or treatment)
- Cerebrovascular accident
- Infusion reactions that result in cessation of further infusions

Reviewer Comment: Two comments regarding the Applicant's pre-selected AEs. First, the selected AEs include some events specifically associated with one of the medications. For example, leukopenia and hemorrhagic cystitis occur frequently in cyclophosphamide treated patients, while infusion reactions occur only with infusions, such as with IV rituximab, not with oral cyclophosphamide. Second, the category of infection may be too broad to illustrate the actual risk associated with treatment. Although selection of Grade \geq 3 infection will capture the infections of similar magnitude, it does not capture the infections related to a particular body system that may be of particular importance in these diseases. For example, upper and lower respiratory tract infections may be of greater significance in a patient with pulmonary involvement of Wegener's Granulomatosis. The results of the pre-specified secondary safety endpoint are discussed in Section 7.3.4.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Because this submission contains a single pivotal study, there was no pooling of data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure of patients in RAVE was acceptable given the limited patient population and the fact that the safety profile of rituximab has been established in other patient populations. Baseline demographics and disease activity suggest that Study ITN021AI(RAVE) enrolled patients representative of those seen in clinical practice with +ANCA vasculitis including patients already on glucocorticoid therapy, and a proportion of patients who had been previously treated, either with full courses of cytotoxic therapy for relapsing disease or with short treatment as a temporizing measure for newly diagnosed disease.

7.2.2 Explorations for Dose Response

There was no exploration for dose response in this study. The dose used is identical to that approved for lymphoma. As discussed in Section 6.1.8, the dose of RTX was based upon published studies of RTX in patients with AAV. In addition, the studied dose is exactly the same as approved for relapsed or refractory, low-grade or follicular, CD20 positive B-cell NHL, for initial course or for retreatment. As such, there is no information on other dosing in the population in this study. This is acceptable given the limited patient population and the fact that the safety profile of rituximab at the proposed dose is well-described for other populations.

7.2.3 Special Animal and/or In Vitro Testing

Rituximab is an approved product. There was no special testing done for this new indication.

7.2.4 Routine Clinical Testing

Routine clinical testing during the study was adequate. It included hematologic and general chemistry testing consistent with rituximab and cyclophosphamide labeled guidelines for laboratory monitoring and with monitoring that is commonly done in clinical practice. Urinalysis, hematologic and general chemistry testing was done at screening, baseline, weekly for the first four weeks, then every 2 months between month 2 and month 6. After month 6, during the remission maintenance phase, testing was performed every 3 months, at months 9, 12, 15, and 18. Testing for HACAs was done at baseline, then at months 4, 6, 9, 15, and 18.

7.2.5 Metabolic, Clearance, and Interaction Workup

This is an approved drug and there is available metabolic, clearance, and interaction information in the product labeling for rituximab. Additionally, the Applicant provided a PK study to test covariates (e.g., age, race, ethnicity, albumin, body surface area, sex, and HACA) effect on PK. The results did not demonstrate any clear effect of these covariates on PK.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no currently approved similar drugs in this class, nor are there other approved drugs for this indication. However, rituximab is approved for lymphoid malignancies and for rheumatoid arthritis. For these indications, some known potential adverse events are related to the indication, tumor lysis syndrome in NHL, for example. Other known potential adverse events across different patient populations are mucocutaneous reactions, infusion reactions, infection (viral, bacterial, fungal), and infection reactivation, including Progressive Multifocal Leukoencephalopathy (PML), and hepatitis B and C. Infusion reactions and infection will be described in detail in 7.4.1 Common Adverse Events

In Study ITN021A1(RAVE), these potential adverse events were addressed with inclusion/exclusion criteria, appropriate screening, monitoring, and patient counseling.

7.3 Major Safety Results

7.3.1 Deaths

Deaths across the treatment groups were balanced and do not suggest a safety signal for rituximab. At 6 months, there was 1 death in the RTX group due to multiorgan failure, and 2 deaths in the CYC group due to infection. By 18 months there was 1 additional death in the RTX group due to pulmonary alveolar hemorrhage.

Of the 2 deaths due to infection in the CYC group, both occurred prior to 6 months during the active CYC treatment, prior to starting azathioprine for maintenance of remission. Infection is a known potential risk associated with CYC treatment. In contrast, both deaths in the RTX group, 1 before 6 months and the other between 6 months and 18 months were associated with vasculitis disease manifestation.

Short summaries of the deaths are shown below:

- RTX - Patient 5007 was a 65 yo WM treated with RTX for WG including renal and pulmonary involvement. He received 3 doses of study medication, but his conditioned worsened. He developed multi-organ failure and *E. coli* sepsis and died on Study Day^{(b)(6)}
- CYC - Patient 6111 was a 68 yo WF treated with CYC for a recent diagnosis of MPA, with renal involvement. Within one month of treatment she developed anemia. Her treatment was also

complicated by COPD exacerbation and pneumonia, requiring hospitalization. She died on Study Day (b) (6) secondary to pneumonia with *P. aeruginosa* sepsis and MSOF.

- CYC - Patient 6112 was an 80 yo WM treated with CYC for a recent diagnosis of MPA, with renal involvement. Within one month of treatment he developed *Pneumocystis jirovecii* pneumonia and MI. His hospitalization was complicated by sepsis. He died on Study Day (b) (6)
- RTX -Patient 9104 was an 77 yo WF with MPA, relapsing disease P-ANCA positive with renal vasculitis. She was treated with RTX and was in remission at Month 6. She experienced a severe flare of disease 9 months after entering the maintenance phase and was started on glucocorticoid plus open label rituximab. She was hospitalized with PAH that started on study Day 499. She received IV glucocorticoid and plasmapheresis, as well as completing the 4th dose of her second course of rituximab. She further deteriorated and died on Day (b) (6) from respiratory failure secondary to pulmonary alveolar hemorrhage.

Reviewer's Comment: Mortality of 1-2% in each treatment arm is a vast improvement over the 63% mortality rate calculated for patients in the historical control from the Walton series seen in Table 8.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were reported in a similar number of patients in each treatment group (33-34%). SAE system organ classes were generally similar between treatment groups except there were more vascular disorders in the CYC group 8 (8.2%) vs. 2 (2.0%) in the rituximab group, which was due to deep venous thrombosis. The increased DVTs could be due to renal disease and proteinuria. There were more GI SAEs (diarrhea) in the rituximab group 4 (4%) compared to 0 in the CYC group. Table 22 shows that the most frequent serious adverse events reported by 6 months in patients initially treated with rituximab were pneumonia (4%), but this was as frequent in the other group. Leukopenia (3%), diarrhea (2%), and pyrexia (2%) were seen more frequently in the patients initially treated with rituximab than in the patients in the CYC group, and the diarrhea occurred in patients who took only rituximab compared to the CYC group, where there was no diarrhea or pyrexia reported.

	Rituximab N=99		Cyclophosphamide N=98
	RTX only n=86	RTX only + RTX Other n=99	CYC only + CYC Other
Number of patients with ≥1 severe adverse event	23 (26.7%)	33 (33.3%)	33 (33.7%)
Deep vein thrombosis	1 (1.2%)	2 (2.0%)	8 (8.2%)
Pneumonia	3 (3.5%)	4 (4.0%)	4 (4.1%)
Anemia	1 (1.2%)	2 (2.0%)	3 (3.1%)
Acute renal failure	0 (0%)	2 (2.0%)	3 (3.1%)
Pulmonary embolism	2 (2.3%)	2 (2.0%)	2 (2.0%)
Leukopenia	2 (2.3%)	3 (3.0%)	0
Pulmonary alveolar	0	0	2 (2.0%)

hemorrhage			
Diarrhea	2 (2.3%)	2 (2.0%)	0
Acute sinusitis	0	0	2 (2.0%)
Dehydration	0	0	2 (2.0%)
Laryngeal stenosis	0	0	2 (2.0%)
Pyrexia	1 (1.2%)	2 (2.0%)	0
Drug hypersensitivity	0	0	2 (2.0%)

Reviewer Comment: The number of SAEs is small, and because patients could receive other therapy, it is more difficult to firmly associate the event with the treatment first received. However, for rituximab it appears that of the SAEs in the RTX group, diarrhea was seen with rituximab only and none in the CYC group, and pyrexia was also more common in the RTX group, although only 1 of the 2 cases was in a patient treated only with rituximab compared to none in the CYC group.

At 18 months, the overall rates of serious adverse events per patient-year were RTX (0.41/patient-year) and CYC (0.36/ patient-year). The most commonly reported type of serious adverse event by 18 months was infection, with similar incidences and rates in the RTX and CYC groups (15.2% and 0.13/patient-year in the RTX group vs. 15.3% and 0.16/patient-year in the CYC group).

Table 23 Most Frequent Serious Adverse Events up to 18 Months Occurring in 2 or More Patients in Either Treatment Group (Safety Population)		
Preferred terms	Rituximab N=99	Cyclophosphamide N=98
Total Number of SAEs	69	77
Number of patients with ≥1 SAE	46 (46.5%)	41 (41.8%)
Deep vein thrombosis	1 (1.0%)	8 (8.2%)
Pneumonia	4 (4.0%)	5 (5.1%)
Anemia	2 (2.0%)	4 (4.1%)
(Acute) renal failure	2 (2.0%)	3 (3.0%)
Pulmonary embolism	2 (2.0%)	2 (2.0%)
Leukopenia	3 (3.0%)	0
Pulmonary alveolar hemorrhage	1 (1.0%)	2 (2.0%)
Diarrhea	2 (2.0%)	0
Dehydration	0	2 (2.0%)
Laryngeal stenosis	2 (2.0%)	2 (2.0%)
Pyrexia	2 (2.0%)	0
Drug hypersensitivity	0	2 (2.0%)
Atrial fibrillation	2 (2.0%)	0
Pancreatitis acute	0	2 (2.0%)
Urinary tract infection	2 (2.0%)	1 (1.0%)
Wegener's Granulomatosis	3 (3.0%)	3 (3.0%)

From the Sponsor Table 8 120 day ISS

7.3.3 Dropouts and/or Discontinuations

Table 24 shows the primary reasons for discontinuation from the study by 6 months. The overall number of patients who discontinued was similar between treatment groups. While it appears fewer RTX than CYC patients withdrew voluntarily, details of the reason for discontinuation were reviewed and information from the individual patients who discontinued shows little difference between voluntary withdrawal and withdrawal for "adverse event" or "other." Therefore, in the RTX group the voluntary withdrawals, adverse events, and other amount to 5, the same number as the voluntary withdrawals in the CYC group. Deaths were discussed above.

	Rituximab N=99	Cyclophosphamide N=98
Discontinued from study	6 (6%)	7 (7%)
Voluntary withdrawal	2 (2%)	5 (5%)
Death	1 (1%)	2 (2%)
Adverse event	2 (2%)	0 (0%)
Other	1 (1%)	0 (0%)

The 6 patients from the RTX group and 7 from the CYC group who discontinued from the study can be further defined by treatment received.

	Rituximab N=6	Cyclophosphamide N=7
Discontinued from study		
Without additional treatment	3 (3%)	5 (5%)
Crossed over then discontinued	1 (1%)	0 (0%)
BMJ then discontinued	2 (2%)	2 (2%)

The totals of 6 RTX patients and 7 CYC patients appear low but the numbers represent only patients who discontinued from the study, not the total of patients who discontinued from assigned treatment. Of the patients who stayed in the study and did not discontinue, cross over and BMJ treatment was allowed. The numbers of patients in each arm who stayed on initially assigned treatment was about the same, 88% in the RTX group, and 87% in the CYC group, which suggests similar tolerability.

	Rituximab N=99	Cyclophosphamide N=98
Randomized		
Did not discontinue before 6m	N=93	N=91
Finished 6m on initial treatment	82 (88%)	79 (87%)
Crossed over to opposite arm	5 (5%)	7 (8%)
Treatment per BMJ at 6 months	6 (6%)	5 (5%)

7.3.4 Significant Adverse Events

Below in Table 27 are the rates and incidence of the selected adverse events that were pre-specified. There were numerically fewer RTX patients who experienced the selected events (22%) compared to the CYC group (35%) and the rates per patient-month and per patient-year are lower in the RTX group than in the CYC group. Of the selected events, the hospitalizations and thrombocytopenia appeared greater in the RTX group compared to the CYC group. The hospitalizations are discussed further below.

Table 27 Pre-Specified Selected Adverse Events (safety population)		
	Rituximab N=99	Cyclophosphamide N=98
Total number of selected AEs	37	45
Number of patients with ≥ 1 selected AE	22 (22.2%)	34 (34.7%)
Sum of patient-months for all patients	571.2	564.1
Rate of selected AEs per patient-month	0.065	0.080
Rate of selected AEs per patient-year	0.78	0.96
Selected adverse events, n (%)		
Death (all causes)	1 (1.0)	2 (2.0)
Grade ≥2 leukopenia	5 (5.1)	17 (17.3)
Grade ≥2 thrombocytopenia	3 (3.0)	1 (1.0)
Grade ≥3 infections	10 (10.1)	10 (10.2)
Hemorrhagic cystitis	1 (1.0)	1 (1.0)
Malignancy	1 (1.0)	2 (2.0)
Venous thromboembolic event (inc dvt & PE)	5 (5.1)	8 (8.2)
Hospitalization	10 (10.1)	4 (4.1)
Cerebrovascular accident	0	0
Infusion reaction	1 (1.0)	0

Of note is the greater number of hospitalizations in the RTX group compared to the CYC group. At 6 months there were 10 and 4, and at 18 months 13 and 5 in the RTX and CYC groups, respectively.

Presented below are the causes for the hospitalizations by Month 6. To better understand the greater number of hospitalizations in the RTX group, the 10 hospitalizations in the RTX group were further broken down based upon additional treatment (if applicable) to further assess potential causality. Of the 10 patients hospitalized in the RTX group, 5 received RTX only and 5 received RTX and other treatment (crossover or BMJ). All hospitalizations in the CYC group were patients that were treated with CYC only. At least 1 of the hospitalizations in the RTX group occurred during a protocol violation when a patient was receiving concomitant CYC, and others occurred after the patient discontinued RTX and was on BMJ. The majority of hospitalizations in both groups were related to infection, or other problems often associated with WG and MPA. There does not appear to be a consistent pattern, other than leucopenia with RTX which is not unexpected.

Table 28 Cause for Hospitalization by 6 Months by Treatment

patients hospitalized by 6 months	RTX N=99 10 (10%)		CYC only N=98 4 (4%)
	RTX only n=5	RTX other n=5	
leukopenia and pneumonia	2		
leukopenia and pyrexia		1	
pneumonia	1		2
pulmonary embolism		1	
pulmonary hemorrhage		1	
bronchitis	1		
renal failure		1	
hypersensitivity	1		
osteomyelitis		1	
ARDS			1
URTI			1

7.3.5 Submission Specific Primary Safety Concerns

There has been a question about a possible association between WG and MPA and malignancy. Additionally, the current standard of care, cyclophosphamide, may be associated with an increase in malignancy. Thus, malignancy was a selected AE in Study ITN021AI(RAVE).

Table 29 presents the malignancies that occurred in patients in Study ITN021AI(RAVE). By 6 months there were a total of 2 malignancies – 1 in each treatment group. Both were prostate cancers diagnosed within 3 months of study entry. The timing makes it unlikely that the 2 cases of prostate cancer were associated with treatment. At 18 months there were 8 malignancies in 7 patients as shown in the table below. These results are confounded by the several factors. Two malignancies in the RTX group occurred in patients with previous exposure to cyclophosphamide. The three remaining malignancies in two patients in the RTX group were disparate, in different tissues, usually associated with different etiologies. Given this small safety database making any conclusion regarding malignancy would be quite difficult.

Patient ID	Malignancy type	Age sex	Study day of diagnosis	Days of treatment exposure prior to diagnosis	Medication prior to study start
RTX group					
002115	Prostate cancer	75/M	93	71 (RTX)	
001020	Uterine cancer	66/F	909	909 (RTX)	MTX
004001	Colon cancer metastatic	74/F	454	454 (RTX)	MTX CYC
006108	Bladder cancer	69/F	811	811	MTX
	Adeno ca colon		1180	1180 (RTX)	
006110	Malignant lung neoplasm	78/M	532	532 (RTX)	CYC
CYC group					
006020	Prostate cancer	53/M	53	53 (CYC)	CYC
001010	Papillary thyroid ca	62/F	798	798 (CYC) 698 (AZA) 306 (RTX)	CYC MTX

Source Sponsors Table 17 120 day ISS

Rituximab is approved for treatment of certain malignancies, and there is currently no warning of increased risk for malignancy in these populations or in the rheumatoid arthritis population.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The overall adverse event profiles were reviewed. Table 30 shows the common AEs listed by preferred term. As shown in the table below, there were a similar number of patients in both treatment groups who reported at least one AE. Diarrhea and peripheral edema were more common in patients in the RTX arm compared to the CYC arm.

Table 30 Adverse Events Occurring in >10% of Patients
 by Initial Treatment from Baseline to Month 6 (safety population)

	Rituximab N = 99 n (%)	Cyclophosphamide N = 98 n (%)	All Patients N = 197 n (%)
Total number of adverse events	997	978	1975
Number of patients with ≥1 adverse event	94 (94.9)	97 (99.0)	191 (97.0)
Rate of adverse events/patient-month	1.75	1.73	1.74
Rate of adverse events/patient-year	20.94	20.81	20.88
Preferred Term			
Nausea	18 (18.2)	20 (20.4)	38 (19.3)
Anemia	16 (16.2)	20 (20.4)	36 (18.3)
Headache	17 (17.2)	19 (19.4)	36 (18.3)
Leukopenia	10 (10.1)	26 (26.5)	36 (18.3)
Fatigue	13 (13.1)	21 (21.4)	34 (17.3)
Muscle spasms	17 (17.2)	15 (15.3)	32 (16.2)
Diarrhea	17 (17.2)	12 (12.2)	29 (14.7)
Increased alanine aminotransferase	13 (13.1)	15 (15.3)	28 (14.2)
Alopecia	9 (9.1)	18 (18.4)	27 (13.7)
Rash	10 (10.1)	17 (17.3)	27 (13.7)
Insomnia	14 (14.1)	12 (12.2)	26 (13.2)
Cough	13 (13.1)	11 (11.2)	24 (12.2)
Decreased white blood cell count	4 (4.0)	19 (19.4)	23 (11.7)
Arthralgia	13 (13.1)	9 (9.2)	22 (11.2)
Peripheral edema	16 (16.2)	6 (6.1)	22 (11.2)
Dyspnea	10 (10.1)	11 (11.2)	21 (10.7)
Pyrexia	8 (8.1)	13 (13.3)	21 (10.7)
Upper respiratory tract infection	8 (8.1)	13 (13.3)	21 (10.7)
Decreased hematocrit	7 (7.1)	13 (13.3)	20 (10.2)
Epistaxis	11 (11.1)	6 (6.1)	17 (8.6)
Hypertension	12 (12.1)	5 (5.1)	17 (8.6)
Increased aspartate aminotransferase	5 (5.1)	11 (11.2)	16 (8.1)

Source Sponsor Table 14 14.3/10.1.1

The Applicant proposed

(b) (4)

Table 31 Incidence of All Adverse Reactions Occurring in $\geq 10\%$ of WG and MPA up to Month 6		
	RTX N = 99 n (%)	CYC N = 98 n (%)
Infection	61 (61.6%)	46 (46.9%)
Nausea	18 (18%)	20 (20%)
Diarrhea	17 (17%)	12 (12%)
Headache	17 (17%)	19 (19%)
Muscle spasms	17 (17%)	15 (15%)
Anemia	16 (16%)	20 (20%)
Peripheral edema	16 (16%)	6 (6%)
Insomnia	14 (14%)	12 (12%)
Arthralgia	13 (13%)	9 (9%)
Cough	13 (13%)	11 (11%)
Fatigue	13 (13%)	21 (21%)
Increased ALT	13 (13%)	15 (15%)
Hypertension	12 (12%)	5 (5%)
Infusion related reaction	12 (12%)	11 (11%)
Epistaxis	11 (11%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Leukopenia	10 (10%)	26 (27%)
Rash	10 (10%)	17 (17%)

By month 6, the most common adverse event reported was infection: 62% (61/99) of RTX patients in the Rituxan group experienced an infection of any type compared to 47% (46/98) CYC patients. In the RTX group, the most common infections were upper respiratory tract infections, urinary tract infections, and herpes zoster. The incidence of serious infections was 11% in the RTX patients and 10% in the CYC patients, with rates of approximately 25 and 28 per 100 patient-years, respectively as seen above in Table 22. The most common serious infection was pneumonia.

Reviewer Comment: Infection is a known potential adverse event associated with immunosuppression and is an already labeled potential risk for rituximab. Pneumonia is common in immunosuppressed patients, and is not unexpected in an immunosuppressed patient population often with underlying pulmonary pathology.

Also included in Table 31 is the broader term of infusion related reactions that includes events as different as cytokine release syndrome, flushing, throat irritation, tremor parasthesia, and headache, which is discussed in greater detail in Section 7.5.2 Time Dependency for Adverse Events.

7.4.2 Laboratory Findings

Parameters in the laboratory monitoring of patients in the ITT population were reviewed. The most pronounced changes from baseline at month 6 occurred in white blood cell and in platelet counts.

Table 32 Laboratory Parameters with Largest Median Change from Baseline to Month 6 (ITT population)		
Median change	RTX N=99	CYC N=98
Hematologic parameters:		
platelet count (10 ⁹ /L)	-51.0	-72.5
white blood cell (10 ⁹ /L)	-5.1	-7.3
Biochemistry parameters:		
AST (U/L)	4.0	5.0
BUN (mg/dL)	-7.0	-7.3

These hematologic changes are known potential AEs with rituximab and monitoring of WBCs and platelets are recommended when rituximab is used for other indications. In both RTX and CYC groups, WBCs and platelets were the hematologic parameters most affected. Less pronounced in both groups were the biochemical changes. In both RTX and CYC groups, AST and BUN were most affected. These changes are not unexpected and the magnitude of the changes is comparable between groups.

Change from baseline to Month 6 in inflammatory markers, ESR and CRP, support the overall efficacy results; the mean ESR and CRP in both groups decreased, indicating decreased inflammation, a feature of decreased disease activity.

Table 33 Mean Change in ESR and CRP from Baseline to Month 6 (ITT population)		
	RTX N=99	CYC N=98
	Mean Δ (95% CI)	Mean Δ (95% CI)
ESR	-14.4 (-18.7, -10.1)	-9.3 (-15.6, -3.0)
CRP	-2.69 (-5.44, 0.06)	-2.84 (-7.07, 1.40)

7.4.3 Vital Signs

The changes in median vital signs and physical findings from baseline to month 6 are presented in Table 34. There does not appear to be any pattern of change or signal for concern.

	RTX N=99 median change from baseline	CYC N=98 median change from baseline
systolic blood pressure (mmHg)	-6.0	-6.5
diastolic blood pressure (mmHg)	0.0	-0.5
Pulse (beats/minute)	1.0	2.5
respiration rate (breaths/minute)	0.0	0.0
Weight (Kg)	3.6	2.2
Temperature (C)	0.1	0.0

7.4.4 Electrocardiograms (ECGs)

Standard 12-lead Electrocardiograms were done at screening, and again at 12 and 18 months, or earlier if the patient withdrew or terminated from the study. Additionally, the protocol specified that for participants with pre-existing cardiac conditions such as arrhythmias and angina, an ECG is required before and after rituximab/rituximab placebo infusion. Review of the study report, integrated summary of safety, and the 120 day safety update did not find a summary table of ECG changes. Rather, there was mention of ECG status in the patient narratives. There was no clear pattern of ECG abnormality. There were 11 cardiac AEs in the RTX group compared to 8 in the CYC group. In the RTX group, the arrhythmias noted were tachycardia (4 cases), atrial fibrillation (3 cases), ventricular tachycardia (1), and supraventricular tachycardia (1).

	RTX only N=86	RTX other N=13	RTX all N=99	CYC all N=98
Any Cardiac AE	8	3	11	8
Any Vascular AE	24	4	28	18
Any Venous thrombotic event	3	2	5	9

In response to an information request, the Sponsor supplied an analysis of ECG data from patients in RAVE. ECG abnormalities and changes were balanced between the treatment groups and did not identify any new safety concerns.

7.4.5 Special Safety Studies/Clinical Trials

There were no specific safety studies or trials in this program.

7.4.6 Immunogenicity

Because RTX is a monoclonal antibody, immunogenicity is expected and has been documented in other patient populations. Serum HACA (human antichimeric antibody) was assessed at screening, and at the study visits for months 4, 6, 9 and 18. Five patients had positive HACA results during the first 6 months of treatment and included 3 (3%) patients from the rituximab arm and 2 (2%) patients from the CYC arm. One patient, who was in the CYC arm, tested positive for HACA antibodies at most study visits, including Screening.

Ten Infusion Related Reactions (IRRs) were reported in 4 patients who tested HACA positive, including 1 CYC patient (001024) who received rituximab as crossover treatment. IRRs were events that occurred within 24 hours of an infusion. All these IRR events were mild to moderate in severity, all occurred prior to the detection of HACA, and none were reported as serious adverse events or resulted in discontinuation of therapy. The events reported as IRRs in the HACA-positive patients comprised cytokine release syndrome (four events), flushing (one event), hypotension (one event), oropharyngeal discomfort (one event), diarrhea (one event), and hyperhidrosis (two events).

In other medications, and other indications, concomitant immunomodulatory therapy has been associated with a lower risk of developing HACA. In RAVE, no concomitant immunomodulatory medication was used during the exposure to RTX or CYC.

The application includes a supportive study to evaluate the PK characteristics of rituximab in WG and MPA patients. An objective of the PK study was to evaluate the relationship between PK parameters and HACA status. The findings did not demonstrate that HACA status has any clearly relevant effect on PK.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Adverse events could not be related to dose as there was only one dose of rituximab used in the study.

7.5.2 Time Dependency for Adverse Events

There was no formal analysis of time dependency of AEs. However infusion related reactions (IRRs) were one class of event that was carefully examined. IRRs were events that occurred within 24 hours of an infusion. This is the Applicant's definition of IRR and may not necessarily be consistent with the infusion reactions described in the Warnings and Precautions section of the rituximab label. Rituximab can cause severe, including fatal, infusion reactions that include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. No such events occurred during this study.

In RAVE, the proportion of patients in the RTX group with an infusion related reaction (as seen below) was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. In RAVE, patients had been pre-medicated with antihistamine and acetaminophen before each infusion and were on background oral corticosteroids which may have mitigated, masked, or changed the presentation of any infusion reaction that might have occurred. Again, no typical, infusion reactions occurred in this study.

Table 36 Most Frequent Infusion-Related Reactions Occurring in >1 Patient in Either Treatment Group in RAVE: Safety Population

	RTX N=99	CYC N=98
Total number of adverse events	46	28
Number of patients with ≥ 1 adverse event	12 (12.1)	11 (11.2)
Cytokine release syndrome	5 (5.1)	2 (2.0)
Flushing	4 (4.0)	4 (4.1)
Throat irritation	2 (2.0)	1 (1.0)
Tremor	2 (2.0)	1 (1.0)
Paresthesia	1 (1.0)	2 (2.0)
Headache	1 (1.0)	2 (2.0)
Hyperhidrosis	0	2 (2.0)
Infusion site extravasation	0	2 (2.0)

7.5.3 Drug-Demographic Interactions

The Sponsor provided an analysis of the safety profile of rituximab with respect to age of the patients. Below, in Table 37, are some categories of adverse events by age and by treatment group. There were more patients with a baseline age ≥ 65 years in the RTX group (36%) compared with the CYC group (19%). The proportion of patients

experiencing AE's including hospitalizations was numerically higher in the older patients in both groups.

Table 37 Safety Profile by Age (<65 and ≥65) and by Initial Treatment

Safety parameter	RTX Number (%)		CYC Number (%)	
	Age <65 N=63	Age ≥65 N=36	Age <65 N=79	Age ≥65 N=19
Any AE	63 (100)	36 (100)	79 (100)	19 (100)
SAE	34 (54)	26 (72.2)	37 (46.8)	10 (52.6)
Death	0	2 (5.6)	0	2 (10.5)
Any Infection	56 (88.9)	33 (91.7)	62 (78.5)	15 (78.9)
Serious Infection	13 (20.6)	9 (25.0)	14 (17.7)	5 (26.3)
Rates/patient-year				
Any AE	6.31	6.88	6.55	7.41
Any Infection	1.06	0.87	0.92	0.85
SAE	0.32	0.57	0.33	0.53

In response to an information request, the Sponsor provided an analysis of the safety profile by gender and by race. The genders were equally represented in the study population, 50% male and 50% female. Safety data was also balanced by gender, without any disproportionate events in males or females. It was difficult to draw any conclusions from the safety data broken down by race since the study population was overwhelmingly caucasian (93%).

7.5.4 Drug-Disease Interactions

Wegener's Granulomatosis and Microscopic Polyangiitis are diseases related to abnormal function of the immune system. Both rituximab and cyclophosphamide are immunomodulatory agents. In this study, infection was the most common AE in all patients. At 6 months the proportion of patients experiencing any infection was higher in patients in the RTX group (61.6%) compared to CYC (46.9%). Upper respiratory tract infections were the most common in both groups. The difference in the proportion of patients with infections was largely due to a greater number of patients in the RTX group with Grade 1 or 2 herpes or common fungal infections.

7.5.5 Drug-Drug Interactions

In addition to study drug (RTX, CYC), and glucocorticoids, participants in Study ITN021AI(RAVE) were on multiple background medications, all recorded. Additionally, patients were on PCP prophylaxis. The most common background medications were vitamins, and an array of antibiotics. There did not appear to be any distinct pattern of interactions between other drugs and rituximab, but this study was not specifically designed to evaluate drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Although rituximab is used to treat lymphoid malignancies, malignancy was an adverse event of interest in Study ITN021AI(RAVE). See section 7.3.5 Submission Specific Primary Safety Concerns.

7.6.2 Human Reproduction and Pregnancy Data

Study ITN021AI(RAVE) included both a contraception contract and a pregnancy reporting contract. There was one pregnancy reported. The pregnancy was in the wife of patient 002015 reported on day 132 (after RTX, during the maintenance of remission phase with azathioprine placebo). Time frame of conception was not reported, but the pregnancy ended in miscarriage. No other pregnancy occurred in association rituximab treatment. However, a 25 year old female became pregnant but miscarried while on azathioprine after cyclophosphamide treatment. She had not had rituximab treatment.

In labeling, rituximab is Category C. There are no adequate and well-controlled studies of rituximab in pregnant women. Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

7.6.3 Pediatrics and Assessment of Effects on Growth

Wegener's Granulomatosis and Microscopic Polyangiitis are adult diseases; the youngest patient in Study ITN021AI(RAVE) was 15 years old. There are no other data related to pediatric use. Safety and effectiveness of rituximab in pediatric patients have not been established; rituximab is not approved for use in pediatric populations or for pediatric indications such as polyarticular juvenile idiopathic arthritis.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No withdrawal effects were observed in Study ITN021AI(RAVE) and no withdrawal phenomena are anticipated with the use of rituximab. Similarly, there is no evidence or expectation of patient abuse of rituximab.

7.7 Additional Submissions / Safety Issues

Retreatment with rituximab was not prespecified although 15 patients did receive a second 4 week course of RTX as described in 6.1.10 Additional Efficacy

Issues/Analyses. Rituximab is approved for multiple courses in other indications and has a known safety profile with multiple courses over a period of time.

Although not presented here, the Sponsor did provide limited data on AEs associated with retreatment in the 15 patients discussed above. These limited data on a small number of patients suggest the safety profile is similar between 1st and 2nd courses. Nevertheless, there is a potential for change in the safety profile after the first course. A different safety profile could be due to immunogenicity, e.g. development of antibodies, to changes in B cell levels associated with prolonged/repeated suppression, or to extended immunosuppression in this particular population. One of the recommendations for a postmarketing observational study of rituximab in clinical use is collection of data related to retreatment.

8 Postmarket Experience

Postmarket experience with rituximab, is reflected in the boxed warning in the current package insert. Warnings include fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, and Progressive Multifocal Leukoencephalopathy. In addition, post market experience has supported the concern for AE's associated with immunosuppression, including reactivation of latent infection. The specific labeled events under 6.5 Postmarketing Experience are:

- Hematologic: prolonged pancytopenia, marrow hypoplasia, and late-onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia.
- Cardiac: fatal cardiac failure.
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections in patients with previously treated lymphoma without known HIV infection.
- Neoplasia: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions.

Because the earliest approval of rituximab was for malignancies, most post marketing experience has been with use of rituximab for treatment of malignancies; some events with these indications, such as tumor lysis syndrome may not be important in the Rheumatoid Arthritis indication or applicable to the Wegener's Granulomatosis and Microscopic Polyangiitis indications.

Post market information for rituximab specifically for Wegener's Granulomatosis and Microscopic Polyangiitis was limited as rituximab is not currently marketed in any country for Wegener's Granulomatosis or Microscopic Polyangiitis. However the

Applicant provided results of two searches in the Global Safety Database for spontaneous serious adverse events for off-label use of rituximab. The results of the first search up to April 30, 2010, resulted in a total of 57 serious adverse events reported in 56 case reports, 52 in WG, 3 in MPA, and 1 in ANCA-positive vasculitis. These events were most commonly in the respiratory, thoracic, and mediastinal disorders SOC, followed by the infections and infestations SOC. The second updated search in the Global Safety Database was for spontaneous serious adverse events in Wegener's Granulomatosis and Microscopic Polyangiitis between May 1, 2010 and September 30, 2010. Nine additional SAEs were reported in Wegener's Granulomatosis patients. All nine cases were consistent with previously reported events, most commonly in the respiratory, thoracic, and mediastinal disorders SOC. Many of these patients were reported to be taking concurrent immunosuppressive therapies that have not been studied.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

This supplemental BLA submission included proposed additions to the existing labeling covering the new indication, and information on the study supporting the new indication. At the time of finalization of this review, the labeling negotiations are ongoing. The following are high level comments regarding the labeling.

- The Applicant proposed (b) (4) and the recommendation is to (b) (4). WG and MPA.
- A new Warnings and Precaution should be included regarding lack of information regarding retreatment
- The existing Warning regarding concomitant biologic agents should be revised to include WG and MPA patients
- Changes to Clinical Trial Experience include
 - The description of the study (RAVE) was made more precise
 - The description of Adverse events was clarified, especially in the section related to Infusion Reactions
- Changes to Pharmacokinetics include additional information that male patients and patients with higher BSA or positive HACA have higher clearance, but that further dose adjustment based on gender and HACA status is not necessary.
- The Medication Guide has minor changes consistent with those in the package insert. The most important is the warning to let your doctor know if you have been treated with rituximab for WG or MPA in the past.

9.3 Advisory Committee Meeting

There was no advisory committee meeting for this application. An advisory committee was not deemed necessary as the safety profile of rituximab is known and the clinical study design was acceptable and agreed upon by the Agency.

9.4 BVAS/WG

BVAS for Wegener's Granulomatosis Evaluation Form

Tick box () or () only if abnormality is ascribable to the presence of active Wegener's Granulomatosis (chronic damage should be scored separately in the Vasculitis Damage Index, VDI.)

Tick box only if the abnormality is **persistent disease activity** since the last assessment and not worse within the **previous 28 days**.

Tick box only if the abnormality is **newly present or worse** within the **previous 28 days**.

If no items are present in any section, tick "none".

Major items are in bold and marked with *

All WG-related clinical features need to be documented on this form if they are related to active disease. Use "OTHER" category as needed.

1. Clinic ID: _____

2. Patient ID: _____

3. Patient name code: _____

4. Date form completed: _____ day _____ month _____ year

5. Visit ID: _____

	Persistent	New/Worse	None		Persistent	New/Worse	None
6. GENERAL			<input type="radio"/>				<input type="radio"/>
a. arthralgia/arthritis	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
b. fever ($\geq 38.0^{\circ}\text{C}$)	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
7. CUTANEOUS			<input type="radio"/>				<input type="radio"/>
a. purpura	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
b. skin ulcer	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
c. * gangrene	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
8. MUCOUS MEMBRANES/EYES			<input type="radio"/>				<input type="radio"/>
a. mouth ulcers	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
b. conjunctivitis/episcleritis	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
c. retro-orbital mass/proptosis	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
d. uveitis	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
e. * scleritis	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
f. * retinal exudates/hemorrhage	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
9. EAR, NOSE & THROAT			<input type="radio"/>				<input type="radio"/>
a. bloody nasal discharge/nasal crusting/ulcer	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
b. sinus involvement	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
c. swollen salivary gland	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
d. subglottic inflammation	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
e. conductive deafness	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
f. * sensorineural deafness	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
10. CARDIOVASCULAR			<input type="radio"/>				<input type="radio"/>
a. pericarditis	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
11. GASTROINTESTINAL			<input type="radio"/>				<input type="radio"/>
a. * mesenteric ischemia	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
12. PULMONARY			<input type="radio"/>				<input type="radio"/>
a. pleurisy	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
b. nodules or cavities	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
c. other infiltrate secondary to WG	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
d. endobronchial involvement	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
e. * alveolar hemorrhage	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
f. * respiratory failure	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
13. RENAL			<input type="radio"/>				<input type="radio"/>
a. hematuria (no RBC casts) ($>1+$ or >10 RBC/hpf)	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
b. * RBC casts	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
c. * rise in creatinine $>30\%$ or fall in creatinine clearance $>25\%$	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
<i>Note: If both hematuria and RBC casts are present score only the RBC casts (the major item).</i>							
14. NERVOUS SYSTEM			<input type="radio"/>				<input type="radio"/>
a. * meningitis	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
b. * cord lesion	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
c. * stroke	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
d. * cranial nerve palsy	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
e. * sensory peripheral neuropathy	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
f. * motor mononeuritis multiplex	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>		<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>
15. OTHER			<input type="radio"/>				<input type="radio"/>
(describe all items and * items deemed major)							
16. TOTAL NUMBER OF ITEMS:							
a	b	c	d				
Major New/Worse	Minor New/Worse	Major Persistent	Minor Persistent				

DETERMINING DISEASE STATUS:

Severe Disease/Flare: >1 new/worse Major item.
 Limited Disease/Flare: >1 new/worse Minor item.
 Persistent Disease: Continued (but not new/worse) activity.
 Remission: No active disease, including either new/worse or persistent items.

17. CURRENT DISEASE STATUS (check only one).

Severe Disease/Flare ()
 Limited Disease/Flare ()
 Persistent Disease ()
 Remission ()

18. PHYSICIAN'S GLOBAL ASSESSMENT (PGA)
 Mark line to indicate the amount of WG disease activity (not including longstanding damage) within the previous 28 days:

Remission |-----| Maximum activity
 0 |-----| 10

19. Value in item #18: _____ (distance from 0 to tick mark in millimeters)

20. DATE FORM REVIEWED: _____

21. STUDY PHYSICIAN ID: _____

22. STUDY PHYSICIAN SIGNATURE: _____

23. CLINIC COORDINATOR ID: _____

24. CLINIC COORDINATOR SIGNATURE: _____

Figure 1. Evaluation form for the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG). RBC = red blood cell; hpf = high-power field.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

CHEMISTRY REVIEW(S)



Center for Drugs Evaluation & Research - Food & Drug Administration

Division of Monoclonal Antibodies
NIH Campus, Building 29B, Room 3NN18, HFD-123
5600 Fishers Lane, Rockville, MD 20857
Telephone (301) 827-0850
Facsimile (301) 827-0852

Date: February 11, 2011

From: Marjorie A. Shapiro, Ph.D. M. Shapiro

Subject: STN 103705.5344 - Immunogenicity assay used to support "Rituxan in combination with glucocorticoids for the treatment of (b) (4)

Through: Kathleen A. Clouse, Ph.D. Director, DMA / Kathleen A Clouse 03/18/2011
To: STN 103705.5344 File

Sponsor: Genentech

License Number: 1048

Contact: Yasameen Qazen, Manager, Regulatory Affairs

Phone: (650) 225-7952

Submitted: October 19, 2011

PDUFA Deadline: April 19, 2011

Table with 2 columns: Submissions reviewed, Date Submitted. Rows include submission numbers 103705.5344.0 through 103705.5344.5004 and their corresponding dates from 10/19/2010 to 02/25/2011.

Executive Summary: The immunogenicity assay used to support the clinical study "Rituxan in combination with glucocorticoids for the treatment of (b) (4) is the same assay that was developed for use in the RA clinical trials and was described in STN 103705.5211 (RA efficacy supplement). This assay was reviewed for STN 103705.5211 and found to be appropriately validated. The current clinical efficacy supplement for (b) (4) provides a copy of the validation report and a study of the quality controls for the immunogenicity assay used to determine immunogenicity in (b) (4) patients. The study was conducted appropriately using a validated assay and appropriate quality controls.

Recommendation: The Immunogenicity Assay is adequate to detect anti-rituximab antibodies in patient sera. Rituximab present at >195ng/mL will interfere with the assay. The immunogenicity data should be reported in the package insert. This assay and the data from the assay can be used to support approval of this supplement.

Reviewer comments are in bold Arial text.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

ENVIRONMENTAL ASSESSMENT



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Center for Drugs Evaluation & Research - Food & Drug Administration

Division of Monoclonal Antibodies
NIH Campus, Building 29B, Room 3NN16, HFD-123
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Date: 1/28/2011

From: Marjorie A. Shapiro, Ph.D. *M. Shapiro*

Subject: BLA 103705.5344: Categorical Exclusion for Environmental Assessment

Through: Kathleen A. Clouse, Ph.D., Director, DMA *K. Clouse 01/28/2011*

To: BLA 103705.5344 File

Sponsor: Genentech

License Number: 1048

Contact: Michelle H. Rohrer, Ph.D, Vice President, Regulatory Affairs

Contact: Jennifer Nicholson, MHA, Manager, Regulatory Affairs

Phone: (650) 225-1708

Date Submitted: October 18, 2010

PDUFA Deadline: April 19, 2011

This supplement is to expand the indication of rituximab for the treatment of (b) (4)

As specified in 21 CFR 25.15(d), Genentech states that this sBLA qualifies for a categorical exclusion from the Environmental Assessment requirement.

A categorical exclusion has been submitted under 21 CFR § 25.31(c). The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. Approval of this biologic product is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. There is no information that indicates extraordinary circumstances exist that would warrant the submission of additional environmental information.

The claim of categorical exemption is accepted.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY sBLA PRIMARY REVIEW

Application number: 103-705
Supporting document/s: 1
Applicant's letter date: October 17, 2010
CDER stamp date: October 17, 2010
Product: Rituxan® (Rituximab)
Indication: Treatment of Wegener's granulomatosis (WG) and
microscopic polyangiitis (MPA)
Applicant: Genentech Inc.
Review Division: Pulmonary, Allergy, and Rheumatology Products
Reviewer: Mamata De, Ph.D.
Team Leader: Timothy W. Robison, Ph.D., D.A.B.T.
Division Director: Badrul Chowdhury, M.D., Ph.D.
Project Manager: Philantha Bowen
Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Rituximab (Rituxan) was initially approved for marketing in the United States in 1997 for the treatment of patients with relapsed or refractory low-grade or follicular CD20-positive B-cell non-Hodgkins lymphoma (NHL). In 2006, it was approved for different oncology indications and rheumatoid arthritis. On October 17, 2011, the Applicant submitted a supplemental application for the treatment of Wegener's granulomatous (WG) and microscopic polyangiitis (MPA) which are the two major forms of systemic vasculitis. No new non clinical studies were submitted with this IND. No new nonclinical studies are required for the new indication.

1.2 Brief Discussion of Nonclinical Findings

Rituximab binds specifically to the CD20 antigen expressed on B cells; the antigen is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effectors functions to mediate B-cell lysis in vitro. The recommended clinical dosage of rituximab for the current indication is 375 mg/m² by IV infusion (4 weekly infusions) in adult patients. The recommended dosage of rituximab in RA is 1g by IV infusion followed two weeks later by a second 1g IV infusion. The AUC associated with this dose regimen was 228 mg•hr/mL. In an intravenous toxicology study with rituximab in Cynomolgus monkey, there was no evidence of significant toxicity that was consistently related to the administration of a dose of 20 mg/kg/week for 8 weeks. However, exaggerated pharmacological effects such as reduction of splenic and lymphatic tissue content and the expression of CD20⁺ B lymphocytes in the mandibular lymph nodes and spleen were observed from this toxicity study.

1.3 Recommendations

For nonclinical sections (i.e., Sections 8.1, 8.3, 8.4, 10, 12.1, 13.1 and 13.2), the content of the recommended product labeling was essentially retained. There were no major corrections in the nonclinical sections of the product labeling. A reference to Section 13.2 was added to the end of Section 8.1. (b) (4)

(b) (4) The text from this section of the label was apparently unintentionally removed from the product label during an earlier labeling revision. The pharmacology/toxicology (PT) Supervisor from DBOP (Dr. Anne Pilaro) was consulted for the product labeling revision as there was some consideration of moving the labeling under Section 13.2 to under Section 8.1, but Dr. Pilaro requested that Sections 8.1 and 13.2 be retained with their current content.

1.3.3 Labeling

Recommended product labeling for Sections 8.1 and (b) (4) are listed below. Changes are denoted in red and underlined. There were no changes for nonclinical labeling under Sections 8.3, 8.4, 10, 12.1, 13.1 and 13.2 (these sections are not shown).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero.

Rituximab was detected postnatally in the serum of infants exposed in-utero.

Non-Hodgkin's lymphoma, moderate-severe rheumatoid arthritis, (b) (4), Wegener's Granulomatosis and Microscopic Polyangiitis are serious conditions that require treatment. Rituximab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months of birth. (See Section 13.2 for a more detailed description).

(b) (4)

Reviewer signature: Mamata De March 9, 2011
Mamata De, Ph.D.

Team Leader signature: Concurrence: Timothy W. Robison March 9, 2011
Timothy W. Robison, Ph.D.,

cc: list:

BowenP, DPARP

DeM, DPARP

RobisonT, DPARP

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA or Supplement

sBLA Number: 103,705

Applicant: Genentech Inc

Stamp Date: November 04,
2010

Product: Rituximab

BLA Type: Supplement

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		
8	Has the applicant submitted all special toxicity studies/data requested by the Division during pre-submission discussions?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		
11	Has the applicant addressed any abuse potential issues in the submission?		x	Not required
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		x	Not required

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter: There are no potential review issues for the sBLA #103,705.

Rituximab is an approved product, no new pharmacology/toxicology data is needed for the current indication. The Applicant is the current marketing license holder for the approved drug product. All of the pharmacology/toxicology studies are owned by the Applicant.

Mamata De <i>Mamata De</i>	November 29, 2010
Reviewing Pharmacologist	Date
<i>Nidhi E. Tane</i>	11/30/2010
Team Leader/Supervisor	Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: sBLA STN 103705

Drug Name: RITUXAN®

Indication(s): [REDACTED] (b) (4)

Applicant: Genentech, Inc.

Date(s): Submitted: October 15, 2010
PDUFA: April 19, 2011

Review Priority: Priority

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Yongman Kim, Ph.D.

Concurring Reviewers: Joan Buenconsejo, Ph.D.

Medical Division: Division of Pulmonary, Allergenic, and Rheumatology Products

Clinical Team: Deborah Seibel, M.D.
Sarah Okada, M.D.
Sally Seymour, M.D.

Project Manager: Philantha Bowen

Keywords: Clinical studies, non-inferiority trial design, sensitivity analyses

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1. EXECUTIVE SUMMARY

The study ITN021AI (RAVE) provided a robust data supporting the efficacy of rituximab in treating Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA). The study met two pre-specified success criteria: non-inferiority (NI) of rituximab to cyclophosphamide (CYC) and superiority of rituximab over historical placebo. In my opinion, the applicant provided rationale for the study design of non-inferiority and justified a single efficacy study in the submission, thereby demonstrating that the quality and quantity of efficacy data were appropriate for rituximab to be efficacious.

As discussed in the pre-sBLA meeting, the Agency was concerned with quality and quantity of efficacy data in the submission. The applicant was advised to justify the assumptions for NI trial, i.e., reliable choice of NI margin, constancy between historical trials of comparator and NI trial, and assay sensitivity of the NI trial. Those assumptions were reasonably justified from my viewpoint when all things are considered. The margin of 20% was supposed to preserve 60% of conservatively estimated entire effect of CYC. Even though there were advances in medical practice handling WG and MPA, the patients would not achieve complete remission without immuno-suppressive cytotoxic treatment such as CYC. Therefore, complete remission rate of placebo in the NI trial if placebo were included would be similar to the rate of historical placebo, which implies that constancy might be a reasonable assumption. A condition for study success is that the complete remission rate of CYC must be greater than 40% when the rate of rituximab is lower than the rate of CYC. This supports the assumption of assay sensitivity. Also most of Agency's advices on the protocol and on the statistical analysis plan were incorporated throughout a long period of regulatory interactions. Study conduct met the standard in maintaining study integrity including blindness of randomized treatment codes to minimize a phenomenon of bias toward null, common in NI trial. Data collection and management met the industry standard as well as regulatory standard. The applicant was also advised to justify the single efficacy study to support efficacy. In my opinion, the applicant provided robust efficacy results since the study was conducted from multi-centers, demonstrated internal consistency of efficacy over various subpopulations, and proved superiority of rituximab over historical placebo. They also argued that the treatment effect shown in the trial is clinically important and meaningful for the patient population with WG and MPA since there is no approved treatment for the severe disease.

There were potential statistical issues such as primary analysis population related to missing data handling and multiplicity in secondary analyses with the primary endpoint and secondary endpoints analyses. However, the impact of missing data was negligible because only 4 out of 197 had their primary endpoint as missing. Their primary analysis called 'as-defined' analysis excluded the four patients with missing primary endpoint from the intent-to-treat (ITT) population. My ITT analysis treating those patients as treatment failures gave very similar results to the applicant's primary analysis on 'as-defined' analysis population. There was no issue for multiplicity in analyses with the primary endpoint because for study success they have to win on both non-inferiority test of rituximab to CYC and superiority test of rituximab over historical

placebo. Also there was no issue in multiple testing of non-inferiority and superiority of rituximab to CYC because they used a sequential approach in testing non-inferiority-then superiority. However, they did not plan on adjustment for secondary endpoints analyses, which was not problematic as long as they did not plan to include statistically significant secondary endpoints in the label. In fact, they did not include any secondary efficacy endpoints even if successful.

My stratified analyses demonstrated that rituximab was shown non-inferior to CYC after adjusting for centers and anti-neutrophil cytoplasmic antibodies (ANCA) types and results were a little bit more favorable to rituximab compared to the original primary analysis.

With all evaluations considered, I conclude that the evidence of efficacy from the RAVE study is substantial and robust in terms of analysis populations such as ITT, per-protocol, as-defined, and as-treated sets, in terms of missing data handling though judged not important due to number of patients with missing data and in terms of subpopulations based on study center, baseline demographic and disease characteristics, and statistical model with covariates of stratification factor.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

The applicant described rituximab in the submission as follows:

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are the two major forms of systemic vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA). The incidence of these conditions in the United States is approximately 6,000 new cases per year, and the estimated prevalence is 25,000–30,000. These conditions are termed *ANCA-associated vasculitides* because of their strong associations with these highly specific autoantibodies. ANCA-associated vasculitides are autoimmune disorders in which tolerance for one of two self antigens, proteinase 3 (PR3) or myeloperoxidase (MPO), has been lost, leading to the production of PR3- or MPO-ANCA. For unknown reasons, those with generalized or severe ANCA-associated vasculitides have either PR3-ANCA or MPO-ANCA, but not both.

Conventional therapies for AAV are associated with a high percentage of treatment failures and disease relapses. Preventing fatal outcomes in severe AAV requires immunosuppressive therapy consisting of glucocorticoids and cytotoxic agents, usually cyclophosphamide (CYC). Although most patients under expert care achieve remission, most also experience disease flares when therapy is tapered or discontinued.

Conventional therapies for AAV are associated with substantial toxicity that frequently results in severe, permanent morbidity and lethal adverse effects. The high adverse event rate is attributed primarily to two conventional therapies, CYC and glucocorticoids. In the NIH longitudinal study on WG, 42% of patients treated with CYC and prednisone

suffered permanent treatment-related morbidity. Opportunistic infections, bone marrow suppression, hemorrhagic cystitis, infertility, and cancer—particularly hematopoietic and bladder malignancies—are some of the adverse effects that may result from treating AAV with CYC. There are also substantial morbidities associated with a repeated and prolonged course of glucocorticoids.

There is preliminary evidence that anti-CD20 therapy (e.g., Rituximab) helps control AAV rapidly and may reestablish tolerance to ANCA target antigens. We anticipate that treatment of AAV with Rituximab will eliminate potentially pathogenic B cells and the disease-amplifying ANCA and at the same time allow the restoration of B-cell tolerance to autoantigens. In investigator-sponsored trials, Rituximab has shown extremely promising results in patients with treatment-refractory AAV. We hypothesize that treatment with Rituximab may result in restoring tolerance to the ANCA antigens, which would lead to the possibility of successfully withdrawing patients from toxic conventional therapies. The presence of pathogenic ANCA in this disease indicates that tolerance to the target antigens for ANCA has been lost. We hypothesize that complete B-cell elimination as induced by Rituximab will allow the exposure of newly formed immature B cells to both PR3 and MPO antigens, resulting in the appropriate recognition of these self-antigens and the restoration of tolerance to these antigens.

Rituximab was first approved for the treatment of non-Hodgkin's lymphoma in 1997. Rituximab, in combination with methotrexate, was then approved in 2006 for the treatment of adult patients with moderately- to severely-active rheumatoid arthritis who had an inadequate response to one or more TNF antagonist therapies. Subsequently, rituximab was approved for the indications for slowing structural damage progression and physical function improvement in rheumatoid arthritis patients in 2008 and in 2009, respectively.

Current submission is seeking for approval of rituximab in treating

(b) (4)

(b) (4)

2.1.2 History of Drug Development and Regulatory Interactions

The following are chronological study milestones with regulatory interactions:

- Pre-IND meeting held (6 April 2004)
- Initial Protocol developed (1 July 2004)
- IND submitted (20 July 2004)
- Study started (21 December 2004)
- Orphan drug designated (14 February 2006)
- SAP finalized (12 January 2009)
- Final Protocol developed (15 July 2009)
- Data cut-off for 6-month analysis (9 January 2010)
- Initial Pre-sBLA meeting cancelled (24 November 2009)
- Regulatory Briefing held (26 February 2010)
- Pre-sBLA meeting held (11 March 2010)
- sBLA submitted (15 October 2010)
- 120-days safety update submitted (10 January 2011)

In pre-IND meeting in 2004, key design issues of the proposed non-inferiority pivotal study were discussed. We advised that the applicant must provide reproducible evidence of efficacy in placebo-controlled studies for CYC, active comparator product in order to provide historical evidence of sensitivity to drug effects (HESDE) and to determine an effect size for the active comparator. However, noting that data from placebo-controlled studies of the comparator were not available, we recommended the applicant to utilize information from literature reports from the pre-CYC era and data demonstrating the effects of CYC in comparison to outcomes that would be seen for untreated patients. We recommended Birmingham Vasculitis Activity Scores for Wegener's Granulomatosis (BVAS/WG) at 6 month as primary endpoint instead of proposed BVAS/WG area-under-the-curve (AUC) over 6-months. For substantial evidence of efficacy, additional study was recommended. In addition, CYC was agreed as an appropriate active comparator.

In subsequent IND meeting in 2004, two papers on the natural history of AAV were discussed. Walton (British Medical Journal, 1958) conducted a meta-analysis for untreated subjects. He showed that 21 out of 56 (38%) had survived at 6 months, but we inferred that none would attain complete remission defined as off-steroid with BVAS/WG of 0. Hollander and Manning (American Internal Medicine, 1967) conducted an analysis for treated subjects prior to CYC and showed that 10 out of 20 (50%) had survived at 6 months. Again we inferred that none would attain complete remission. The Walton's paper provided point and interval estimates for remission rate for historical placebo which was crucial in determining NI margin and a bound used in superiority test over historical placebo.

In pre-sBLA meeting in 2010, we asked the applicant to provide rationale for a single pivotal study as sufficient evidence of efficacy in the submission. We advised that as justification for a single study they must show statistically persuasive results from multicenter trial, consistency of efficacy across subsets, and multiple endpoints measuring different events. Also they have to focus on significant treatment effect on a clinically meaningful endpoint, irreversible morbidity and mortality of the disease, rationale for the NI design, the assay sensitivity, the NI margins (M_1 and M_2), and rationale for the use of historical control.

The applicant received orphan drug designation (b) (4) in 2006 and the current sBLA received priority review status upon submission. In the current submission, the applicant focused on the efficacy data from the 6 months remission induction phase. They also submitted additional analysis results from the one year remission maintenance phase as a part of 120 day safety update.

2.1.3 Specific Study Reviewed

Since main efficacy data in the submission came from a single pivotal phase 2/3 study and other studies included were literature-based open label studies and series of case studies, I focused on the single pivotal study ITN021AI (RAVE) to assess efficacy of the test treatment. The study is a randomized, double-blind, active-controlled, multi-center non-inferiority trial. Approximately 200 patients with severe AAV were randomized to rituximab or CYC in 1:1 ratio being stratified

by center and ANCA types (MPO and PR3). There were eight centers in US and one center in Netherland. Major centers with more than 30 patients were Johns Hopkins University, Mayo Clinic, and Boston University. Three centers from University of California – San Francisco, University of Alabama – Birmingham, and Duke University were so small that they were combined in the statistical analysis to evaluate center effect. The study consists of two phases: 6 months remission induction phase and one year remission maintenance phase. The following features of design are unusual and noteworthy. First, patients were allowed to cross-over to opposite treatment if interim results were ‘bad’ – flare or failure. Second, patients were allowed to switch-over early to pre-specified maintenance phase treatment (azathioprine or placebo) if interim results were ‘good’ - remission. In the primary analysis, cross-over patients were treated as failures and switch-over patients were likely to show complete remission at 6 months. Third, the study employed NI design comparing rituximab with CYC, the active comparator. But, CYC was an unapproved drug and was never tested with a concurrent placebo mainly due to ethical reason – the disease is severe and fatal without treatment. Therefore, there were no reliable effect size data for CYC compared to placebo. To show efficacy, we required the applicant to prove superiority of the test treatment over historical placebo.

2.1.4 Major Statistical Issues

Following is a list of statistical issues found in the submission:

1. Justification for NI design – NI margin, constancy, assay sensitivity
2. Justification for a single efficacy study in the submission – statistically persuasive effects
3. Robustness of efficacy data – analysis sets, missing data, subsets by center, subgroups by demographic characteristics, subgroups by baseline disease characteristics, secondary outcomes, statistical analysis models, covariates (randomization stratified by center and ANCA type)
4. Multiplicity adjustment – NI test then superiority test (no adjustment necessary), NI test and superiority test over historical placebo (no adjustment necessary due to a nature of co-primary hypotheses), secondary endpoints analyses (not planned due to no claim in the label), subgroup analyses (necessary if they would like to claim efficacy in some subgroups).

These issues will be further discussed in detail in the section 5.1 of statistical issues and collective evidence.

2.2 Data Sources

sBLA STN 103705.5344 was submitted on October 15, 2010 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report

including protocols, statistical analysis plan, and all referenced literature can be found in the EDR. SAS codes used in statistical analyses and the electronic SAS data sets with raw and derived variables and data definitions were provided in the EDR using the following path:

\\cber-fs3\m\eCTD Submissions\STN103705\103705.enx

3. STATISTICAL EVALUATION

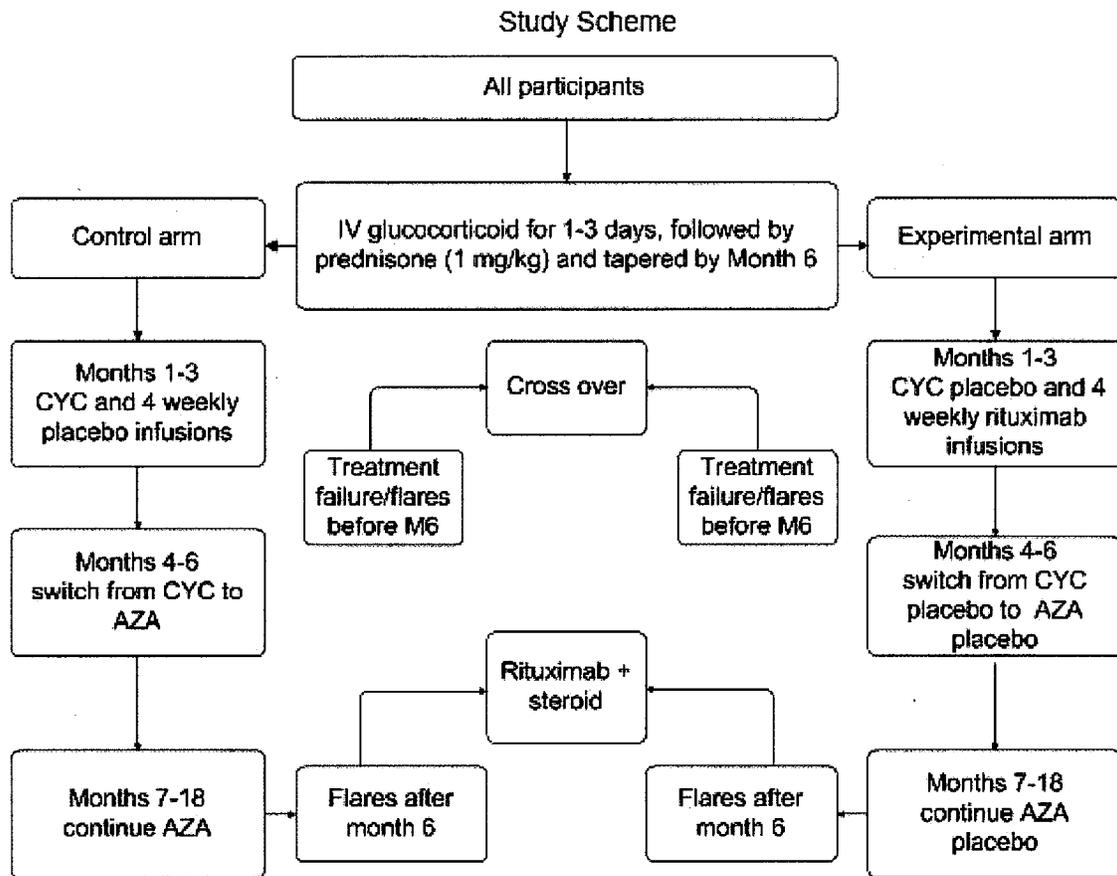
3.1 Data and Analysis Quality

In general, I think that the submitted efficacy data are acceptable in terms of quality and integrity. I was able to reproduce the primary and key secondary efficacy analyses. I found that there are no noticeable deviations between CRFs and analysis datasets relevant to primary and key secondary endpoints. Also I verified the randomized treatment assignments. Since Mayo clinic seems to drive efficacy, we requested the Division of Scientific Investigation (DSI) to audit the center. In the process, DSI found that 15 patients in Boston University center received 10 to 50% overdose of rituximab from the target dose. I assessed the impact of the overdose on the efficacy of rituximab by conducting a couple of sensitivity analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The pivotal efficacy study employed NI trial design with CYC as active comparator. Since the disease is severe, use of placebo control was considered unethical. The NI margin of 20% of difference in complete remission rates was mainly based on clinical judgment supported by literature-based clinical data and was justified as preserving 60% of the entire effect of 50% in complete remission rates based on FDA guidance for Industry on Non-inferiority Clinical Trials. The study employed randomized, multi-center, parallel-group, double-blind, and double-dummy design. The study consists of two phases – 6 months remission induction phase and 1 year remission maintenance phase. Treatment codes were blinded throughout the entire study phases. Unusual feature of the design is that, during remission induction phase, patients with early treatment failure were allowed to crossover to the opposite treatment, i.e., rituximab patients get CYC or vice versa and patients with disease remission were allowed to switchover to treatment supposed to receive during remission maintenance phase. The following diagram depicts a schematic of the study design.



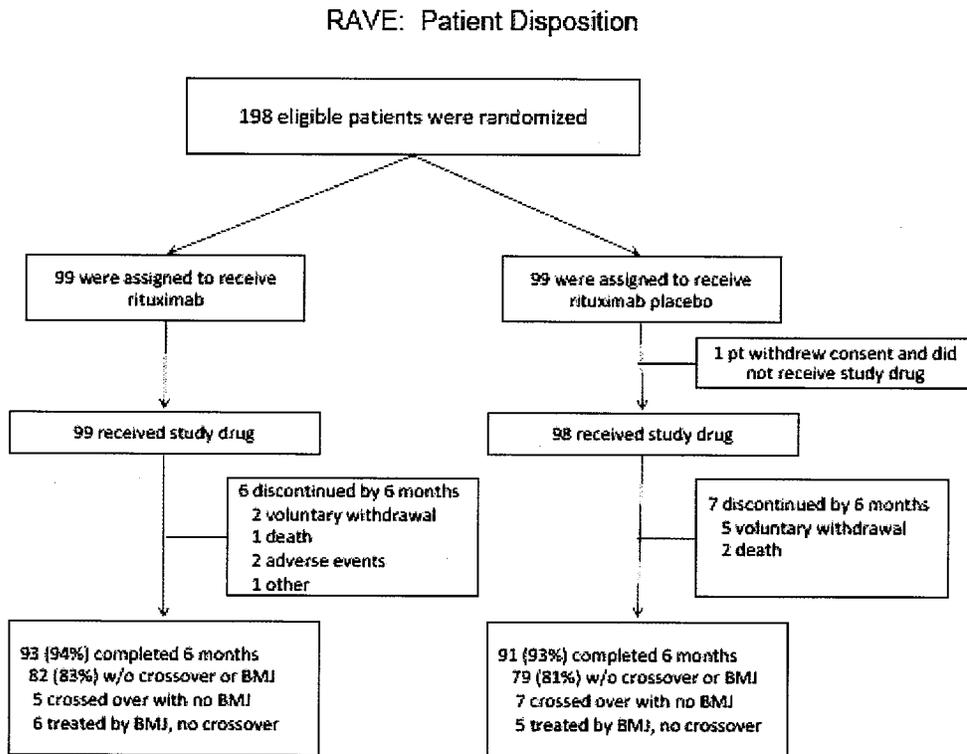
Excerpted from the clinical study report (page 23).

The primary endpoint was complete remission, which was defined as having a BVAS/WG of 0, and complete off steroids at 6 months. BVAS/WG is a clinical index of disease activity based on evidence of active disease in 9 organ systems. The score ranges from 0 (no disease activity) to 68 (highest disease activity). Key secondary endpoints included partial remission (BVAS/WG <3 & complete steroid taper), remission with partial steroid taper (BVAS/WG=0 & prednisone < 10mg/day), cumulative steroid dose, duration of complete remission defined as time to flare after complete remission. Adjustment on multiple secondary endpoints analyses was not planned. Therefore, other analyses than primary analysis are to be treated as exploratory from a regulatory perspective and are discouraged to be included in the label.

Study seemed to be conducted properly based on the submission when I assessed the history of regulatory interactions, protocol revisions/amendments, study report, study datasets, and internal consistency among those components. Their effort to keep blindness was noteworthy. In addition, patients were supposed to wear hats during clinic visit to conceal potential side effect of thinning hair from cytotoxic comparator. The safety officer was also different from the investigator who dealt with any infusion-related adverse events.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Major inclusion criteria for the study were that patients are diagnosed with WG or MPA, have active disease with BVAS/WG > 2 that requires treatment with CYC, and must be positive for either PR3-ANCA or MPO-ANCA. The following chart describes the patient disposition by the applicant.



BMJ=best medical judgment.

Note: One patient (001001) randomized to the cyclophosphamide group withdrew consent and discontinued the study prior to the first treatment.

Excerpted from the integrated summary of efficacy (page 35).

Since there was a discrepancy in number of crossover patients between applicant and me, I included a table for patient disposition in the appendix. My analysis has six crossover patients from CYC completers whereas there were seven such patients in the applicant chart.

There were no noticeable imbalances of the demographics and baseline characteristics between treatment groups as shown below.

Baseline Demographic Characteristics (ITT Population)

	Rituximab N=99	Cyclophosphamide N=98	All Patients N=197
Age at screening, years			
Mean (SD)	54.0 (16.76)	51.5 (14.07)	52.8 (15.49)
Gender (%)			
Male	46.5	54.1	50.3
Female	53.5	45.9	49.7
Primary race (%)			
White	91.9	94.9	93.4
Black or African American	3.0	3.1	3.0
Asian	1.0	0.0	0.5
Other	4.0	2.0	3.0
Ethnicity (%)			
Not Hispanic or Latino	91.9	94.9	93.4
Hispanic or Latino	6.1	3.1	4.6
Unknown	2.0	2.0	2.0

Excerpted from the clinical study report, table 7 (page 71).

Baseline Disease Characteristics (ITT Population)

	Rituximab N=99	Cyclophosphamide N=98	All Patients N=197
ANCA-associated vasculitis type (%)			
Wegener's granulomatosis	73.7	75.5	74.6
Microscopic polyangiitis	24.2	24.5	24.4
Indeterminate	1.0	0	0.5
Missing	1.0	0	0.5
Newly diagnosed at enrollment (%)	48.5	49.0	48.7
BVAS/WG score ^a (mean [SD])	8.1 (2.82)	8.0 (3.41)	8.0 (3.12)
Creatinine clearance (mean [SD]) mL/min	76.5 (46.27)	91.4 (49.24)	83.9 (48.23)
Organ involvement (%) ^b			
Renal	65.7	66.3	66.0
Hematuria	28.3	28.6	28.4
Red blood cell casts	37.4	35.7	36.5
Rise in creatinine >30% or fall in creatinine clearance >25%	34.3	36.7	35.5
Pulmonary	52.5	54.1	53.3
Alveolar hemorrhage	27.3	23.5	25.4
Endobronchial involvement	4.0	9.2	6.6
Nodules or cavities	18.2	27.6	22.8
Other lung infiltrate	25.3	21.4	23.4
Pleurisy	8.1	9.2	8.6
Respiratory failure	2.0	0	1.0
Systemic ^c	55.6	66.3	60.9
Ear/nose/throat	60.6	56.1	58.4
Mucous membranes/eyes	27.3	25.5	26.4
Nervous system	25.3	15.3	20.3
Cutaneous	20.2	16.3	18.3
Gastrointestinal	2.0	0	1.0
Mesenteric ischemia	2.0	0	1.0
Cardiovascular	0	1.0	0.5
Pericarditis	0	1.0	0.5

Positive immunofluorescence assay ANCA results ^a	97 (100)	94 (100)	191 (100)
C-ANCA	65 (67.0)	61 (64.9)	126 (66.0)
P-ANCA	33 (34.0)	33 (35.1)	66 (34.6)
Positive ELISA results for ANCA ^{a,b}	97 (98.0)	98 (100)	195 (99.0)
PR3	66 (68.0)	65 (66.3)	131 (67.2)
MPO	32 (33.0)	33 (33.7)	65 (33.3)

Excerpted from the clinical study report, table 8 (pages 73-74).

The efficacy analysis was conducted on the intent-to-treat (ITT) population. The ITT set included all randomized participants who received study drug. As a secondary analysis set, per protocol population was defined as a subset of ITT population excluding:

- participants without any BVAS/WG observation post randomization
- participants with a less than 75% of total 375 mg/m² x 4 rituximab/placebo infusions
- participants with major protocol deviations, which was determined by blinded sponsor review prior to database lock.

The applicant defined two additional analyses sets which served as their primary and secondary analysis populations. First, ‘as-defined set’ was a subset of ITT population in which patients who experienced early treatment failure (defined as failure to achieve disease response by the Month 1 study visit or inability to complete at least 3 infusions of rituximab or rituximab placebo) were classified as experiencing failure for the primary endpoint. Second, ‘as-treated set’ was a subset of ITT population in which patients who experienced early treatment failure but continued on their initial treatment under best medical judgment by the investigator were not automatically classified as failure for the primary endpoint at 6 months. The following table summarizes the analysis sets.

Analysis Populations

	RTX	CYC
ITT	99	98
As-defined	98	95
As-treated	97	95
Per protocol	95	94

The as-defined set ended up a subset of ITT population excluding patients who had missing primary endpoint (complete remission) at 6 months. There were 4 such patients, three of them from CYC group and one from rituximab group. They were subset of 13 dropouts. Other 9 dropouts had non-missing primary endpoint as 'failure'. Applicant used this analysis set as the primary analysis population.

3.2.3 Statistical Methodologies

To show the efficacy of rituximab, two analyses must show a statistical significance – non-inferiority of rituximab to CYC and superiority of rituximab to historical placebo.

For the non-inferiority testing of rituximab to CYC, the confidence interval approach using normal approximation was used. The lower bound of two-sided 95.1% confidence interval for the difference in rates of complete remissions is greater than -20%, then the non-inferiority is claimed. In this case, if the observed rate of rituximab is lower than that of CYC, the observed rate of CYC must be at least 40% to conclude non-inferiority of rituximab to support assumption of assay sensitivity of the trial. The superiority of rituximab to historical placebo is shown if the lower bound of two-sided 95.1% confidence interval for the rate of complete remission in rituximab group is greater than 50%, the upper bound of two-sided 95.1% confidence interval for the rate in historical placebo group.

The significance level of 0.049 was used in the final analysis after adjusting for multiplicity due to an interim analysis although the purpose of the analysis was not for stopping the trial due to early treatment success or futility. Lan-DeMets procedure for alpha spending function and O'Brien-Fleming boundary were used for interim analysis.

For the secondary analysis of superiority testing of rituximab to CYC, the same confidence interval approach was used. The lower bound of two-sided 95.1% confidence interval is greater than 0%, then the superiority is claimed. There is no need for adjustment for this multiple tests because a sequential approach in testing non-inferiority-then superiority is used.

For all binary secondary endpoints, chi-square test was conducted and for all continuous secondary endpoints, Wilcoxon rank-sum test was conducted.

Patients with missing primary endpoint due to discontinuation of study drug were not imputed in the as-defined population and excluded in the primary analysis. In my opinion, a primary analysis should not exclude patients with missing data because when there are more dropouts from test group than from comparator group, the exclusion of dropouts may lead to bias toward no difference or 'null', which is anti-conservative. Therefore, I conducted the analysis on the ITT population treating those patients as treatment failures.

To assess robustness of efficacy data, applicant conducted sensitivity analysis with respect to analysis populations - ITT, per-protocol, as-defined, and as-treated.

Applicant conducted several subgroup analyses based on demographics and baseline characteristics – age group (<52, ≥52), sex, disease status (new, relapsing), renal involvement (≥1 major, 0 major), creatinine clearance (<60, ≥60), serum creatinine (>1.2, ≤1.2), alveolar hemorrhage (with, without), ANCA type (MPO+, PR3+), AAV type (MPA, WG), systemic disease (yes, no).

To assess internal consistency among sites, applicant conducted a subset analysis by site after combining smaller sites to have at least 30 patients per site after pooling. They also conducted analysis after excluding most influential site to assess impact of dominant site.

3.2.4 Results and Conclusions

In this presentation of the results, I focused on the data from the 6 months remission induction phase in the original submission and presented descriptive analyses on the remission status at 12 and 18 months based on the 1-year data from the remission maintenance phase via 120-day safety update.

The single pivotal study RAVE met the criteria for the study success: non-inferiority of rituximab to CYC and superiority of rituximab to historical placebo. Overall, data from the study provides quite robust evidence of efficacy from tilting the assumptions used in the analyses.

The following is the applicant’s primary analysis.

Applicant’s primary analysis on As-defined population

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	98	95		
Complete Remission	63 (64)	52 (55)	9.5	-4.3, 23.4
95.1% CI	54.8, 73.8	44.7, 64.8		

Excerpted from the clinical study report, table 10 (page75).

However the analysis was conducted on the as-defined set, not on the ITT population. This analysis excluded four patients with missing primary endpoint at 6 months. It is noteworthy that, among the four patients with missing primary endpoint, three were from the comparator group and one from the experimental treatment group. Therefore, the ITT analysis end up a little bit more favorable to rituximab compared to the as-defined analysis because more CYC patients were imputed as treatment failures than rituximab patients – three vs. one. Below is my analysis conducted on the ITT population treating these four patients as treatment failures.

Reviewer’s primary analysis on ITT population

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	99	98		
Complete Remission	63 (64)	52 (53)	10.6	-3.2, 24.3
95.1% CI	54.1, 73.2	43.1, 63.0		

Based on my table, the lower bound of the confidence interval for the difference, -3.18%, is greater than the non-inferiority margin, -20%. Therefore, the study met the non-inferiority criterion. Also the rate of complete remission of rituximab, 64% is greater than that of CYC, 53%, which is greater than pre-specified 40% to support assay sensitivity of the trial. The lower bound of the confidence interval for the rate of complete remission of rituximab, 54%, is greater than the upper bound of the confidence interval for the rate of complete remission of historical placebo, 50%. Therefore, the study met the superiority criterion. However, since the lower bound of the confidence interval for the difference, -3.2%, is less than 0%, the study failed to show that rituximab is superior to CYC.

Following tables include sensitivity analyses.

Applicant’s per-protocol analysis

	RTX N=95 n (%)	CYC N=94 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	95	94		
Complete Remission	62 (65)	51 (54)	11.0	-3.0, 25.0
95.1% CI	55.7, 73.2	44.1, 64.4		

Excerpted from the clinical study report, table 9.1.1.2 (page 147).

Applicant’s primary analysis on as-treated population

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	97	95		
Complete Remission	63 (65)	52 (55)	10.2	-3.7, 24.1
95.1% CI	55.4, 74.5	44.7, 64.8		

Excerpted from the clinical study report, table 9.1.1.3 (page 148).

As expected, the difference in rates of complete remission in per-protocol analysis is bigger than that in ITT analysis in favor of rituximab. The same conclusion as with the ITT analysis is drawn from the per-protocol analysis. Similar conclusion was drawn from ‘as-treated’ analysis.

The following are tables for secondary efficacy endpoints analyses supporting the efficacy of rituximab.

Secondary efficacy endpoints analyses

Rates of remission on <10mg/day prednisone at 6 months (Applicant):

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	99	98		
Complete Remission	70 (71)	61 (62)	8.5	-4.7, 21.6
95.1% CI	61.7, 79.7	56.6, 71.8		

Excerpted from the clinical study report, table 13 (page 78).

Rates of remission regardless of prednisone use at 6 months (Applicant):

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	99	98		
Complete Remission	80 (81)	65 (66)	14.5	2.3, 26.6
95.1% CI	73.1, 88.6	60.0, 75.7		

Excerpted from the clinical study report, table 17 (page 81).

Rates of off-steroid use at 6 months (Reviewer):

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	90	88		
Off-Steroid	71 (79)	65 (74)	5.0	-7.5, 17.5
95.1% CI	70.4, 87.4	64.6, 83.1		

Cumulative prednisone dose through 6 months (Applicant):

	RTX N=99	CYC N=98
Mean (SD)	3324 (984.7)	3691 (1244.9)
Median	3310	3450
Min, Max	1030, 6883	660, 8306

Excerpted from the clinical study report, table 16 (page 81).

Change in ANCA status (Applicant):

	RTX N=99 n (%)	CYC N=98 n (%)
ANCA+ at Baseline	88 (89)	78 (80)

ANCA+ to ANCA-	39/88 (44)	23/78 (29)
MPO+ at Baseline	28 (28)	22 (22)
MPO+ to MPO-	11/28 (39)	9/22 (41)
PR3+ at Baseline	61 (62)	56 (57)
PR3+ to PR3-	29/61 (48)	14/56 (25)

Excerpted from the clinical study report, table 24 (page 86).

- Rates of remission on <10 mg/day prednisone at 6 months were numerically higher in the rituximab arm compared to the CYC arm (71% vs. 62%).
- A higher proportion of patients in the rituximab arm achieved remission (BVAS/WG=0) at 6 months, independent of prednisone use, compared with the CYC arm (81% vs. 66%).
- A numerically higher proportion of patients in the rituximab arm achieved off-steroid at 6 months compared with the CYC arm (79% vs. 74%).
- Cumulative prednisone use through Month 6 was numerically lower in the rituximab arm (3310 mg vs. 3450 mg).
- The proportion of patients who became seronegative for ANCA was higher in the rituximab arm compared with the CYC arm (44% vs. 29%), and rituximab treatment had a greater impact on conversion to seronegativity for patients who were PR3+ compared with the CYC arm (48% vs. 25%).

The following table describes complete remission status at 6, 12, and 18 months.

Applicant's analysis on ITT population

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
Complete remission at 6 months:				
N	99	98		
Complete Remission	63 (64)	52 (53)	10.6	-3.2, 24.3
Complete remission at 12 months:				
N	99	98		
Complete Remission	44 (44)	37 (38)	6.7	-7.0, 20.4
Complete remission at 18 months:				
N	99	98		
Complete Remission	38 (38)	30 (31)	7.8	-5.5, 21.0

Excerpted from the 120-day safety update, table 28 (page 102).

In the rituximab group, 44% of patients achieved complete remission at 6 and 12 months, and 38% of patients achieved it at 6, 12, and 18 months. In patients who switched from the cyclophosphamide to azathioprine at 6 months, 38% of patients achieved complete remission at 6 and 12 months, and 31% of patients achieved it at 6, 12, and 18 months.

3.3 Evaluation of Safety

The assessment of the safety aspects of the study drug was mainly conducted by reviewing medical team, Drs Seibel and Seymour. I only reviewed the pre-selected adverse events analysis using statistical model. Applicant compared rates of the pre-selected AEs per patient month between the treatment groups. Rates of rituximab is numerically lower compared to that of CYC (0.065 vs. 0.080, difference (95.1% CI) = -0.015 (-0.046, 0.030)), but the confidence interval for the difference includes the null value and values that correspond to a more favorable outcome with CYC, so that the direction of the difference in risk, if any, is not known with much confidence. They used Poisson regression model adjusting for covariates of center and ANCA type.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In addition to standard subgroup analyses based on patient demographics, I included subgroup analyses by center to see if there is any significant inconsistency of efficacy among centers and by baseline disease characteristics.

4.1 Gender, Race, Age, and Geographic Region

The following analysis is the subgroup analysis by demographics.

Applicant's subgroup analysis by demographics

Male:

	RTX N=46 n (%)	CYC N=53 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	46	53		
Complete Remission	28 (61)	27 (51)	9.7	-9.7, 29.5
95.1% CI	46.7, 75.0	37.4, 64.5		

Female:

	RTX N=53 n (%)	CYC N=45 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	53	45		
Complete Remission	35 (66)	25 (56)	10.5	-8.9, 29.9
95.1% CI	53.2, 78.8	41.0, 70.1		

Age (<52):

	RTX N=43 n (%)	CYC N=48 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	43	48		
Complete Remission	28 (65)	25 (52)	13.0	-7.1, 33.2
95.1% CI	50.8, 79.4	37.9, 66.3		

Age (≥52):

	RTX N=56 n (%)	CYC N=50 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	56	50		
Complete Remission	35 (63)	25 (54)	8.5	-10.3, 27.3
95.1% CI	49.8, 75.2	40.1, 67.9		

Excerpted from the clinical study report, tables 9.3.5.5 & 9.3.5.6 (pages 157 – 158)

Reviewer's subgroup analysis by age cut at 65**Age (≤65):**

	RTX N=65 n (%)	CYC N=79 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	65	79		
Complete Remission	43 (66)	44 (56)	10.5	-5.5, 26.4
95.1% CI	54.6, 77.7	44.7, 66.7		

Age (>65):

	RTX N=34 n (%)	CYC N=19 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	34	19		
Complete Remission	20 (59)	8 (42)	16.7	-11.1, 44.5
95.1% CI	42.2, 75.4	19.8, 64.4		

Each subgroup by demographics showed that non-inferiority criterion was met and there seems no interaction between treatment and demographic factors.

The following analysis is the subset analysis by center.

Applicant’s subset analysis by study center

Complete Remission	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)	Difference in Rate %	Two-Sided 95.1% CI of Difference
Center 002	24/26 (92.3)	16/27 (59.3)	33.0	11.8, 54.3
Center 006	11/21 (52.4)	12/22 (54.5)	-2.2	-32.1, 27.8
Center 001	14/17 (82.4)	11/18 (61.1)	21.2	-7.8, 50.3
Centers 004 and 009	9/18 (50.0)	7/17 (41.2)	8.8	-24.2, 41.8
Centers 003, 005, 007, and 008	5/17 (29.4)	6/14 (42.9)	-13.4	-47.4, 20.5
All centers except Center 002	39/73 (53.4)	36/71 (50.7)	2.7	-13.7, 19.1

Excerpted from the clinical study report, table 12 (page 77).

Except for centers 001 (Johns Hopkins University) and 002 (Mayo Clinic), the non-inferiority testing failed. However, this is not surprising because study was not powered to show non-inferiority in each center. Excluding the center 002, the dominating center in terms of patient numbers and effect size, study was still able to meet the non-inferiority criterion. This is reassuring that efficacy was not driven by a seemingly dominant center.

Since DSI found protocol deviations of rituximab overdose from 15 patients from Boston University (BU) center, I conducted a couple of sensitivity analyses: an analysis excluding all patients from BU center and an analysis treating all rituximab patients from BU center as treatment failures.

Reviewer’s sensitivity analysis excluding Boston University Center

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	78	76		
Complete Remission 95.1% CI	52 (67) 56.2, 77.2	40 (53) 41.4, 63.9	14.0	-1.4, 29.4

Reviewer’s sensitivity analysis treating all RTX patients from Boston University Center as failures

	RTX N=99 n (%)	CYC N=98 n (%)	Difference in Rate %	Two-sided 95.1% CI of Difference
N	99	98		

Complete Remission	52 (53)	52 (53)	-0.5	-14.5, 13.5
95.1% CI	42.6, 62.4	43.1, 63.0		

Both analyses met the NI criterion. In addition, the first analysis demonstrated superiority of rituximab over historical placebo. However, the second analysis failed to show superiority of rituximab over historical placebo. I think that this was true mainly because all rituximab patients from BU were treated as failures.

4.2 Other Special/Subgroup Populations

The following analyses are the subgroup analyses by baseline characteristics.

The applicant's subgroup analysis by baseline characteristics

Relapsing Disease at Baseline:

	RTX N=99 n (%)	CYC N=98 n (%)	Difference (95.1% CI)
New disease at Baseline	29/48 (60)	31/48 (65)	-4.2 (-23.6, 15.3)
Relapsing disease at Baseline	34/51 (67)	21/50 (42)	24.7 (5.8, 43.6)

Excerpted from the clinical study report, table 18 (page 82).

Renal Item at Baseline:

	RTX N=99 n (%)	CYC N=98 n (%)	Difference (95.1% CI)
≥1 major renal item on BVAS/WG	31/51 (61)	32/51 (63)	-2.0 (-20.9, 17.0)
No major renal item on BVAS/WG	32/48 (67)	20/47 (43)	24.1 (4.6, 43.6)

Excerpted from the clinical study report, table 19 (page 83).

Creatinine clearance at Baseline:

	RTX N=99 n (%)	CYC N=98 n (%)	Difference (95.1% CI)
CCl < 60 mL/min	25/45 (56)	18/28 (64)	-8.7 (-31.8, 14.3)
CCl ≥ 60 mL/min	38/54 (70)	34/70 (49)	21.8 (4.8, 38.8)

Excerpted from the clinical study report, table 20 (page 83).

Serum creatinine at Baseline:

	RTX N=99 n (%)	CYC N=98 n (%)	Difference (95.1% CI)
Creatinine ≤ 1.2 mg/dL	36/52 (69)	21/53 (40)	29.6 (11.3, 47.9)
Creatinine > 1.2 mg/dL	27/47 (57)	31/45 (69)	-11.4 (-31.1, 8.2)

Excerpted from the clinical study report, table 21 (page 84).

Alveolar hemorrhage at Baseline:

	RTX N=99 n (%)	CYC N=98 n (%)	Difference (95.1% CI)
With Alv Hem	16/27 (59)	11/23 (48)	11.4 (-16.3, 39.1)
Without Alv Hem	47/72 (65)	41/75 (55)	10.6 (-5.2, 26.4)

Excerpted from the clinical study report, table 22 (page 85).

ANCA type at Baseline:

	RTX N=99 n (%)	CYC N=98 n (%)	Difference (95.1% CI)
MPO+ at Baseline	20/33 (61)	21/33 (64)	-3.0 (-26.5, 20.5)
PR3+ at Baseline	43/66 (65)	31/65 (48)	17.5 (0.7, 34.3)

Excerpted from the clinical study report, table 23 (page 85).

Of patients with relapsing disease at Baseline, numerically higher proportion of patients in the rituximab arm achieved the primary endpoint compared with the CYC arm (67% vs. 42%). This was also observed in the subgroup of patients with a creatinine level ≤ 1.2 mg/dL at Baseline (69% vs. 40%), creatinine clearance ≥ 60 mL/min (70% vs. 49%), without a major renal item on BVAS/WG at Baseline (67% vs. 43%), or with PR3 antibodies at Baseline (65% vs. 48%). Rituximab appeared to provide outcomes not significantly different compared with CYC for patients with more severe manifestations of disease, such as renal disease and alveolar hemorrhage.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Agency was concerned with quality and quantity of efficacy data in the submission. These issues had been raised and discussed through regulatory interactions. Related to the quality, we asked the applicant to justify non-inferiority study design with assumptions such as the NI margin, constancy, and assay sensitivity. Given that there were no historical placebo controlled comparator studies, the choice of NI margin largely depended on clinical judgment although there were relevant literature data to derive the margin. The inherent weakness of the design was supplemented by requiring superiority of the test treatment over ‘historical’ placebo. Also, literature data were put together in highly conservative manner giving rise to ‘reasonable’ 20% margin.. Even though there were advances in medical practice handling WG and MPA, the patients would not achieve complete remission without immuno-suppressive cytotoxic treatment such as CYC. Therefore, complete remission rate of placebo in the NI trial if placebo were included would be similar to the rate of historical placebo, which implies that constancy might be a reasonable assumption. Requirement that remission rate for CYC should be greater than 40% supports assay sensitivity assumption. Related to the quantity, we asked the applicant to justify that efficacy data from a single efficacy study is sufficient for approval. They provided rationale for a single study in the submission based on FDA guidance for industry: “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” (section II.C.3). In my opinion, they demonstrated statistically persuasive results for non-inferiority against active control and for superiority to historical control, a multicenter study design, and consistency of results across subsets and across endpoints measuring different events. Also a finding of less than superiority, but with the lower bound of a 95.1% confidence interval for the difference considerably bigger than M_2 (20%), is also statistically persuasive based on FDA guidance for industry: “Non-Inferiority Clinical Trials” (section III.B.2). Robustness of efficacy data was shown by various sensitivity analyses – analysis sets, missing data, subsets by center, subgroups by demographic characteristics, subgroups by baseline disease characteristics, secondary efficacy endpoints, statistical analysis models with covariates (randomization stratified by center and ANCA type).

I conducted several stratified analyses to see how the stratification factors used in randomization of center and ANCA type have impact on the primary analysis. These analyses showed results a little bit more favorable to rituximab as expected due to increase in power with stratified analysis, but they were generally consistent with the original ‘pooled’ analysis without adjustment for stratification factors (see appendix for the results). Also, I conducted a logistic regression analysis on the complete remission data. In the analysis, I converted the metric from difference to odds ratio between rates of complete remission. The NI margin in terms of odds ratio was converted from -20% to 0.429 (see the appendix for its derivation). Estimated odds ratio and its 95.1% confidence interval were 1.715 and (0.935, 3.145). Therefore, after adjusting for center and ANCA type via logistic regression, the lower bound for difference 0.935 was greater than the new NI margin of 0.429, but it was not greater than 1, which implied the non-inferiority, but not superiority of rituximab to CYC.

Regarding multiplicity adjustment, the procedure for conducting NI test and if significant, then conducting superiority test does not make adjustment necessary. Also the study success criteria of NI test and superiority test over historical placebo do not need adjustment because two hypotheses are co-primary hypotheses. Applicant did not plan for multiplicity adjustment on secondary endpoints analyses because they did not seem to include successful endpoints in the label. However, they need to adjust for multiplicity for subgroup analyses if they would like to claim superiority in some subgroups.

In their primary analysis, they excluded four patients with missing primary endpoint. But they conducted a sensitivity analysis including those patients treating them as treatment failures. This analysis is considered an ITT analysis. Nine other dropouts and 12 crossover patients were treated as treatment failure, which in my opinion, is appropriate.

There was one interim analysis mainly for stopping the trial when test treatment is inferior to active control – about 30% inferior with the half of total patients at 6 months. They did not plan to stop the trial with sign of early efficacy or futility. However, they adjusted for multiplicity for the interim analysis using Lan-DeMets alpha spending function and O'Brien-Fleming boundary approach. Alpha level for the interim analysis was 0.003 and final analysis was 0.049, which is, I think, appropriate.

5.2 Comments on the proposed label

Following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the study description and primary analysis results and their interpretation.

One potential issue is the inclusion of their description for (b) (4) regarding ' (b) (4) (b) (4). The applicant said " (b) (4). Although the (b) (4) (b) (4), the study was not (b) (4) (b) (4)

Therefore, the statement should be deleted from the label.

(b) (4)

(b) (4)

Table 13
Percentage of Patients Who Achieved
Complete Remission at 6 Months (Intent-to-Treat Population)

	Rituxan (n=99)	Cyclophosphamide (n=98)	Treatment Difference (Rituxan – Cyclophosphamide)
Rate			(b) (4)
95.1% ^b CI			^a

^a non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin ($(\frac{(b)}{(4)})\% > -20\%$).

^b The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

(b) (4)

5.3 Conclusions and Recommendations

The single pivotal study ITN021AI (RAVE) provided a robust data supporting the efficacy of rituximab in treating (b) (4). The study employed a non-inferiority trial design with the margin of 20% in remission rate mainly based on clinical judgment with information from literature and some non-placebo controlled trials with cyclophosphamide, the active control. Due to lack of data for effect size of CYC and concern on assay sensitivity due to potential violation of constancy assumption in the NI trial, in order for the rituximab to be efficacious, the rituximab must be non-inferior to CYC and at the same time it must be superior to the historical control group with only background steroid treatment. Data from the RAVE study demonstrated that the two criteria for study success were met.

The applicant provided robust efficacy results from multicenter trial and internal consistency of efficacy over various subpopulations and also proved superiority of rituximab over historical placebo. They also provided the treatment effect shown in the trial is clinically important and meaningful for the patient population with AAV since there is no approved treatment for the severe disease.

With all the above evaluations, I conclude that the evidence of efficacy from the RAVE study is substantial and robust in terms of analysis populations such as ITT, per-protocol, as-defined, and as-treated sets, in terms of missing data handling though judged not important due to number of patients with missing data and in terms of subpopulations based on study center, baseline demographic and disease characteristics, and statistical model with covariates of stratification factor.

APPENDICES

Applicant's Patient Disposition

	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)
Randomized and treated ^a	99 (100)	98 (100)
Completed 6 months	93 (93.9)	91 (92.9)
Without crossover or BMJ	82 (82.8)	79 (80.6)
Crossed over without BMJ by 6 months	5	7
BMJ by 6 months, no crossover	6	5
Discontinued by 6 months	6 (6.1)	7 (7.1)
Without crossover or BMJ	3	5
Crossed over without BMJ by 6 months	1	0
BMJ by 6 months, no crossover	2	2
Primary reason for discontinuation by 6 months		
Voluntary withdrawal	2	5
Death	1	2
Adverse event ^b	2	0
Other	1	0

Excerpted from the clinical study report, table 5 (page 68).

Reviewer's Patient Disposition

	RTX	CYC
Randomized (ITT)	99 (100%)	98 (100%)
Without crossover or BMJ	85 (86%)	85 (87%)
Crossover	6 (6%)	6 (6%)
BMJ	8 (8%)	7 (7%)
Completed	93 (94%)	91 (93%)
Without crossover or BMJ	82	80
Crossover	5	6
BMJ	6	5
Discontinued	6 (6%)	7 (7%)
Without crossover or BMJ	3	5
Crossover	1	0
BMJ	2	2

Reason for Discontinuation	6	7
Voluntary withdrawal	2	5
Death	1	2
AE	2	0
Other	1	0

Selected Adverse Events (Applicant):

	Rituximab N=99	Cyclophosphamide N=98
Total number of selected AEs ^a	37	45
Number of patients with ≥ 1 selected AE, n (%)	22 (22.2)	34 (34.7)
Sum of patient-months for all patients	571.2	564.1
Rate of selected AEs per patient-month	0.0648	0.0798
Rate of selected AEs per patient-year	0.78	0.96
Selected adverse events, n (%)		
Death (all causes)	1 (1.0)	2 (2.0)
Grade ≥2 leukopenia	5 (5.1)	17 (17.3)
Grade ≥2 thrombocytopenia	3 (3.0)	1 (1.0)
Grade ≥3 infections	10 (10.1)	10 (10.2)
Hemorrhagic cystitis ^b	1 (1.0)	1 (1.0)
Malignancy	1 (1.0)	2 (2.0)
Venous thromboembolic event ^c	5 (5.1)	8 (8.2) ^d
Hospitalization ^e	10 (10.1)	4 (4.1)
Cerebrovascular accident	0	0
Infusion reaction ^f	1 (1.0)	0

Excerpted from the clinical study report, table 28 (page 99).

Derivation of the NI margin in terms of odds ratio:

I assumed 70% of complete remission rates for both rituximab and CYC when I converted original NI margin of 20% in terms of difference to a new NI margin in terms of odds ratio.

$$\begin{aligned}
 M_2 \text{ in terms of odds ratio} &= (P_R - M_2) \cdot (1 - P_C) / [P_C \cdot \{1 - (P_R - M_2)\}] \\
 &= (70 - 20) \cdot (100 - 70) / [70 \cdot \{100 - (70 - 20)\}] \\
 &= 0.429.
 \end{aligned}$$

Results of stratified analyses:

	Difference in Rates %	Two-sided 95.1% CI of Difference
Original 'Pooled' Weights	10.6	-3.18, 24.33
Minimum Risk Weights	12.2	0.11, 24.28
Inverse Variance Weights	18.3	6.79, 29.71
CMH Weights	11.7	-0.50, 23.83

The statistical methods used in the analyses can be found in the paper titled 'Minimum risk weights for comparing treatments in stratified binomial trials' by Mehrotra and Railkar (Statistics in Medicine, 2000; 19: 811-825). SAS macro code for the methods is as follows:



(b) (4)

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Yongman Kim, Ph.D.



Date: March 14, 2011

Concurring Reviewer(s): Joan Buenconsejo, Ph.D.



Statistical Team Leader: Joan Buenconsejo, Ph.D.

Biometrics Division Director: Thomas Permutt, Ph.D.

cc:

Philantha Bowen

Deborah Seibel, M.D.

Sarah Okada, M.D.

Sally Seymour, M.D.

Yongman Kim, Ph.D.

Joan Buenconsejo, Ph.D.

Thomas Permutt, Ph.D.

Edward Nevius, Ph.D.

Ram Tiwari, Ph.D.

Lillian Patrician

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial:

Protocol Number (s): ITN021AI

Protocol Title (optional): Rituximab therapy for the induction of remission and tolerance in ANCA-associated vasculitis (AAV)

Phase: 2/3

Control: Active Control of cyclophosphamide (CYC)

Blinding: Double-Blind

Number of Centers: 9

Region(s) (Country): US, Netherlands

Duration: 6 Months

Treatment Arms: Rituximab

Treatment Schedule: 375 mg/m², four weekly infusions

Randomization: Yes

Ratio: 1:1

Method of Randomization: stratification, Central via an IVRS

If stratified, then the Stratification Factors: center and ANCA type

Primary Endpoint: Complete remission at 6 months

Primary Analysis Population: ITT, As-defined, Per-Protocol...)

Statistical Design: Non-Inferiority

If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data? Yes, but not with concurrent placebo control.

Margin = 20% of remission rate difference

%Retained = 60%

Adaptive Design: No

Primary Statistical Methodology: 95.1% confidence interval approach

Interim Analysis: Yes

If yes:

No. of Times: 1

Method: group sequential method

α Adjustment: Yes

α Spending Function: Lan-Demets spending function with O'Brien-Fleming boundary

DSMB: Yes

Sample Size: 200

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

Statistic = 95.1% CI based on normal approximation

Power= 83%

Δ = 0% (under equivalence alternative hypothesis)

α = 0.049

- Was there an **Alternative Analysis** in case of violation of assumption? No
 - Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
 - Were the **Covariates** pre-specified in the protocol? Yes
 - Did the Applicant perform **Sensitivity Analyses**? Yes
 - How were the **Missing Data** handled? Treated as treatment failures
 - Was there a **Multiplicity** involved? Yes
- If yes,
- Multiple Arms: No
 - Multiple Endpoints: Yes
 - Which method was used to control for type I error: Not planned
- **Multiple Secondary Endpoints:** Are they being included in the label? No
 - **Were Subgroup Analyses Performed:** Yes
 - Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report?
- No
- Overall, was the study positive? Yes

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 103705 Applicant: Genentech Stamp Date: 10/15/10
 Drug Name: Rituximab NDA/BLA Type: Supplemental BLA

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

<i>Y. J. ... Kim</i>	<i>12/6/10</i>
_____ Reviewing Statistician	_____ Date
<i>J. ...</i>	<i>12/8/10</i>
_____ Supervisor/Team Leader	_____ Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA	103705, supplement 5344
BB-IND	11831
Submission Date:	10/15/2010
Brand Name	RITUXAN®
Submission Type	Efficacy Supplement
Generic Name	Rituximab
OCP Reviewer	Elizabeth Shang, Ph.D.
Team Leader (Acting)	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer	Elizabeth Shang, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Pulmonary, Allergy and Rheumatology Products (DPARP)
Sponsor	Genentech
Formulation; Strength(s); Administration Route	Single-use vial of concentrated solution of 100 mg/10 mL and 500 mg/50 mL; Intravenous infusion
Proposed Indication in this Efficacy Supplement	Rituxan in combination with glucocorticoids for the treatment of [REDACTED] (b) (4)
Proposed Dosage Regimen	375 mg/m ² IV once weekly for 4 weeks

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4	Population Pharmacokinetics Analysis Review.....	8

1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology perspective, this application is acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

This is an efficacy supplement submitted in support of the sought indication of using rituximab in combination with glucocorticoids for the treatment of (b) (4)

). Rituximab was granted orphan drug designation for AAV (Wegener's Granulomatosis, Microscopic Polyangiitis, and Churg-Strauss Syndrome) on February 14, 2006.

The clinical pharmacology program included primarily the assessment of rituximab pharmacokinetic characteristic in AAV patients. The PK parameters were estimated by population PK analysis from pivotal Phase II/III study (ITN021AI/RAVE). Based on the population pharmacokinetic analysis of data in 97 AAV patients who received 375 mg/m² rituximab once weekly by IV infusion for four weeks, the estimated median terminal elimination half-life was 23 days. Rituximab mean clearance and volume of distribution were 0.312 L/day and 4.50 L, respectively. Sex, human anti-chimeric antibodies (HACA), and body surface area (BSA) are important covariates explaining inter-individual variability on clearance (CL). Female patients had 21% lower CL than male patients. HACA positive patients had 43% faster clearance than HACA negative patients. CL was 24% higher for a BSA of 2.30 m² compared to a person with BSA of 1.9 m². SEX and BSA were also important covariates explaining the inter-individual variability on volume of distribution (V). Female patients had 21% smaller volume of distribution than male patients. Volume of distribution was 20% larger for a BSA of 2.30 m² compared to a person with BSA of 1.9 m². However, further dose adjustment based on sex and HACA status is not necessary.

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Chemistry and Physico-Chemical Properties: Rituximab is a genetically engineered chimeric murine/human monoclonal IgG₁ kappa antibody produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin.

Rituximab has an approximate molecular weight of 145 kD.

Formulation: 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 in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Water for Injection. The pH is 6.5.

2.1.2. What is the proposed indication, dosage and route of administration?

Proposed Indication: (b) (4)

Reviewer's comments:

Based upon the findings from clinical review, the medical officer is recommending rituximab for 'Wagner's Granulomatosis and Microscopic Polyangiitis', (b) (4) (b) (4); sought by the sponsor.

Dosage and Route of Administration: Administer rituximab as a 375 mg/m² intravenous infusion once weekly for 4 weeks. (b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical trials used to support the proposed dosing or claims?

There were no new clinical pharmacology studies to support this efficacy supplement. The clinical efficacy data pivotal to the current application is derived from a Phase II/III, multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international non-inferiority study (ITN021AI/RAVE).

The dose selection was based upon twelve published clinical studies (uncontrolled and case series) as well as one investigator-initiated, randomized, controlled study (RITUXVAS) of patients with AAV. All these studies have used rituximab 375 mg/m² weekly for 4 weeks and achieved induction of remission

The clinical pharmacology program consisted of a population PK report that included analysis of sparse blood samples collected for PK measurement from study RAVE.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Concentrations of rituximab were determined in human serum samples with validated colorimetric sandwich enzyme-linked immunosorbent assay (ELISA), which was the same assay used for determining serum levels in the submission for indication of rheumatoid arthritis.

2.2.3 What are the PK characteristics of rituximab in AAV patients?

Due to the nature of sparse PK sampling, PK parameters of rituximab in AAV patients are estimated by population PK analysis. For complete review of population PK analysis, see Section 4.

2.2.4 Pharmacodynamics

The number of peripheral-blood CD19-positive B cells decreased to < 10 cells/ μ L after two infusions of rituximab and remained at that level in most patients through 6 months (see Table 1). At 6 months, 70 of 84 patients (83%) in the rituximab group had this degree of CD19-positive depletion. By Month 12, the majority of patients showed signs of B cell return with 66 of 82 (80.5%) patients with counts > 10 cells/ μ L. By Month 18, 61 of 70 patients (87.1%) had counts > 10 cells/ μ L.

Table 1. Proportion of Patients with CD counts ≤ 1 and <10 Cells/ μL over Time

	Rituximab n=99	Cyclophosphamide n=98
Baseline (no. of evaluable patients)	94	93
<10 cells/ μL	2 (2.1%)	3 (3.2%)
Week 2	93	95
≤ 1 cell/ μL	39 (41.9%)	0
< 10 cells/ μL	87 (93.5%)	6 (6.3%)
Month 1	92	92
≤ 1 cell/ μL	46 (50.0%)	0
< 10 cells/ μL	87 (94.6%)	9 (9.8%)
Month 2	91	89
≤ 1 cell/ μL	46 (50.5%)	1 (1.1%)
< 10 cells/ μL	84 (92.3%)	40 (44.9%)
Month 4	73	74
≤ 1 cell/ μL	30 (41.1%)	6 (8.1%)
< 10 cells/ μL	67 (91.8%)	49 (66.2%)
Month 6	84	74
≤ 1 cell/ μL	33 (39.3%)	3 (4.1%)
< 10 cells/ μL	70 (83.3%)	44 (59.5%)
Month 12	82	73
≤ 1 cell/ μL	2 (2.4%)	2 (2.7%)
< 10 cells/ μL	16 (19.5%)	26 (35.6%)
Month 15	74	69
≤ 1 cell/ μL	2 (2.7%)	0
< 10 cells/ μL	13 (17.6%)	26 (37.7%)
Month 18	70	64
≤ 1 cell/ μL	2 (2.9%)	0
< 10 cells/ μL	9 (12.9%)	18 (28.1%)

Source: 120-Day Safety Update (AAV), Table 23.

2.3 Intrinsic Factors

2.3.1 *What were the immunogenicity findings for rituximab? What was the impact of immunogenicity on exposure and/or safety and efficacy?*

A positive HACA is defined as > 5 RU/mL and immunodepletable with rituximab. A negative HACA is ≤ 5 RU/mL, or > 5 RU/mL and not immunodepletable with rituximab. The serum anti-rituximab antibodies was measured using validated colorimetric sandwich ELISA assays identical to that reported previously in the submission for rheumatoid arthritis indication. Details on the validation of the immunogenicity assay are reviewed by Marjorie A. Shapiro, Ph.D. Division of Monoclonal Antibodies.

During the first 6 months of treatment, five patients had positive HACA results. Three (3%) patients were from the rituximab arm and 2 (2%) patients were from the cyclophosphamide (CYC) arm. One patient, who was in the CYC arm, tested positive for HACA antibodies at most study visits, including Screening. Of the 5 patients, one patient, who was randomized to the rituximab, had an infusion reaction 2 days after the third infusion.

The rate of HACA formation increased overtime. In all, 28 (22.6%) patients (of a total of 124 patients ever exposed to rituximab) tested HACA positive after exposure to rituximab up to the common closeout date of 27 January 2010 (corresponding to the last patient's 18-month visit), whichever occurred earlier. Cumulative incidence of HACA over time is listed in the table below:

Table 2. Cumulative Incidence of HACA Over Time

	Rituximab n=99	Cyclophosphamide n=98
Up to 6 Months	3 (3.0%)	2 (2.1%)
Up to 12 Months	15 (15.2%)	2 (2.0%)
Up to 18 Months	23 (23.2%)	3 (3.1%)
Up to the CCO date	25 (25.3%)	6 (6.1%)

BMJ=best medical judgment; CYC=cyclophosphamide; CCO=common closeout; HACA=human anti-chimeric antibody.

Notes: Of the 6 patients who tested HACA positive in the CYC group during the study, 3 tested HACA positive after receiving rituximab via either crossing over, open-label RTX, or BMJ. Of the remaining 3 patients, 2 (006115 and 009103) did not receive any rituximab during the study. The other CYC patient (002032) tested HACA positive 3 months prior to the first dose of rituximab (crossover) and tested negative later.

Source: 120-Day Safety Update (AAV), Table 21.

The Summary of overall safety profile in HACA-positive and HACA-negative patients who received rituximab during the study is listed in Table 3.

Table 3. Safety Profile by HACA Status in Rituximab-Exposed Patients

	HACA Positive ^b n=26	HACA Negative n=96
Patient-years of follow-up	62.7	271.3
No. of patients with ≥ one AE	27 (96.4%)	95 (99.0%)
Rate (events per patient-year)	5.99 (5.48-6.54)	6.37 (6.07-6.67)
No. of patients with ≥ one serious AE	18 (64.3%)	54 (56.3%)
Rate (events per patient-year)	0.44 (0.31-0.60)	0.41 (0.34-0.49)
No. of patients with ≥ one selected AE ^c	12 (42.9%)	39 (40.6%)
Rate (events per patient-year)	0.22	0.28
No. of patients with ≥ 1 IRR ^d	4 (14.3%)	11 (11.5%)

AE = adverse event; HACA = human anti-chimeric antibody; IRR = infusion-related reaction.

^a Includes all patients who received any active dose of rituximab either as initial treatment, crossover treatment, open-label treatment, or best medical judgment.

^b HACA-positive patients are those who tested HACA positive after being exposed to rituximab.

^c Selected AEs include death, Grade ≥ 2 leukopenia, Grade ≥ 2 thrombocytopenia, Grade ≥ 3 infection, hemorrhagic cystitis, malignancy, venous thromboembolic event, hospitalization, cerebrovascular accident, and IRR leading to discontinuation of further infusions.

^d IRR refers to any AE occurring within 24 hours of an infusion and considered infusion related by the investigator.

Source: 120-Day Safety Update (AAV), Table 22.

The sponsor concluded that the overall safety profile was similar in HACA-positive and HACA-negative patients.

3 Labeling Recommendation

Below is the proposed labeling change from Clinical Pharmacology perspective. Proposed additions to the label from the clinical pharmacology team are indicated by underline and the ~~strikethrough~~ words indicate the deletions. Refer to the BLA action letter for the full text of the final labeling.

12.2 Pharmacodynamics

(b) (4)

12.3 Pharmacokinetics

(b) (4)

4 Population Pharmacokinetics Analysis Review

Key Issues

In this supplemental BLA submission, a population PK modeling approach was used to obtain estimates of typical PK parameters for rituximab in subjects with AAV, and determine the covariates that may significantly impact the PK parameters.

The aim of this review is to review sponsor's population PK analyses and verify the labeling statements derived based on these analyses.

Sponsor's Analysis

Population PK analysis was performed using the available serum concentration data from a pivotal Phase 2/3 Study ITN021AI (RAVE).

The population PK analysis contained 487 rituximab serum concentrations from 97 patients who received 375 mg/m² rituximab IV infusion weekly for 4 weeks. The evaluable subjects in the population data sets must have received at least 1 rituximab dose and had at least 1 measurable serum rituximab concentration randomized.

Study Description:

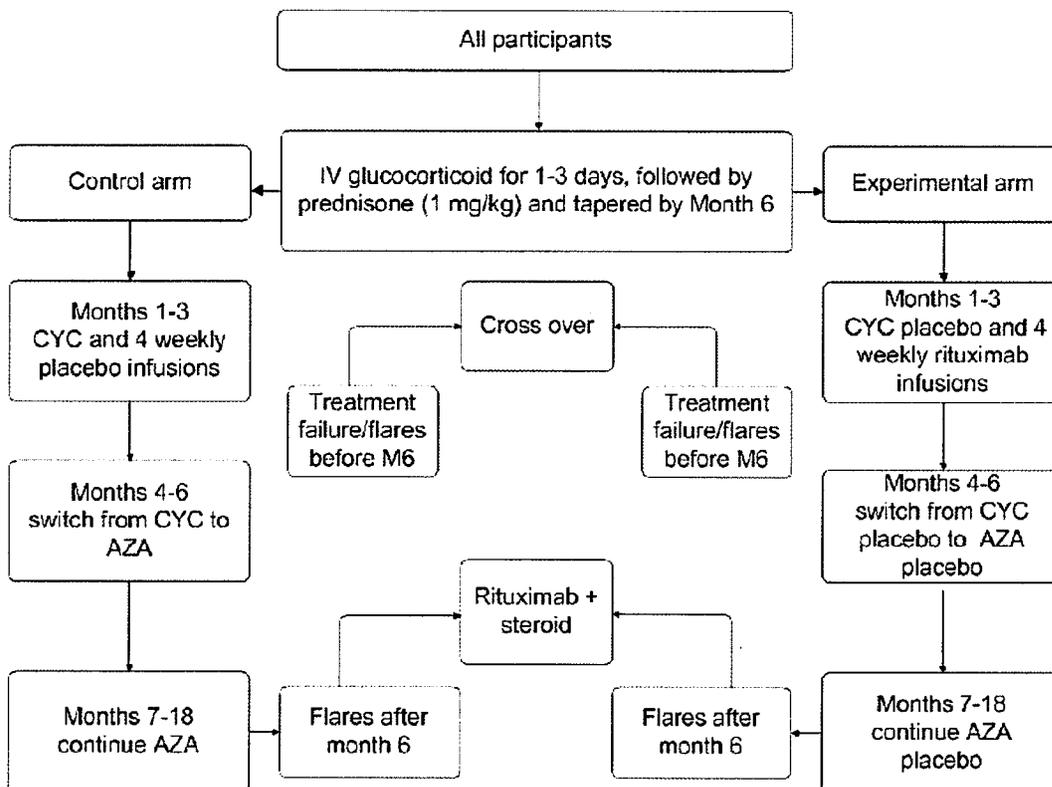
Study ITN021AI (RAVE): RITUXIMAB THERAPY FOR THE INDUCTION OF REMISSION AND TOLERANCE IN ANCAASSOCIATED VASCULITIS.

This was a randomized, multicenter, double-blinded, double-dummy, placebo-controlled, non-inferiority study of rituximab (375 mg/ m²) in patients with severe AAV. The study consisted of two phases: a 6-month remission induction phase followed by a 12-month remission maintenance phase (Figure 1). During the remission induction phase, patients in the control arm (conventional treatment) received oral prednisone daily, rituximab placebo infusions once weekly for 4 weeks, and oral CYC daily (2 mg/kg/day) for 3 to 6 months. Patients in the experimental arm (rituximab and glucocorticoids) received oral prednisone daily, rituximab (375 mg/ m²) infusions once weekly for 4 weeks, and CYC placebo daily for 3 to 6 months. During the remission maintenance phase, patients in the control arm discontinued CYC and started oral

azathioprine (AZA) (2 mg/kg/day), and patients in the experimental arm discontinued CYC placebo and started oral daily AZA placebo. Both arms continued oral AZA/AZA placebo daily up to Month 18.

Two hundred patients were to be randomized in a 1:1 ratio to the experimental or control arm.

Figure 1
Study Scheme



PK sampling:

Time Point	Screening	Baseline ²	Week ¹			Month								Post-Treatment Follow-Up	
			V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Every 6 Months after V12 ²
Visit	V-1 ⁴	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V6-month interval	V _{CD}
Day	0	1	8	15	22	29	60	120	180	270	365	455	545		
Serum PK (rituximab levels) ²⁵	x			x			x	x	x	x				x	x

²⁵ According to Manual of Operations.

Rituximab levels were evaluated prior to the first and third doses, then on Days 29, 60, 120, 180, 270, and 545 from the first dose. This report presents the findings of a planned analysis after all enrolled patients had completed 6 months of evaluation. Therefore, these data represent data on some patients who had data collected around nominal time of 270 days per the schedule of assessment of the study protocol.

Methods:

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Data

The population PK dataset contained a total of 487 measurable serum rituximab concentration values from 97 subjects who received multiple infusions of rituximab in combination with glucocorticoid.

The demographic data are listed in the following two tables:

Summary of Baseline Values for Continuous Covariates
for Patients in the Population PK Analysis

Covariate	AGE (yr)	BSA (m ²)	ALBU (g/d L)
Mean ± SD	54.3 ± 16.8	1.93 ± 0.233	3.63 ± 0.712
Median, n	55, 97	1.90, 97	3.9, 69
Min, max	16, 92	1.43, 2.45	2.2, 8

ALBU=baseline albumin concentration; BSA=body surface area; min=minimum value; max=maximum value; n=number of patients with available covariate information; PK=pharmacokinetic; SD=standard deviation.

Summary of Categorical Covariates
for Patients in the Population PK Analysis

Covariate	Number (%) Patients (N=97)
RACE	
White	89 (91.8%)
Black or African-American	3 (3.09%)
Asian	1 (1.03%)
Other	4 (4.12%)
SEX	
Male	45 (46.4%)
Female	52 (53.6%)
ETHN	
Not Hispanic or Latino	90 (92.8%)
Hispanic or Latino	5 (5.15%)
Unknown	2 (2.05%)
HACA	
Positive	20 (20.6%)
Negative	77 (79.4%)

ETHN=ethnicity; HACA=human anti-chimeric antibodies; PK=pharmacokinetic.

Model

A two-compartment linear PK model using zero-order input (infusion) and first-order elimination was selected as the structural PK model to describe the serum concentration-versus-time profiles of rituximab following IV infusion. It is parameterized in terms of systemic clearance (CL), apparent volume of distribution in the central (V1), and rate constant between central and peripheral compartments (K12, K21). This model was used to describe the rituximab PK data in patients with RA and was confirmed to be the appropriate model to describe rituximab PK data in patients with AAV in this study.

The rituximab PK samples were not collected during the initial distribution phase (first week after the end of infusion) in this study. Therefore, K12 and K21 could not have been well estimated. The value of 0.141 and 0.153 /day for K12 and K21 were fixed based on previous PK knowledge in RA patients. It was assumed that K12 and K21 are similar between different indications (i.e., RA Report No. 05-1074, and AAV). Additional features of this model include: exponential error model used to describe between-patient variability for CL, and V1, and the full error model (proportional plus additive) used to define the residual error. The additive error variance was set to 0.5 mcg/mL, which is the BLQ level.

The population PK data were analyzed using nonlinear mixed-effects modeling with the NONMEM software system, Version VI, Level 1.1 (GloboMax LLC, Hanover, MD) with the PREDPP model library and NMTRAN subroutines.

Covariates

The effects of potential covariates on CL1 and V1 of rituximab were evaluated. The covariates examined included demographic characteristics (Age, Race, Ethnicity, and BSA), albumin levels, and anti-human anti-chimeric antibody (HACA) status.

Covariate model building was conducted for CL1, and V1 independently in three steps:

- Step 1: Screening of covariate effects by adding covariates one by one to the base model.
- Step 2: Construction of the full model by incorporating the significant covariates from Step 1.
- Step 3: Elaboration of the reduced model by testing the full model against restricted models by removing each covariate in turn. The reduced models for each PK parameter obtained at Step 3 were then combined in a new full model, and the final model for patient covariates was elaborated by testing the full model against restricted models by removing each covariate in turn.

A critical change in MOF of ≥ 6.63 as a significant covariate for the FOCE INTER method (nominal $\alpha = 0.01$, $df = 1$) was predefined.

Results:

Base model:

Table 4. Summary of Rituximab Population PK Parameter Estimates of the Base Model
Population Parameter Point Estimates (%SEE) for the Base Model

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability (%SEE)
Clearance		
CL (mL/day)	289 (4.39)	42.1% (13.8)
Volume of Distribution in Central Compartment		
V ₁ (mL)	4420 (3.21)	26.8% (18.9)
Rate Constant from Central to Peripheral Compartment		
K ₁₂ (1/day)	0.141 FIX	---
Rate Constant from Peripheral to Central Compartment		
K ₂₁ (1/day)	0.153 FIX	---
Correlation		
ρ (CL, V ₁)	0.406 (32.4)	---
Proportional Residual Error		
	16.9% (7.28)	---
Additive Residual Error (ug/mL)		
	0.500 FIX	---

%SEE=percent of standard error of estimation; ρ=correlation coefficient.

Final model:

On initial screening, the significant covariates influencing CL were HACA and SEX demonstrated by ΔMOF by -10.8, and -7.32, respectively. The following factors were added to the base model to form a full model for CL1.

$$\hat{CL} = \theta_1 \cdot \theta_2^{(SEX)} \cdot \theta_3^{(HACA)}$$

In the second stage of covariate model building, the full model was tested by removing HACA and SEX covariate one at a time. ΔMOF showed increase by 7.77 and 11.3, respectively. Therefore, HACA and SEX were remained as statistically significant covariates on CL.

On initial screening, SEX, BSA, and RACE were found to be statistically significant covariates on V1, demonstrated by ΔMOF -26.6, -26.4, and -9.87 respectively. Therefore, the full covariate model for V1 was as follows:

$$\hat{V}_1 = \theta_2 \cdot (BSA / 1.90)^{\theta_5} \cdot \theta_6^{(SEX)} \cdot \theta_7^{(RACE)}$$

The full model for V1 was tested by removing BSA, SEX, and RACE covariate one at a time. ΔMOF showed increase by 12.1, 12.0, and 3.14 respectively. Therefore, BSA and SEX were remained as statistically significant covariates on V1.

In the last stage of the model building, the full covariate model was tested by removing SEX, and HACA effect on CL, and SEX, and BSA effect on V1 on at time. ΔMOF showed increase by 22.8, 11.3, 18.1, and 12.6 points, respectively.

Therefore, the final covariate models for CL, and V1 were as follows:

$$\hat{CL} = \theta_1 \cdot \theta_3^{(SEX)} \cdot \theta_4^{(HACA)}$$

$$\hat{V}_1 = \theta_2 \cdot (BSA/1.90)^{\theta_5} \cdot \theta_6^{(SEX)}$$

The typical values of estimated PK parameters are listed in Table 5.

Table 5. Summary of population pharmacokinetic parameters of rituximab and the significant covariates to rituximab PK.

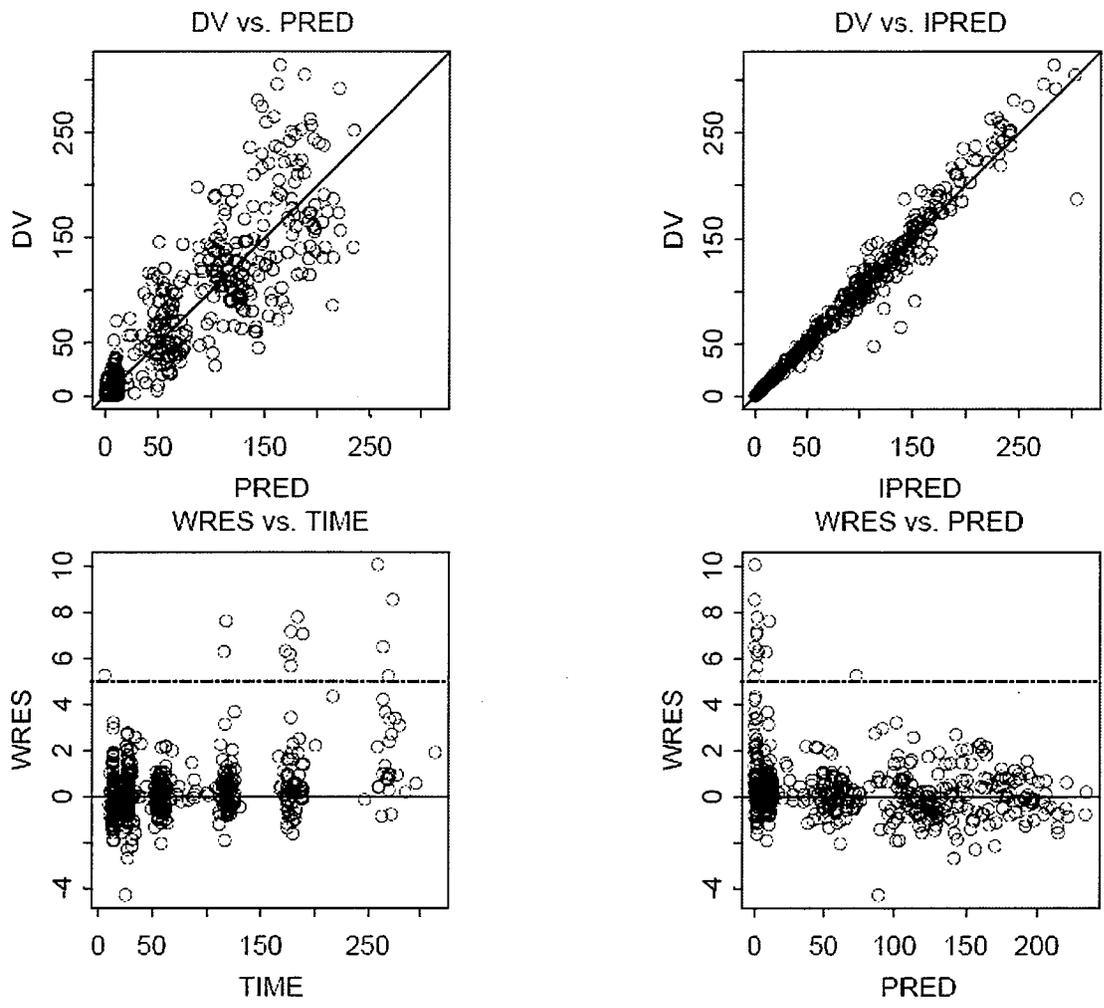
Population Parameter Estimates (%SEE) for the Final Covariate Model

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability (%SEE)
Clearance		
CL (mL/day)	330 (5.82)	35.2% (15.8)
Influence of SEX on CL	0.686 (7.35)	
Influence of HACA on CL	1.37 (8.69)	
Volume of Distribution in Central Compartment		
V ₁ (mL)	4960 (4.40)	17.8% (19.9)
Influence of SEX on V ₁	0.784 (6.06)	
Influence of BSA on V ₁	0.871 (32.0)	
Rate constants between central and peripheral compartment		
K ₁₂ (1/day)	0.141 FIX	---
K ₂₁ (1/day)	0.153 FIX	---
Correlation		
p (CL, V ₁)	0.00688 (26.9)	
Proportional Residual Error		
	16.8 (7.14)	---
Additive Residual Error (ug/mL)		
	0.5 FIX	---

%SEE=percent standard error of estimation; p=correlation coefficient.

The goodness of fit (GOF) plots for the final PK model reported by the Sponsor are shown in Figure 1 and Figure 2. Visual predictive check plot generated from 500 Monte Carlo simulation replicates of the study data using final PK model is presented in Figure 3. The stratified nonparametric bootstrap procedure resulted in 95% CIs (calculated from 500 runs with successful convergence) for population PK parameter estimates, which are presented in Table 6.

Figure 1. General Goodness of Fit for the Final Model.



Note: Solid lines are the lines of unity; dotted lines are $|WRES|$ or $|IWRES|=5$

Figure 2. Selected Individual Observed (DV), Model Predicted (PRED), and Individual Predicted (IPRED) Concentration-Time Plots for Subjects in the Population PK Data Set - Final Model.

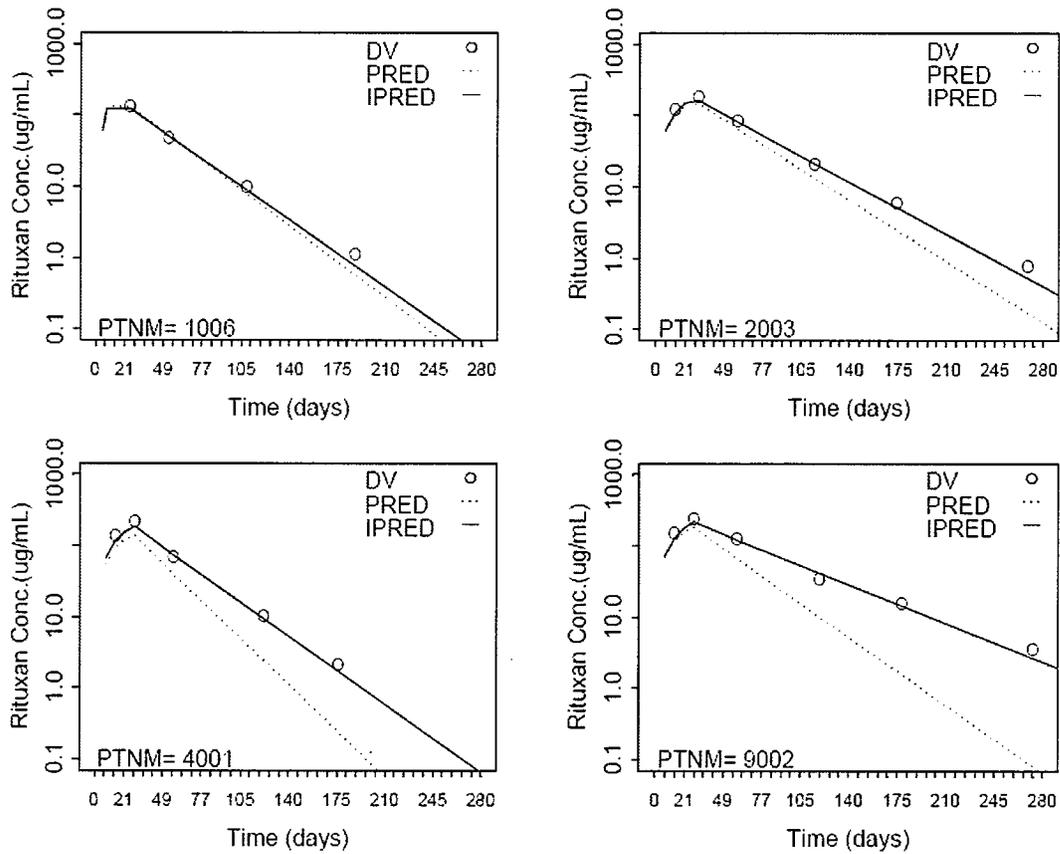
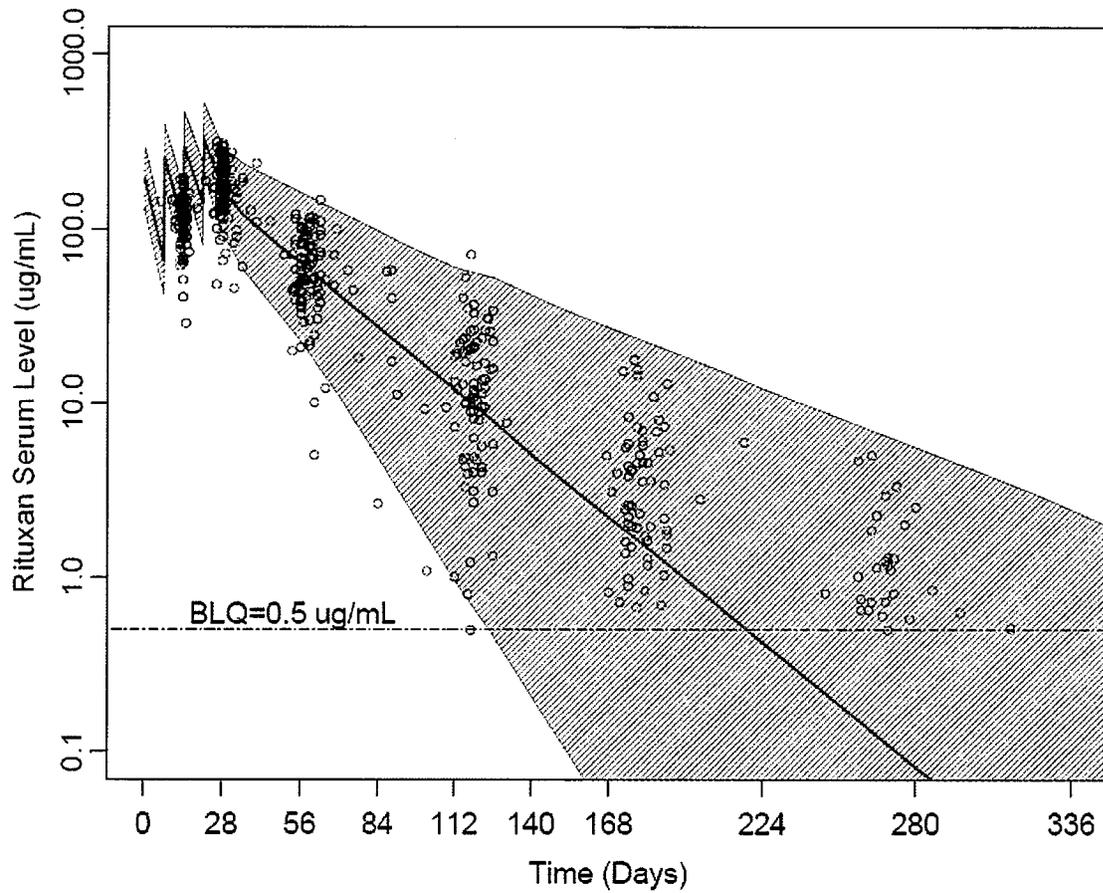


Figure 3. The Coincidence between the Observed and Simulated



^a Dots represent the original observations; shaded area represent the 97.5th, 50th, and 2.5th percentiles of the simulated data.

Table 6. Stratified Nonparametric Bootstrap Results.

Population Mean and 95% CI for Population PK Parameter Estimates
from Final Model and Bootstrapping of Final Model

Parameter	Final Model Point Estimates (95% CI) ^a	Bootstrap Final Model Median (2.5th, 97.5th percentiles) ^b
Typical CL (mL/day)	330 (292, 368)	330 (295, 371)
Typical V ₁ (mL)	4960 (4533, 5387)	4950 (4565, 5390)
HACA on CL	1.37 (1.14, 1.60)	1.37 (1.16, 1.62)
SEX on CL	0.686 (0.587, 0.785)	0.683 (0.581, 0.809)
BSA on V ₁	0.871 (0.324, 1.42)	0.846 (0.301, 1.37)
SEX on V ₁	0.784 (0.691, 0.877)	0.783 (0.690, 0.881)
σ_{prop} (%)	0.168 (0.144, 0.192)	0.168 (0.142, 0.191)
ω_{CL} (%)	0.124 (0.0856, 0.162)	0.118 (0.0820, 0.160)
ω_{V_1} (%)	0.0318 (0.0194, 0.0442)	0.0305 (0.0194, 0.0434)

CI=confidence interval; CL=clearance; V₁=volume of distribution in central compartment; HACA=HACA status; ω =standard error of inter-individual variability for random effects distribution of parameter; σ_{prop} =proportional component of residual variability.

^a CI from standard error of parameter estimates.

^b Percentiles of 500 bootstrap estimates.

Effect of Covariates on Rituximab PK Parameters:

The magnitude of SEX and HACA effect on CL, SEX and BSA effect on V₁ are summarized in the following table:

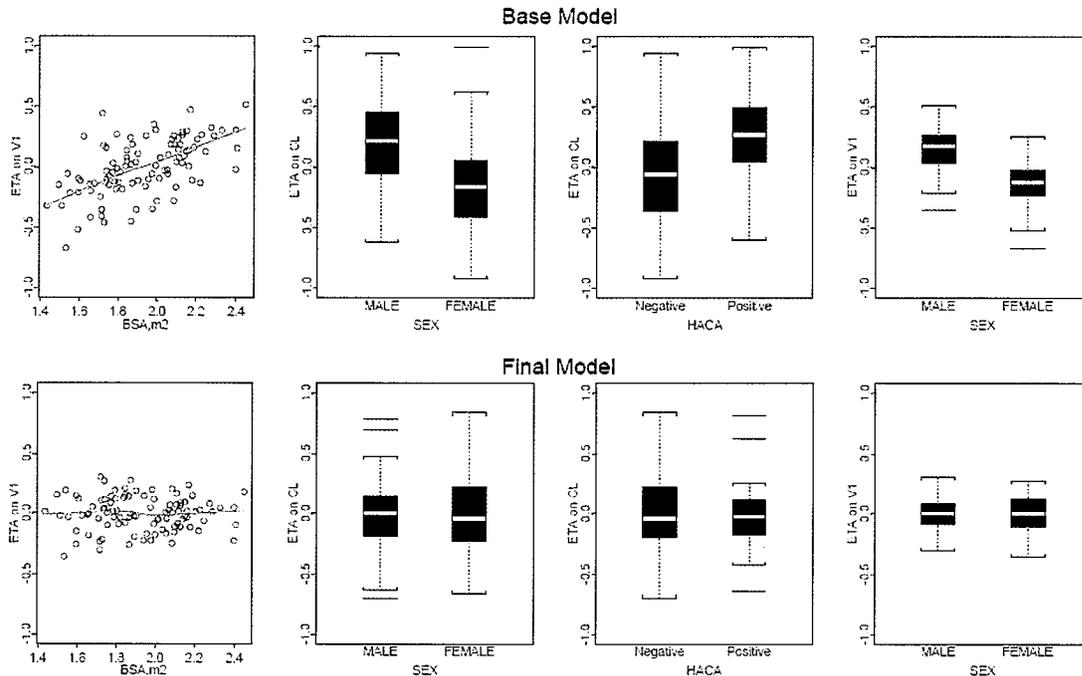
Impact of the Covariate Changes on Rituximab PK

PK Parameter and Covariate	Baseline Covariate Value or Category	Value	Change from Typical ^a (%)
Typical CL (mL/day)		330	
SEX	Male	0	330
	Female	1	229
			-31.4
HACA	Negative	0	330
	Positive	1	452
			37.0
Typical V₁ (mL)		4960	
SEX	Male	0	4960
	Female	1	3889
			-21.6
BSA (m ²)	5 th percentile	1.55	4158
	95 th percentile	2.30	5853
			18.0

^a Theoretical effect (percent change with respect to typical value) of the covariate considered alone, with the reference category (male patients).

A comparison between the base and final models on the random effect (ETA) versus different covariates is illustrated in the following Figure 4.

Figure 4. Random Effect (η) for Rituximab CL and V1 by Covariates for Base and Final Models



Reviewer's Analysis/Comments

The reviewer finds the population pharmacokinetic analysis conducted by the sponsor acceptable. The estimates of the base model for population PK were reproducible. NONMEM VI codes were executed on a 48-core Sun Grid Engine cluster consisting of six Rehdar Linux servers. Post-NONMEM analyses were conducted with popPK tool, an R package for automated population PK reporting.

Additional covariate effect of BSA on CL was identified. This is demonstrated by additional Δ MOF by -9.97 in comparison with sponsor's final model. The final full model for CL is shown below:

$$CL = \theta_1 \cdot \theta_2^{(SEX)} \cdot \theta_3^{(HACA)} \cdot \left(\frac{BSA}{1.9} \right)^{\theta_4}$$

In addition, estimation of the correlation between V1 and CL was removed in the Reviewer's final model. Estimated correlation from the sponsor's final model was -0.00688 with very large RSE which was not different from zero.

Names of NONMEM control streams and location on the Agency's internal share drive used in the review is listed in Appendix 1.

The GOF plots for the Reviewer's final model are shown in Figure 5. The GOF plots for the re-run of the Sponsor's final model are shown in Figure 5.

Figure 5. General Goodness of Fit for the Final Model – Reviewer's Final Analysis. The Solid Line Represents Line of Unit. The Dash Line Represents Loess Smooth Line.

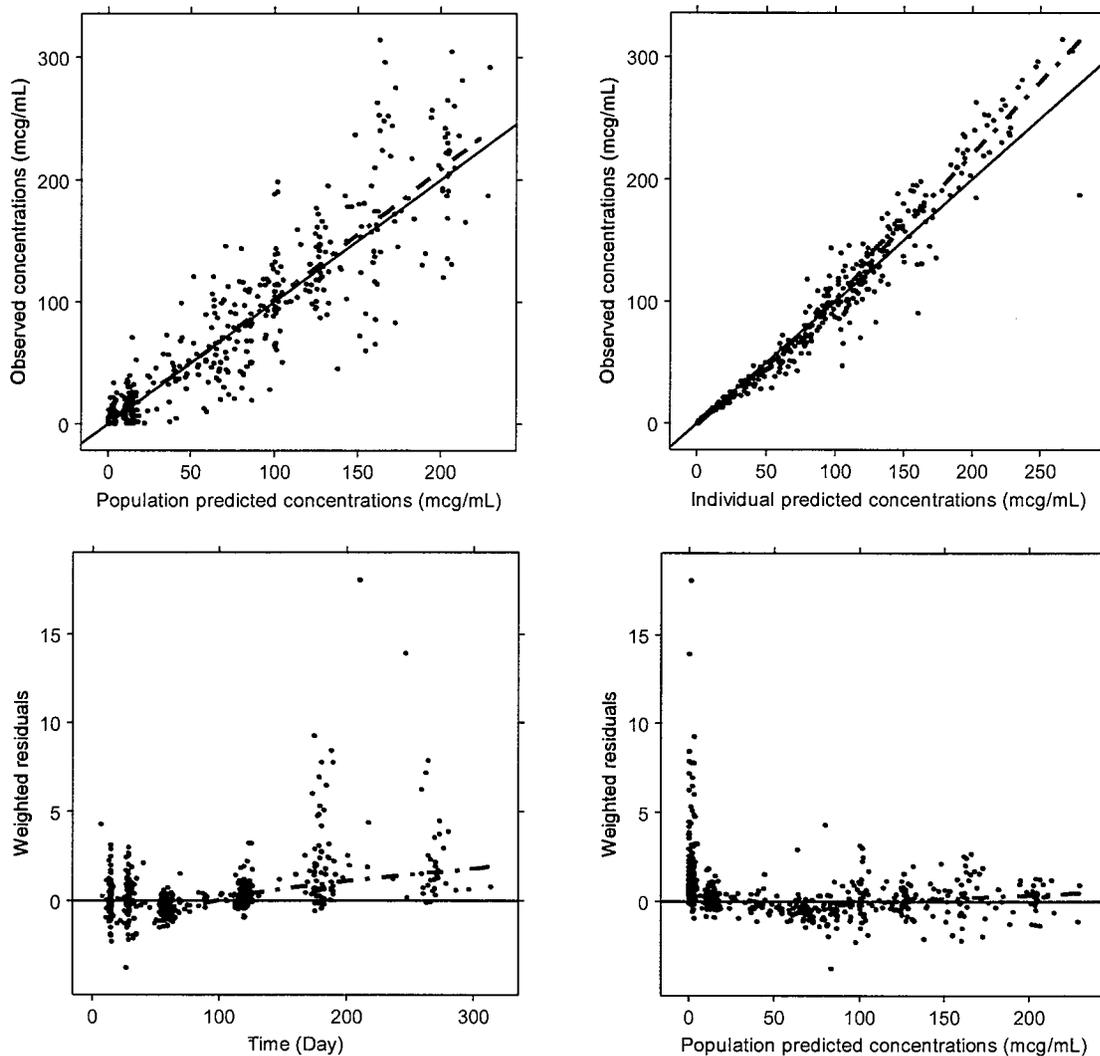
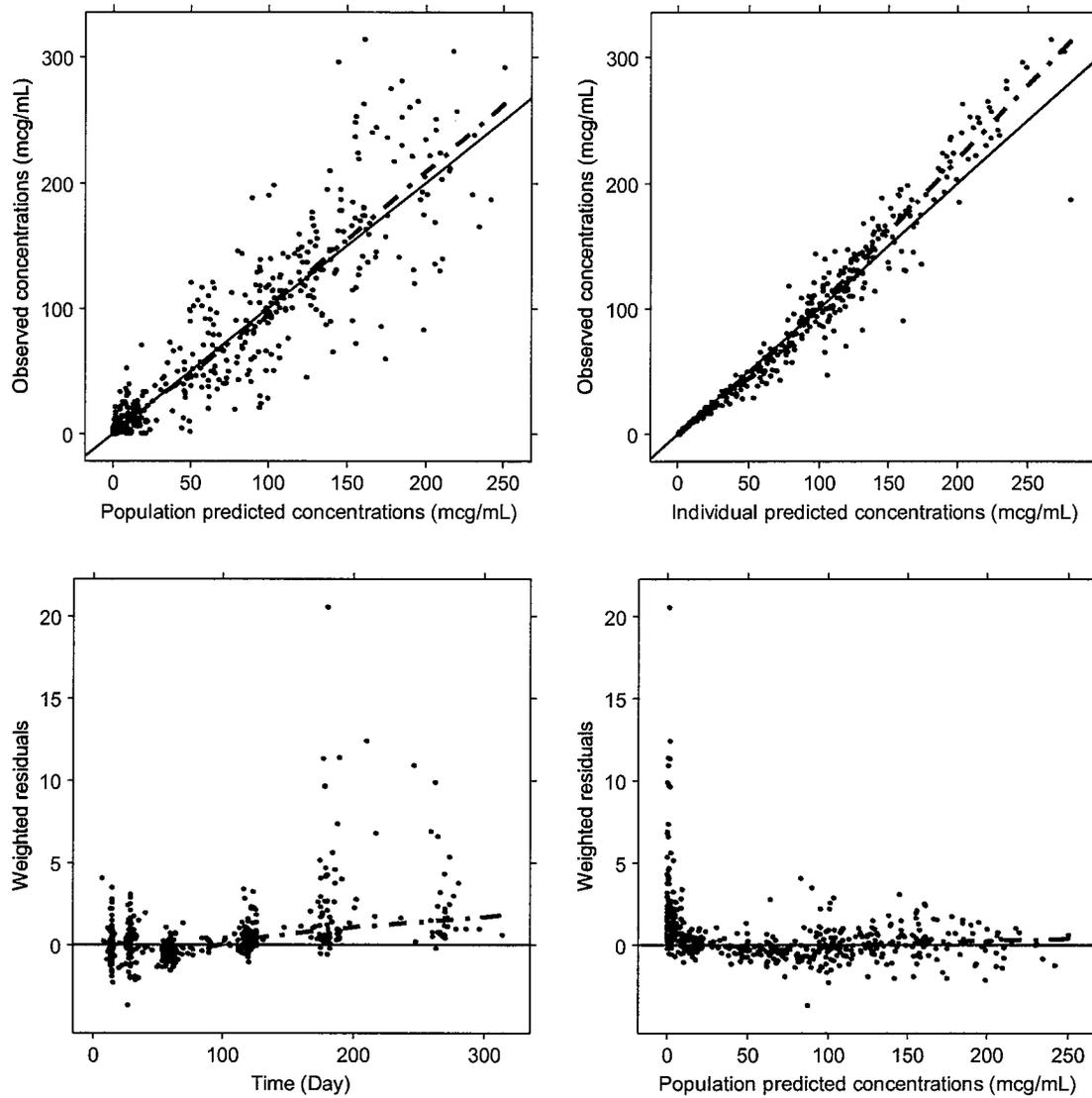


Figure 6. General Goodness of Fit for the Sponsor's Final Model – Re-run by the Reviewer. The Solid Line Represents Line of Unit. The Dash Line Represents Loess Smooth Line.



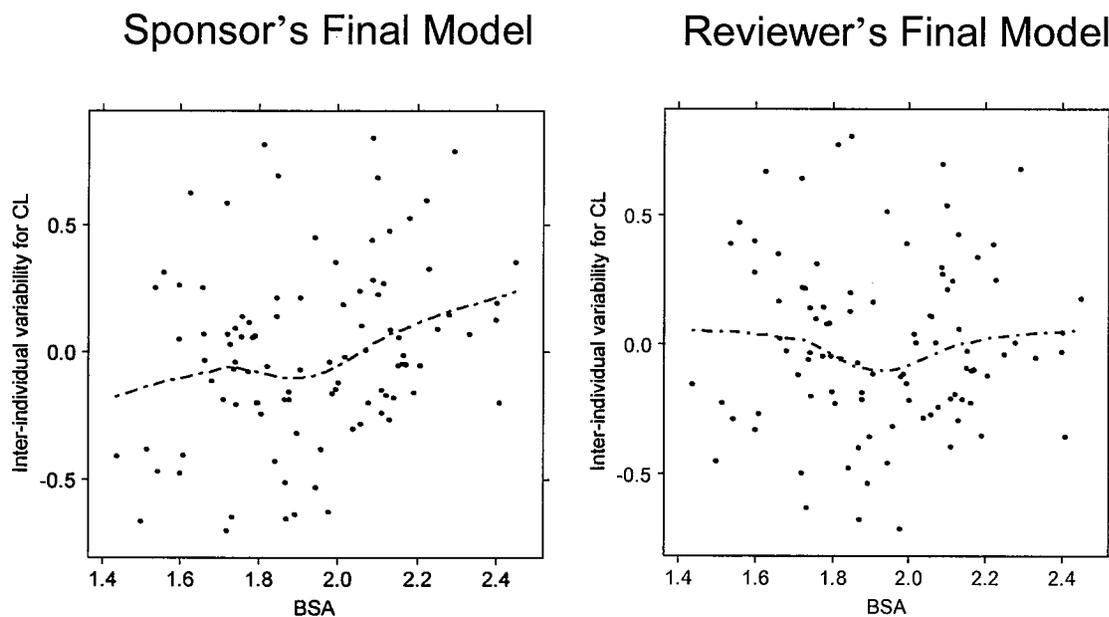
The typical values of estimated PK parameters are listed in Table 7.

Table 7. Summary of Population PK Parameters of Rituximab and the Significant Covariates to Rituximab PK – Reviewer’s Final Analysis

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability (%SEE)
Clearance		
CL (mL/day)	300 (6.90)	33.3% (15.5)
Influence of SEX on CL	0.792 (9.37)	
Influence of HACA on CL	1.43 (8.88)	
Influence of BSA on CL	1.12 (32.1)	
Volume of Distribution in Central Compartment		
V ₁ (mL)	4920 (4.13)	17.9% (19.5)
Influence of SEX on V ₁	0.792 (5.90)	
Influence of BSA on V ₁	0.958 (26.6)	
K ₁₂ (1/day)	0.141 FIX	---
K ₂₁ (1/day)	0.153 FIX	---
Proportional Residual Error	16.8 (7.08)	---
Additive Residual Error (mcg/mL)	0.5 FIX	---

Random effect (ETA) versus CL is illustrated in the following Figure 7.

Figure 7. Comparison of Random Effect (η) for Rituximab CL by BSA



The magnitude of SEX, HACA status, BSA effect on CL, SEX and BSA effect on V₁ from Reviewer’s final model is summarized in Table 8.

Table 8. Impact of the Covariate Changes on Rituximab PK – Reviewer’s Final Analysis.

PK Parameter and Covariate	Baseline Covariate Value or Category	Value	Change from Typical (%)
Typical CL (mL/day)		300	
SEX Male	0	300	0
Female	1	238	- 20.8
HACA Negative	0	300	0
HACA Positive	1	429	43.0
BSA (m ²) 5 th percentile	1.55	239	-20.4
BSA (m ²) 95 th percentile	2.30	372	23.9
Typical V₁ (mL)		4920	
SEX Male	0	4920	0
Female	1	3897	- 20.8
BSA (m ²) 5 th percentile	1.55	4048	-17.7
BSA (m ²) 95 th percentile	2.30	5908	20.1

In conclusion, sex, HACA, and BSA are important covariates explaining inter-individual variability on CL. Female patients had 21% lower CL than male patients. HACA patients had 43% faster clearance than HACA negative patients. CL was 24% higher for a BSA of 2.30 m² compared to a person with BSA of 1.9 m². SEX and BSA were also important covariates explaining the inter-individual variability on V₁. Female patients had 21% smaller volume of distribution than male patients. V₁ was 20% larger for a BSA of 2.30 m² compared to a person with BSA of 1.9 m².

The covariate analysis has demonstrated moderate covariates effect on CL and V₁.

Individual PK parameters (CL, V₁, t_{1/2}, AUC_{0-tau}) from the 97 patients were also estimated with the final population PK model. Descriptive summary of individual rituximab PK parameters are presented in Table 9.

Table 9. Descriptive Summary of PK Parameters of Rituximab

PK parameters	N	Mean	SD	Median	Range
CL, mL/day	97	312	130	281	115-728
V₁, mL	97	4504	1098	4373	2208-7518
t_{1/2}, day	97	24.3	8.04	23.4	9.37-48.8
AUC_{0-tau}, mg/mL•day	97	2.68	1.01	2.57	0.974-6.10

Effect of Covariates on Rituximab Efficacy

HACA status versus the outcome of complete remission, defined as a Birmingham Vasculitis Activity Score (BVAS) score of 0 was investigated. Twenty patients were HACA positive. The treatment success rate in HACA positive patients was 75% (15/20), versus 62% (48/77) success rate in HACA negative patients. HACA positive patients have lower exposure owing to the higher clearance, however, HACA status did not decrease the outcome of complete remission.

The summary effect of SEX on the outcome of complete remission is presented in Table 10. In male patients, 62% of patients responded to rituximab infusion compared to 52% responding to cyclophosphamide. Rituximab treatment resulted in a 10% more treatment success rate compared to the positive control arm.

In female patients, 66% of patients responded to rituximab compared to 58% response rate to cyclophosphamide. Rituximab treatment resulted in a 8% more treatment success rate compared to the positive control arm.

Male patients had lower rituximab exposure resulting from higher clearance, yet they had similar percentage difference (10%) in response rate to those of female patients (8%).

Table 10. Treatment Success Following Rituximab versus Cyclophosphamide Stratified by Sex.

Sex	Rituximab	Cyclophosphamide	Difference ^a
Male	28/45 (62%)	27/52 (52%)	10%
Female	35/53 (66%)	25/43 (58%)	8%

^a Percentage difference between rituximab and cyclophosphamide treated groups

Taken together, neither SEX nor HACA status impacted the outcome of complete remission. Although moderate covariate effects on CL and V1 were found, further dose adjustment based on SEX or HACA status is not necessary.

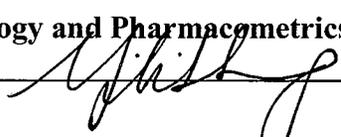
Labeling language supported by this population pharmacokinetic analysis can be seen in Section 3 (Labeling Recommendation (12.3 pharmacokinetics)) of this review.

Appendix 1

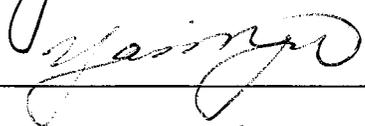
Control stream file name	Model structure	Description	Locations of NONMEM Code in \\cdsnas\pharmacometrics\
Run3.mod	Base model (Sponsor)		Reviews\Ongoing PM Reviews\Rituximab_sBLA103705_EShang\PPK Analysis\Base Model
Run4.mod	Final model (Sponsor)		Reviews\Ongoing PM Reviews\Rituximab_sBLA103705_EShang\PPK Analysis\Sponsor's Final Model
Run6.mod	Final model (Reviewer)	Add BSA to CL (power function) to Run4.mod; Take off omega block from Run4.mod	Reviews\Ongoing PM Reviews\Rituximab_sBLA103705_EShang\PPK Analysis\Review's Final Model

Signatures

Elizabeth Y. Shang
Clinical Pharmacology and Pharmacometrics
Reviewer _____

 3/25/11

Yaning Wang
Pharmacometrics TL _____

 3/25/11

Suresh Doddapaneni
Clinical Pharmacology Acting TL _____

 3/25/11

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	103705	Brand Name	Rituxan
OCP Division (I, II, III, IV, V)	II	Generic Name	Rituximab
Medical Division	DPARP	Drug Class	
OCP Reviewer	Elizabeth Shang, Ph.D.	Indication(s)	(b) (4)
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Injectable
Pharmacometrics Reviewer	Elizabeth Shang/Yaning Wang	Dosing Regimen	375 mg/m ² every week for 4 weeks
Date of Submission	10/18/2010	Route of Administration	IV
Estimated Due Date of OCP Review		Sponsor	Genentech Inc
Medical Division Due Date		Priority Classification	P
PDUFA Due Date			4/19/2011

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

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pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	X	1		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:				
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		Total 3 analyses all from 1 Phase 3 trial

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

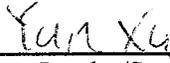
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Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X		
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X	
Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Provide in-study bioanalytical reports for Study ITN021A1.

Elizabeth Shang, Ph.D.		November 29, 2010
Reviewing Clinical Pharmacologist		Date
		Dec 9, 2010
Team Leader/Supervisor		Date

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BACKGROUND

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are the two major forms of systemic vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA). The combined incidence of these conditions in the United States is approximately 6,000 new cases per year, and the estimated prevalence is 25,000–30,000. These conditions are termed ANCA-associated vasculitis (AAV) because of their strong association with highly specific autoantibodies. The prognosis for untreated WG is poor with a low likelihood of survival. There are no approved therapies for the treatment of AAV.

Rituximab is a chimeric murine/human monoclonal antibody specific for the CD20 antigen on the surface of B cells. It is currently approved for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis in combination with methotrexate in adult patients with moderately-to-severely active RA who have inadequate response to one or more TNF antagonist therapies.

Preliminary evidence suggests that anti-CD20 therapy (e.g., rituximab) helps rapidly control AAV and possibly re-establishes tolerance to ANCA target antigens. This is a supplemental BLA for the indication of rituximab for ^{(b) (4)}.

CLINICAL PHARMACOLOGY PROGRAM

The clinical pharmacology program in this sBLA included following three analyses:

1. Rituximab population pharmacokinetic analysis using serum concentrations obtained in pivotal trial RAVE (Study ITN021AI). The primary goals for this analysis are to evaluate the PK characteristics of rituximab in AAV patients by quantifying the PK parameters (e.g., clearance, volume of distribution and the terminal half-life [t_{1/2}]), as well as the relationship between PK parameters and covariates in this study. The population PK analysis encompassed a total of 487 rituximab serum concentrations from 97 patients who received multiple infusions of rituximab in combination with glucocorticoid. The structural model that best described rituximab PK was a two-compartment linear model. The typical population estimates (% standard error of estimate [SEE]) of rituximab clearance (CL), and volume of distribution in central compartment (V₁) were 0.289 L/day (4.39%), and 4.42 L (3.21%) respectively. The inter-patient variability (%SEE) for CL, and V₁, were 42.1% (13.8%), and 26.8% (18.9%) respectively. The median of individual estimates of t_{1/2} of rituximab for 97 patients with AAV was 23.4 days (range: 9.38–48.7 days). Sex covariate (SEX) and human anti-chimeric antibodies (HACA) were important covariates explaining inter-individual variability on CL. Male patients had approximately 31.4% faster CL than female patients, and HACA-positive patients had 37% faster clearance than HACA-negative patients. SEX and body surface area (BSA) were important covariates explaining the inter-individual variability on V₁. Male had 21.6% larger V₁ than females. Patients associated with larger BSA had larger V₁. V₁ was 18% larger for a BSA of 2.30 m². The estimate of t_{1/2} based on the final model was very similar between male patients and female patients (23.6 and 24.9 days respectively). The HACA positive patients were associated with shorter t_{1/2} than HACA-negative patients (19.0 vs. 25.6 days). The sponsor claimed that this analysis demonstrated that population PK parameters for rituximab in patients with AAV are similar to those estimated for other IgG antibodies (Frazer 1999). Inter-patient variability for CL and V₁ was moderate, with values of 42.1% and 26.8% in the base model, respectively. The covariate effects in the final model explained about 30% inter-patient variance for CL and 56% of inter-patient variance for V₁. Given the moderate inter-patient variability and the moderate covariates effect on CL and V₁, these findings support the tested covariates (e.g., subject age covariate [AGE], race covariate

BLA 103705

Rituximab

Clinical Pharmacology and Biopharmaceutics Filing Form

[RACE], ethnicity [ETHN], albumin concentration [ALBU], BSA, SEX and HACA) have no clearly relevant effect on PK.

2. Pharmacodynamic analysis on the changes of number of peripheral blood CD19⁺ B-cell decreased to < 10 cells/ μ L after two infusions of rituximab (Weeks 1 and 2) and at Months 1, 2, 4, and 6. In the rituximab group, 95% had CD19⁺ depletion (CD19⁺ B-cell decreased to < 10 cells/ μ L) at 1 month and 84% had this degree of CD19⁺ depletion at 6 months. The pattern of peripheral B cell depletion and repletion was similar to that previously observed in patients with RA.
3. The relationship between exposure [AUC_{0-inf}]) and efficacy was explored in RAVE. No meaningful difference in remission or complete remission at 6 months was noted between patients with a lower AUC_{0-inf} (AUC_{0-inf} < median) and patients with a higher AUC_{0-inf} (AUC_{0-inf} \geq median)

CONCLUSIONS

It is fileable from clinical pharmacology perspective.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: BLA 103705/5344
Name of Product: Rituxan® (rituximab)
Applicant: Genentech
Review Date: January 31, 2011

Material Reviewed:

Submission Date(s): October 15, 2010

Receipt Date(s): October 18, 2010

Submission Date of Structure Product Labeling (SPL): October 15, 2010

Type of Labeling Reviewed: Package Insert, Medication Guide, Carton/Container Labels

Background and Summary

Genentech submitted an efficacy supplement for Rituxan® for use in patients with (b) (4)
(b) (4).

The proposed labeling was provided in SPL. The submission includes carton and container labels, and a Medication Guide. Draft labeling text was also submitted in Word format (.doc) for review.

OSE and DDMAC were consulted regarding the PI, carton/container, and MG, as appropriate to their discipline, for recommendations regarding the label/labeling.

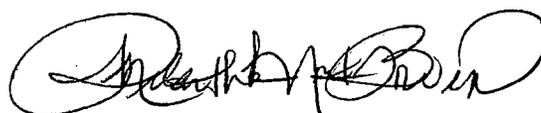
Review

The proposed package insert was compared to the last approved labeling dated February 18, 2010, for sBLA 103705/5311. Sections of the PI and Medication Guide have been revised and/or updated with information to reflect the addition of proposed new indication. Except for minor editorial revisions, there were no additional changes or revisions to the label/labeling other than those proposed in this supplement.

With regards to the carton and container label, the Office of Biotechnology Products (OBP) labeling reviewer will evaluate the CMC content of the carton/container labels, as well as, the content of the PI from the CMC perspective.

Recommendations

I recommend approval of this supplement from the RPM perspective.



/Phlantha Montgomery Bowen/
Phlantha Montgomery Bowen
Sr. Regulatory Project Manager
CDER, OND, ODE II, DPARP

Supervisory Comment/Concurrence:



/Sandy Barnes/
Sandy Barnes
Chief, Project Management Staff
CDER, OND, ODE II, DPARP

Drafted: Bowen/January 25, 2011

Initialed: Barnes/January 31, 2011

Finalized: Bowen/January 31, 2011

CSO LABELING REVIEW OF PLR FORMAT

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Patient Labeling Review

Date: March 14, 2011

To: Badrul Chowdhury, M.D., Division Director
**Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN *LaShawn Griffiths 3-14-11*
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Melissa Hulett, MSBA, BSN, RN *Melissa Hulett 3-14-11*
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Robin Duer, MBA, BSN, RN *Robin E. Duer*
Senior Patient Labeling Reviewer *3/14/11*
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name: Rituxan (rituximab) for injection

Application Type/Number: BLA 103705/5344

Applicant/sponsor: Genentech

OSE RCM #: 2010-2497

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Rituxan (rituximab) for injection. Genentech submitted a supplemental BLA on October 15, 2010 adding a new indication for (b) (4)

(b) (4), to be reviewed by DPARP.

Following review of the supportive data, DPARP notified Genentech that the indication should be changed from (b) (4) to (b) (4) (b) (4) indication of Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA). Genentech submitted the revised Rituxan labeling including the revised indication to the Agency on March 7, 2011.

The Division of Biologic Oncology Drug Products (DBOP) is the lead review division for the Rituxan labeling for the oncology indications. DRISK provided a comprehensive review of the Rituxan MG for DBOP on November 3, 2009, but many of DRISK's recommendations were not included in the approved Rituxan MG. On March 7, 2010 DRISK asked DPARP if another comprehensive review of the MG should be done, or a targeted review of the labeling for the addition of the new WG and MPA indication only. DPARP requested a targeted review.

2 MATERIALS REVIEWED

- Draft Rituxan (rituximab) for injection Prescribing Information (PI) submitted on March 7, 2011 and received by DRISK on March 7, 2011
- Draft Rituxan (rituximab) for injection Medication Guide (MG) submitted on March 7, 2011 and received by DRISK on March 7, 2011
- DRISK review of the Rituxan (rituximab) for injection MG for the DBOP oncology indications dated November 3, 2009

3. REVIEW METHODS

In our review of the MG we have:

- ensured that the MG is consistent with the PI
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The proposed MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.
- Please re-consult DRISK for a comprehensive review of the MG at the next labeling opportunity.

Please let us know if you have any questions.

Following this page, 10 pages withheld in full - (b)(4) Draft Labeling

REQUEST FOR CONSULTATION

TO (Division/Office):

OSE

FROM:

Philantha Montgomery Bowen, Project Manager
Division of Pulmonary, Allergy, and Rheumatology Drug
Products ,HFD-570

DATE
November 19, 2010

IND NO.

BLA NO.

sBLA 103705/5344

TYPE OF DOCUMENT

Efficacy Supplement

DATE OF DOCUMENT

October 15, 2010

NAME OF DRUG

Rituxan® (rituximab)

PRIORITY CONSIDERATION

Priority

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE

March 14, 2011

NAME OF FIRM: Genentech

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Efficacy Supplement to add a new indication: (b) (4); PI and Medication Guide have been revised based on the proposed indication. Consult request to review label/labeling

EDR link: \\cber-fs3\m\CTD Submissions\STN103705\103705.enx.

Labeling Meeting: March 2, 2011

PDUFA Date: April 19, 2011

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

e-MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: 03/17/11

To: Philantha Bowen, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Twyla Thompson, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC) *R. Szydlo 3-17-11* *3/17/11*

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, DTC Group Leader
Olga Salis, Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: BLA 103705/5344
DDMAC labeling comments for Rituxan (rituximab) Injection for
Intravenous Use

DDMAC has reviewed the proposed Package Insert (PI), proposed carton/container labeling, and proposed Medication Guide (Med Guide) for Rituxan (rituximab) Injection for Intravenous Use, which was submitted for consult on November 19, 2010. DDMAC's comments on the proposed PI and Med Guide are based on the proposed draft marked-up labeling titled "DPARP Complete PI &MG (3-2-11).doc" that was sent via email from DPARP to DDMAC on March 7, 2011.

DDMAC's comments on the PI and Med Guide are provided directly in the marked-up document attached (see below).

DDMAC has reviewed and has no comments at this time on the carton/container labeling located in the EDR at:

- \\cbsap58\MeCTD Submissions\STN103705\01116\m1\us\114-label\114-1-draft-label\114-1-3-draft-label-text\sp\lc0073dbb-8dd2-452d-bc34-b8cf9f740651-01.jpg
- \\cbsap58\MeCTD Submissions\STN103705\01116\m1\us\114-label\114-1-draft-label\114-1-3-draft-label-text\sp\lc0073dbb-8dd2-452d-bc34-b8cf9f740651-02.jpg
- \\cbsap58\MeCTD Submissions\STN103705\01116\m1\us\114-label\114-1-draft-label\114-1-3-draft-label-text\sp\lc0073dbb-8dd2-452d-bc34-b8cf9f740651-03.jpg

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions regarding the Med Guide, please contact Twyla Thompson at (301) 796-4294 or twyla.thompson@fda.hhs.gov.

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **ER-DDMAC-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)
Philantha Montgomery Bowen, Project Manager
Division of Pulmonary, Allergy, and Rheumatology Drug Products,
HFD-570, (Ph) 301-796-2466

REQUEST DATE November 19, 2010	IND NO.	NDA/BLA NO. sBLA 103705/5344	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Rituxan® (rituximab)	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) March 14, 2011
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NAME OF FIRM: Genentech	PDUFA Date: April 19, 2011
----------------------------	----------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
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CBER EDR link to submission: <\\cber-fs3\m\CTD Submissions\STN103705\103705.enx>

The submission dated October 15, 2010, contains a PI and carton/container labeling.

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

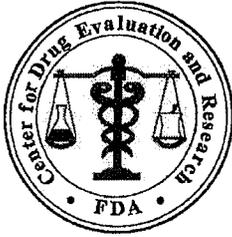
Mid Cycle Review: January 28, 2011

Labeling Meeting: March 2, 2011

T-con with sponsor: TBD

SIGNATURE OF REQUESTER  11/19/10

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 17, 2011

Application Type/Number: BLA # 103705

Through: Todd Bridges, RPh, Acting Deputy Director *T. Bridges 3/17/11*
Carol Holquist, RPh, Director *Carol Holquist 3/17/11*
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator *3/17/11*
Division of Medication Error Prevention and Analysis *DB*

Subject: Labeling Review

Drug Name(s): Rituxan (Rituximab) Injection
100 mg/10 mL and 500 mg/50 mL vials

Submission Number: S-5344

Applicant: Genentech

OSE RCM #: 2010-2500

1 INTRODUCTION

This review evaluates the insert labeling for Rituxan (Rituximab) Injection, which was submitted to add an indication for treatment of (b) (4) (b) (4) in conjunction with glucocorticoids. DMEPA evaluated the labels and labeling in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)¹, principals of human factors, and lessons learned from post marketing experience in our evaluation of the labels and labeling of drug products. We also searched the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors due to labels and labeling have occurred with the existing marketed product, Rituxan.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

A search of the AERS database was conducted on March 10, 2011, using the High Level Group Terms (HGLT) 'Medication Errors' and 'Product Quality Issues', with the search criteria active ingredient "rituximab", trade name "Rituxan" and verbatim substance search term, "Ritux%". DMEPA previously performed an AERS search for Rituxan in OSE# 2007-1929 dated December 5, 2007. For this review, DMEPA performed an updated AERS search beginning December 1, 2007 for medication errors submitted for Rituxan since the aforementioned review.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Those that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse events not related to a medication error, accidental exposure, overdose, no medication errors, errors due to knowledge or performance deficit) were excluded from further analysis. If an error occurred, the reports were categorized by type of error and evaluated for contributing factors to the medication errors. Additionally the reports were reviewed to determine if the error could be applicable to the labels and labeling of Rituxan and thus pertinent to this review.

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the most recently revised insert labeling dated March 2, 2011. Additionally, we compared this version with the approved labeling (dated January, 2011).

3 RESULTS

The following section describes the results of our AERS search.

3.1 AERS SELECTION OF CASES

A total of 18 cases were retrieved in the AERS search, however, after excluding cases as described in Section 2.1, only 3 cases involved a medication error with Rituxan Injection and concerned confusion between Remicade and Rituxan. However, this wrong drug error is already

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

known to DMEPA and is being reviewed separately (OSE review # 06-0295). Thus it will not be discussed further in this review of current labeling revisions.

4 CONCLUSIONS AND RECOMMENDATIONS

Although we retrieved no relevant reports of medication errors involving Rituxan, we identified areas where information in the insert labeling can be clarified and improved upon to minimize the potential for medication errors. Section 4.1 (*Comments to the Division*) contains our recommendations for the insert labeling. We request these recommendations be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nichelle Rashid at 301-796-3904.

4.1 COMMENTS TO THE DIVISION

1. In view of the critical nature of cancer chemotherapy, the abbreviation, CVP, should be defined when it is initially used to minimize the risk of misinterpretation by the user.
2. Due to the continuing confusion between 'IV' and other abbreviations (such as 'IU' for international units), FDA discourages the use of the abbreviation, 'IV', in labels and labeling. Please revise all 'IV' statements in the insert labeling to 'intravenous' or 'intravenously' whichever is appropriate.
3. Subsection 2.7 (Recommended Concomitant Medications):
 - a. To reflect the new terminology, revise the last sentence, (b) (4) to read 'PCP prophylaxis is also recommended for patients with 'Wegener's Granulomatosis and Microscopic Polyangiitis' during treatment (b) (4) (b) (4).
 - b. Revise the definition for PCP from 'Pneumocystis jiroveci pneumonia' to 'Pneumocystis carinii pneumonia'.
4. In subsection 2.6 (Recommended Dose for Wegner's Granulomatosis and Microscopic Polyangiitis) revise the second bulleted narrative to read 'Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered (b) (4) (b) (4). This revision is recommended to decrease redundancy and it is consistent with the glucocorticoid statement in Subsection 2.5.

5. REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 103705/5344

Name of Drug: RITUXAN[®] (rituximab)

Sponsor: Genentech, Inc.

Material Reviewed: RITUXAN[®] (rituximab)
Highlights and Prescribing Information

Submission Date: October 15, 2010

EXECUTIVE SUMMARY

The changes to the prescribing information label for RITUXAN[®] (rituximab) were reviewed and found to conform to regulations under 21 CFR 610 –Subpart G and 21 CFR 201.57. Please see the Conclusions section for comments.

Background:

Genentech, Inc. has submitted a supplement to BLA 103705 to use rituximab in combination with glucocorticoids for the treatment of (b) (4)

(b) (4)

Review:

RITUXAN[®] (rituximab)
Highlights
Description
How supplied

Conclusions:

1. Highlights
 - a. Product Title

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103705 / S-5344

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

October 15, 2010

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Jessica Benjamin

Subject: **License No. 1048**
STN: BL 103705
Rituxan[®] (Rituximab)
Supplemental Biologics License Application
User Fee ID No. PD3010697

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (rituximab), initially approved on 26 November 1997. Reference is also made to the Investigational New Drug Application for Rituxan (b)(4) IND 11831, submitted by the NIH's Division of Allergy, Immunology, and Transplantation of the National Institute of Allergy and Infectious Diseases (DAIT NIAID) on 20 July 2004 (Serial No. 0000). Lastly, reference is made to the orphan drug designation (b)(4) obtained by Genentech on 14 February 2006.

The purpose of this submission is to provide the sBLA for Rituxan in combination with glucorticoids for the treatment of (b)(4). This is a joint development project between Genentech Inc., Biogen Idec, Inc., and F. Hoffmann-La Roche, Ltd.

A Type B pre-sBLA meeting was held with the Agency on 11 March 2010 in which agreement was reached on the proposed contents of a supplement to our Biologics License Application (sBLA) for Rituxan based on the data from Study ITN201AI (RAVE), entitled "Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-associated Vasculitis." RAVE was a pivotal Phase II/III, multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international non-inferiority

study. This study demonstrated non-inferiority against an active-control and superiority to historical control in the induction of remission in patients with severely active AAV.

As agreed to at the 11 March 2010 Type B meeting, Genentech is providing:

- An integrated safety summary (ISS) and integrated efficacy summary (ISE) which focus on data from RAVE and include other known data with Rituxan (b) (4). Summary data from other approved indications for Rituxan are included as supportive information.
- A detailed rationale for the submission of this sBLA based on the single Study ITN201AI (RAVE) based on the FDA Guidance on "Providing Clinical Evidence of Effectiveness for a Human Drug and Biologic Products" and the FDA Draft Guidance for "Non-Inferiority Clinical Trials".

A 120-Day Safety Update for Study ITN201AI (RAVE) will be provided following the submission of the sBLA.

As discussed at the 11 March 2010 Type B, pre-sBLA meeting with the Agency, Genentech is seeking Priority Review for this application based on the potential for Rituxan to provide a safe and effective approved therapy for patients with (b) (4) where no satisfactory alternative to cyclophosphamide therapy exists. During the pre-sBLA meeting the FDA indicated that the use of Rituxan appears to address a serious condition where no approved therapy exists and, therefore, would likely qualify for Priority Review.

To facilitate FDA's review of this sBLA, Genentech would like to propose meeting with the review team at the Agency to review the technical aspects of the submission in the electronic Common Technical Document (eCTD) format and to provide FDA the opportunity to ensure clarity and ask questions regarding the organization of the data and documents.

Genentech would also like to inform the Agency that the proposed changes in the USPI relating to Section 5.5 Warnings and Precautions, Hepatitis B Virus (HBV) Reactivation is also being updated via a Changes Being Effected (CBE) Labeling Supplement" which was submitted on 28 September 2010 to STN: BL 103705, Sequence No. 0115. The changes proposed in the CBE are also reflected in the draft label included in this sBLA, as supported by data in (b) (4) patients from post marketing safety reports.

This submission is provided in eCTD format according to ICH and FDA guidelines for electronic submissions. One Linear Tape-Open (LTO) (approximately 10GB) is provided herein, along with one additional LTO archival copy. Symantec Norton Antivirus Corporate Edition (Program version 9.05.1000, with the most recent Virus Definition File version) was used to ensure that the submission LTOs are virus-free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory affairs at (650) 225-6508.

Badrul Chowdhury, M.D., Ph.D.

October 15, 2010

Page 3

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michelle H. Rohrer".

Michelle H. Rohrer, Ph.D.

Vice President

Regulatory Affairs



BL 103705/5344

**PRIOR APPROVAL SUPPLEMENT
ACKNOWLEDGEMENT**
DATE: November 12, 2010

Genentech, Inc.
1 DNA Way MS#241B
South San Francisco, CA 94080-4990

Attention: Yasameen Qazen, Manager
Regulatory Affairs

Dear Ms. Qazen:

Please refer to your Supplemental Biologics License Application (sBLA) dated October 15, 2010, received October 18, 2010, submitted under section 351 of the Public Health Service Act for the following:

BL NUMBER: 103705
SUPPLEMENT NUMBER: 5344
PRODUCT NAME: Rituxan® (rituximab)
DATE OF SUBMISSION: October 15, 2010
DATE OF RECEIPT: October 18, 2010

This supplemental application proposes the use of Rituxan® in the treatment of (b) (4)
(b) (4).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 17, 2010 in accordance with 21 CFR 601.2(a). If the application is filed, the user fee goal date will be April 19, 2011.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-2466.

Sincerely,



/ Philantha Montgomery Bowen /

Philantha Montgomery Bowen, M.P.H., RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 103705(5344)	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Rituxan® Established/Proper Name: rituximab Dosage Form: Intravenous Strengths: 100 mg/10 ml and 500 mg/50 ml		
Applicant: Genentech Agent for Applicant (if applicable):		
Date of Application: October 15, 2010 Date of Receipt: October 18, 2010 Date clock started after UN:		
PDUFA Goal Date: April 19, 2011		Action Goal Date (if different):
Filing Date: December 17, 2010		Date of Filing Meeting: November 18, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): treatment of (b) (4) (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 11831				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?					
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].					
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?					
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm					

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA</i>s/<i>NDA</i> efficacy supplements only)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i>s only)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including:</p>	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			✓	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	✓			

<p>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</p> <p>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			✓	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			✓	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		✓		Orphan Designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			✓	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>	✓			MG only REMS; revised to reflect new indication
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?				
<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packageing, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		✓		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): March 11, 2010	✓			

<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		✓		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT
MEMO OF FILING MEETING

DATE: November 18, 2010

BLA/NDA/Supp #: 103705/5344

PROPRIETARY NAME: Rituxan®

ESTABLISHED/PROPER NAME: rituximab

DOSAGE FORM/STRENGTH: Intravenous; 100 mg/10 ml and 500 mg/50ml

APPLICANT: Genentech

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of (b) (4)
(b) (4)

BACKGROUND: This is a filing meeting for a supplemental BLA for Rituxan® (rituximab), an approved product for a new indication. The proposed indication is (b) (4) (b) (4) in combination with glucocorticoids. There are currently no approved treatments for this indication (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Philantha Bowen, MPH	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sally Seymour		Y
Clinical	Reviewer:	Deborah Seibel, PhD	Y
	TL:	Sally Seymour, PhD	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Elizabeth Shang, PhD	Y
	TL:	Yun Xu, PhD	Y
Biostatistics	Reviewer:	Yongman Kim, PhD	Y
	TL:	Joan Buenconsejo, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mamata De, PhD	Y
	TL:	Molly Topper, PhD	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Sean Fitzsimmons, PhD	N
	TL:	Marjorie Shapiro, PhD	N
Product Quality (CMC)	Reviewer:		
	TL:	Marjorie Shapiro, PhD	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Kimberly Rains, PharmD	N
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Robin Duer	N
	TL:	Melissa Hulett	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	
	TL:	
Controlled Substance Staff (CSS)	Reviewer:	
	TL:	
Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: <i>exclusion under 21CFR Section 25.31(c)</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CMC Labeling Review	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul A. Chowdhury, MD, PhD	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <i>*Communicated in filing letter</i> <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other



/Philantha Montgomery Bowen/
 Philantha Montgomery Bowen, MPH, RN
 Sr. Regulatory Project Management Officer
 CDER, OND, ODE II

Date: November 18, 2010

Supervisory Comment/Concurrence:



/Sandy Barnes/
 Sandy Barnes
 Chief, Project Management Staff
 CDER, OND, ODE II

Date: November 18, 2010

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

DSI CONSULT: Request for Clinical Inspections

Date: November 19, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Deborah Seibel, M.D. Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Sally Seymour, M.D. Deputy Director for Safety,
Division of Pulmonary, Allergy, and Rheumatology Products

From: Philantha Bowen, MPH
Senior Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: Request for Clinical Site Inspections

I. General Information

Application#: sBLA 103705/5344

Applicant/ Applicant contact information (to include phone/email):

Yasameen Qazen, Manager, Regulatory Affairs

yasameen.qazen@gene.com or qazeny1@gene.com

Genentech

1 DNA Way MS#241B

South San Francisco, CA 94080-4990

(650) 225-7952 FAX: (650) 467-3198

Drug Proprietary Name: Rituxan (rituximab)

NME or Original BLA (Yes/No): No

Review Priority: **Priority** Review

Study Population includes < 17 years of age (Yes/No): Yes – not a pediatric study, but included patients 15 years of age and older

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): treatment of [REDACTED] (b) (4) in combination with glucocorticoids

DSI Consult

version: 5/08/2008

PDUFA: April 19, 2011

Action Goal Date: April 5, 2011

Inspection Summary Goal Date: April 1, 2010

II. Protocol/Site Identification

Study ITN201AI (RAVE)

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Boston University School of Medicine, Vasculitis Center, E-533, 715 Albany Street Boston, MA 02118	Study ITN201AI (RAVE)	43	(b) (4)
The Johns Hopkins Vasculitis Center, 5501 Hopkins Bayview Circle, Room 1B.1A The Johns Hopkins Asthma and Allergy Center, Baltimore, MD 21224	Study ITN201AI (RAVE)	35	(b) (4)
Mayo Clinic 200 First Street SW Rochester, MN 55905	Study ITN201AI (RAVE)	53	(b) (4)

III. Site Selection/Rationale

This supplemental application is for a new indication for rituximab (Rituxan). The proposed indication is the treatment of (b) (4) in combination with glucocorticoids. This is an (b) (4). The clinical program consists of a single pivotal study, ITN201AI(RAVE), which enrolled only 197 patients at 9 centers. The 3 centers chosen had the highest enrollment, and together had 65% of the entire study population. In addition, Mayo Clinic had a remission rate higher than the overall remission rate, and may drive the results.

The submission is electronic and can be found at the following link [\\cber-fs3\m\eCTD_Submissions\STN103705\103705.enx](file:///c:/fs3/m/eCTD_Submissions/STN103705/103705.enx). The submission date is October 15, 2010.

Rationale for DSI Audits

This application is for a new indication and would be the first drug approved for (b) (4) and relies on one clinical trial at a small number of sites. We have no specific concerns about particular efficacy or safety data at this stage of the review. We have chosen the sites with the highest enrollment and one of these sites may drive the efficacy results.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify): Mayo Clinic enrolled the most patients and had a remission rate higher than the overall remission rate: RTX (92.3%) vs CYC (61.5%) compared to overall remission rate RTX (64.3%) vs. CYC(54.7%)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): single study with small relatively small number of patients

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

We have no specific data to verify other than the primary efficacy endpoint and general collection and reporting of safety information. The primary endpoint was the percentage of patients who achieved complete remission at 6 months, as defined by a BVAS/GW of 0 and successful completion of the glucocorticoid taper at 6 months.

Should you require any additional information, please contact Philantha Bowen at 301-796-2466 or Deborah Seibel at 301-796-1178.

Concurrence: (as needed)

 11/19/10 Medical Team Leader
Medical Reviewer
Division Director (for foreign inspection requests or requests for 5 or more sites only)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 103705/5344

FILING ISSUES
December 17, 2010

Genentech, Inc.
1 DNA Way MS#241B
South San Francisco, CA 94080-4990

Attention: Yasameen Qazen, Manager
Regulatory Affairs

Dear Ms. Qazen:

Please refer to your biologics license application (BLA) dated October 15, 2010, received October 18, 2010, submitted under section 351 of the Public Health Service Act for Rituxan® (rituximab).

We have completed an initial review of your application for Rituxan® to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The user fee goal date is April 19, 2011. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 28, 2011.

During our filing review of your application, we identified the following potential review issue:

Study ITN021AI included a 6 month remission phase and an additional 12 month remission maintenance phase. Your submission did not include the data from the additional 12 month remission maintenance phase, which provides information on duration of treatment effect and long term safety. Without the remission maintenance

phase data, the adequacy of your application to support the proposed indication will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

We also request that you submit the following information:

Provide in-study bioanalytical reports for Study ITN021A1.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Because this biological product [REDACTED] ^{(b) (4)} has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

Badrul A. Chowdhury

/Badrul A. Chowdhury/

Badrul A. Chowdhury, M.D., Ph.D.

Director

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

January 12, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344
Rituxan[®] (Rituximab)
sBLA Amendment: BL 103705/5344/0.001
120-Day Safety Update and Response to Request from Day 60 Letter

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (Rituximab), initially approved on November 26, 1997. Reference is also made to the Investigational New Drug Application for Rituxan (rituximab) (b)(4), IND 11831, submitted by the NIH's Division of Allergy, Immunology, and Transplantation of the National Institute of Allergy and Infectious Diseases (DAIT NIAID) on July 20, 2004 (Serial No. 0000). Reference is made to the orphan drug designation (b)(4) obtained by Genentech on February 14, 2006. Lastly, reference is made to the sBLA for (b)(4) submitted on October 15, 2010.

The purpose of this submission is to provide the 120-Day Safety Update (also referred to 4-Month Safety Update in this submission) to the Integrated Safety Summary (ISS) for Study ITN201A1 (RAVE). This update to the ISS summarizes cumulative safety data and efficacy data collected up to the common close out date of RAVE.

This submission also provides a response to Agency's requests as outlined in the Day 60 letter received by GNE on December 17, 2010. Included within this response are assay validation reports which were previously submitted to the Agency within STN BL 103705/5211.0000 on August 25, 2005.

Badrul A. Chowdhury, M.D., Ph.D.

January 12, 2011

Page 2

If you have any questions regarding this submission, please contact
Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in black ink, appearing to read "Michelle H. Rohrer". The signature is stylized and includes a large, sweeping flourish on the left side.

Michelle H. Rohrer, Ph.D.

Vice President

Regulatory Affairs



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 1, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466

Subject: BLA 103705/5344 - FDA Information Request

Total no. of pages including cover: 3

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: February 1, 2011

Your submissions dated October 15, 2010, and January 12, 2011, to BLA 103705/5344, are currently under review. We have the following comments and/or requests for information. If any of the requested information is already included in your submission, provide the location of the information.

1. Discuss the methods to ensure compliance with cyclophosphamide and submit additional compliance information for cyclophosphamide, e.g. percentage of cyclophosphamide taken of planned total.
2. Provide the breakdown in each treatment group of patients who received 1, 2, or 3 bolus doses of methylprednisolone following randomization. Perform a subgroup analysis for the primary endpoint based upon number of doses of methylprednisolone received.
3. Submit subgroup analysis of the primary endpoint at 6 months for the following age subgroups: ≤ 18 years of age, 18 to < 65 years, ≥ 65 years of age
4. Submit data on the proportion of patients by treatment group and by diagnosis who met the pre-specified criteria for clinical tolerance. Submit this information in tabular format.
5. Submit the following subgroup analyses related to durability of remission (12 and 18 months)
 - a. AAV type
 - b. ANCA type
 - c. renal involvement
 - d. alveolar hemorrhage
 - e. age (< 52 , ≥ 52 ; < 65 , ≥ 65)
 - f. gender (Male, Female)
 - g. systemic disease
6. Submit a discussion of predictors of treatment failure.
7. Provide an analysis of patients who were randomized to rituximab and did not receive cross over or other rescue treatment (BMJ) and when they received treatment with rituximab again.
8. Submit the datasets for the information provided in the 120 day safety update.
9. Submit information regarding the immunogenicity assays used in RAVE.

10. Clarify the choice of oral cyclophosphamide as the active comparator instead of intravenous cyclophosphamide.
11. Submit information regarding the use of cyclophosphamide prior to enrollment in patients in both treatment groups and by new disease at baseline vs. relapsing disease. Submit results for complete remission at 6 months based upon subgroup analysis of new disease vs. relapsing disease at baseline and whether patients had previous treatment with cyclophosphamide.

Submit your response officially to the BLA and forward a courtesy copy to me via email by February 10, 2011. If you should have any questions, contact me at 301-796-2466.

Sincerely,



/Philantha M. Bowen/

Philantha M. Bowen, MPH, BSN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Seymour/January 28, 2011

Clearance: Barnes/January 31, 2011
Seymour/February 1, 2011

Finalized: Bowen/February 1, 2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 10, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466

Subject: BLA 103705/5344 - FDA Information Request

Total no. of pages including cover: 2

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: February 10, 2011

Your submissions dated October 15, 2010, and January 12, 2011, to BLA 103705/5344, are currently under review.

We cannot locate the in-study bioanalytical reports for Study ITN021AI in your submissions.

Submit the full report officially to the BLA and forward a courtesy copy to me via email by COB February 14, 2011.

If you should have any questions, contact me at 301-796-2466.

Sincerely,



/Philantha M. Bowen/

Philantha M. Bowen, MPH, BSN

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Drafted: Shang/February 9, 2011

Clearance: Barnes/February 10, 2011
Shang/February 9, 2011
Xu/February 9, 2011

Finalized: Bowen/February 10, 2011

Genentech

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REGULATORY AFFAIRS

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(650) 225-1558
FAX: (650) 467-3198

February 10, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344
RITUXAN[®] (Rituximab)
sBLA Amendment: BL 103705/5344/0.002
Amendment to a Pending Application: Response to
FDA Clinical Requests for Information

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (rituximab), initially approved on November 26, 1997. Reference is also made to the Investigational New Drug Application for Rituxan (rituximab) (b)(4), IND 11831, submitted by the NIH's Division of Allergy, Immunology, and Transplantation of the National Institute of Allergy and Infectious Diseases (DAIT NIAID) on July 20, 2004 (Serial No. 0000) and to the orphan drug designation (b)(4) obtained by Genentech on February 14, 2006.

We also refer to the sBLA for (b)(4) submitted on October 15, 2010 and to a previous amendment to this pending application submitted on January 12, 2011 (BL 103705/5344/0.001) which included the 120-Day Safety Update and a response to the Agency's requests as outlined in the Day 60 letter.

The purpose of this submission is to provide a response to the FDA Clinical Requests for Information received by email from the Agency on February 1, 2011.

Badrul A. Chowdhury, M.D., Ph.D.

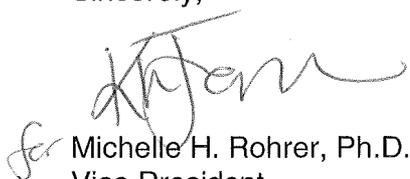
February 10, 2011

Page 2

This submission is being submitted electronically via the FDA ESG (Approximate Size: 135 MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus-free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Information at (650) 225-6508.

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in black ink, appearing to read "Michelle H. Rohrer", is written over a horizontal line. To the left of the signature is a small, stylized mark that looks like a lowercase "f" or a similar flourish.

Michelle H. Rohrer, Ph.D.
Vice President
Regulatory Affairs

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

February 11, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344
RITUXAN[®] (Rituximab)
sBLA Amendment: BL 103705/5344/0.003
Amendment to a Pending Application: Response to
FDA Clinical Pharmacology Request for Information

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b)(4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec.

We also refer to two previous amendments to this pending application:

- 1) BL 103705/5344/0.001 submitted on January 12, 2011, which included the 120-Day Safety Update and a response to the Agency's requests as outlined in the Day 60 letter.
- 2) BL 103705/5344/0.002 submitted on February 10, 2011, which provided a response to the FDA Clinical Requests for Information received by email from the Agency on February 1, 2011.

The purpose of this submission is to provide a response to the FDA Clinical Pharmacology Request for Information received by fax from the Agency on February 10, 2011. This amendment includes the in-study PK Bioanalytical Report for Study ITN021A1, a courtesy copy of which was also provided to the Agency via email on February 10, 2011.

Badrul A. Chowdhury, M.D., Ph.D.

February 11, 2011

Page 2

The HACA Bioanalytical Report was previously submitted within the above referenced BL 103705/5344/0.002.

This submission is being submitted electronically via the FDA ESG (Approximate Size: 2 MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michelle H. Rohrer".

Michelle H. Rohrer, Ph.D.
Vice President
Regulatory Affairs



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466

Subject: BLA 103705/5344 - Immunogenicity Information Request

Total no. of pages including cover: 2

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: February 18, 2011

Your submissions dated February 10 and 14, 2011, to BLA 103705/5344 are currently under review and we have the following comment and request for information:

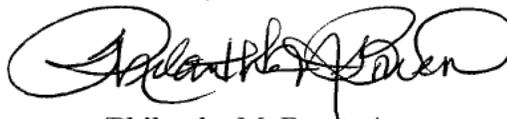
Report 4.C2B8.5.AVR_0, dated February 17, 2004, describes the validation of the immunogenicity assay developed for the purpose of testing samples from patients enrolled in the rheumatoid arthritis clinical studies. Appendix A in the report states that the (b) (4) (b) (4) anti-rituximab stock solution (Genentech lot 40036-26 or equivalent) has an expiration date of 5 years from the date of preparation when stored at -60oC or below.

In study U2639S describing the application of this assay to assess samples from patients enrolled in the ANCA-Associated Vasculitis clinical studies, we note that in Table 1, which provides the list of reagents used in this assay, the source of the (b) (4) anti-rituximab stock solution is also lot 40036-26.

Submit information regarding the re-qualification of this material for use in this assay or information regarding the qualification of a new lot of (b) (4) anti-rituximab stock solution.

Submit an official response to the BLA and forward a courtesy copy to me via email by February 25, 2011. If you should have any questions, contact me at 301-796-2466.

Sincerely,



/Philantha M. Bowen/

Philantha M. Bowen, MPH, BSN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/February 17, 2011

Clearance: Barnes/February 17, 2011
Shapiro/February 18, 2011

Finalized: Bowen/February 18, 2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466
Subject: BLA 103705/5344 - Clinical Information Request	

Total no. of pages including cover: 3

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES X NO

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: February 18, 2011

Your submissions dated October 15, 2010, and January 12 and February 1, 2011, to BLA 103705/5344, are currently under review.

We have the following comments and/or requests for information. If any of the requested information is already included in your submissions, provide the location of the information.

1. To understand when patients required a second course of rituximab submit:
 - Information regarding patients who received rituximab as blinded treatment during the first 6 month period and who received additional dose(s) of rituximab after the initial 4 week course of therapy;
 - The number of patients who were retreated with rituximab and for each patient, include the time course for retreatment; and
 - Any information regarding efficacy and safety in those patients who were retreated and any differences compared to the first course of rituximab.
2. Provide the following subgroup analyses related to durability of remission (12 and 18 months):
 - a. $\text{CrCl} < 60\text{mL/min}$ and $\text{CrCl} \geq 60\text{mL/min}$
 - b. $\text{Creatinine} > 1.2 \text{ mg/dL}$ and $\text{Creatinine} \leq 1.2 \text{ mg/dL}$
 - c. New vs. relapsing disease at baseline
3. In your submission, there are references to *previously diagnosed patients*. For example, you state that of the 101(51.3% of total) patients classified as previously diagnosed 79 (78.2%) had been previously treated with CYC. Clarify the classifications of newly diagnosed vs. previously diagnosed and compare/contrast this classification to your other subgroups of new disease vs. relapsing disease.

Submit an official response to the BLA and forward a courtesy copy to me via email by February 25, 2011. If you should have any questions, contact me at 301-796-2466.

Sincerely,

A handwritten signature in black ink, appearing to read "Philantha M. Bowen". The signature is fluid and cursive, with the first name being the most prominent.

/Philantha M. Bowen/

Philantha M. Bowen, MPH, BSN

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Drafted: Bowen/February 18, 2011

Clearance: Barnes/February 18, 2011
Seymour/February 18, 2011
Seibel/February 18, 2011

Finalized: Bowen/February 18, 2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 16, 2011

TO: BLA 103705/5344 File

THROUGH : Sally Seymour, M.D., Deputy Director for Safety, DPARP

FROM: Philantha Montgomery Bowen, MPH, RN, Sr. Regulatory Project Management Officer, DPARP

SUBJECT: **FDA Teleconference to Communicate Review Status: Labeling, PMC, and Information Requests**

APPLICATION/DRUG: Rituxan® (rituximab)

On March 16, 2011, the FDA initiated a teleconference to communicate the review status of the application with Genentech, Inc. The FDA commented that the review of the application is ongoing, as well as the inspections; however at this time, no new issues have been identified for the application. The FDA stated that the wrap-up meeting for the application was held in early March, however the primary review completion due date is March 26, 2011. In terms of FDA information request, Genentech can expect to receive a clinical information request regarding sub-analyses within the week. The FDA stated that the regulatory action will take place as planned on the specified due date.

Labeling

The FDA stated that if Genentech had any recently approved labeling for supplements related to the Rituxan® product, they should be incorporated into the response to the FDA's initial labeling request. The FDA plans to send a request for revised labeling by Friday, March 18, 2011, and is requesting a response by March 28, 2011. The FDA pointed out that no in depth discussion would be entertained during the teleconference regarding the label. However, following review of the Agency's labeling recommendations, Genentech may request a labeling teleconference to discuss/clarify any issues. The FDA informed Genentech of two important changes in the label: 1) The addition of a new warning/precaution regarding retreatment. Since there is limited information regarding retreatment for the RA indication, it was determined that this fact needed to be highlighted; and 2) A modification in the proposed indication of (b) (4). The Agency (b) (4) (b) (4) to WG and MPA, since Genentech did not (b) (4) (b) (4).

PMC/PMR

The FDA requested a post-marketing observational study to obtain information about treating patients with WG and MPA, in order to enhance the knowledge base of clinicians; to address retreatment with Rituxan®; and the use of concomitant maintenance medications. The FDA felt that a controlled trial would be a difficult challenge. The FDA requested that Genentech submit a study proposal for review. The proposal should allow for obtainment of information to bridge the gaps in knowledge about the safety of retreatment, when to retreat, and the use of concomitant medications. Genentech summarized the Agency's request for a proposal as an observational, uncontrolled study to evaluate retreatment with efficacy data and concomitant medications to obtain long-term data. The FDA responded that the Agency was open to other designs, such that if Genentech proposes an alternate design, the Agency would review it. The FDA requested that Genentech submit a proposal by March 28, 2011, to include the PMC milestone timelines.



/Philantha M. Bowen/

Philantha M. Bowen

Sr. Regulatory Project Management Officer

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 16, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466
Subject: BLA 103705/5344 - Clinical Information Request	

Total no. of pages including cover: 2

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES X NO

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: March 16, 2011

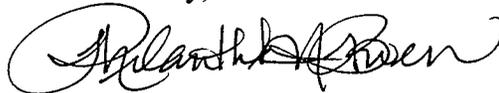
Your submission dated October 15, 2010, to BLA 103705, is currently under review. We have the following requests for information. If any of the requested information is already included in the submission, provide the location of the information.

1. On page 171/2423 in the electronic version of the ITN021AI Study Report is Table 14.2/9.6.2 entitled "HACA Positive Patients by 6 Months after Randomization." The identical table is presented on the following page 172/2423. Clarify if this is a duplication or if another table was omitted.
2. Regarding the HACA, provide a discussion on why the frequency of HACA increased at Months 12 and 18.
3. Submit additional information in each treatment group regarding disease flares, specifically the organ system involved and the severity of the flares.
4. Submit subgroup analysis for the safety profile of rituximab based upon sex and race.
5. Submit an analysis/discussion of the patient ECG data obtained during Study ITN021AI(RAVE). Include an overview of ECG changes, organized in a similar manner to the laboratory section.

Submit the requested information officially to the BLA by Thursday, March 24, 2011, and forward a courtesy copy to me via email.

If you should have any questions, contact me at 301-796-2466.

Sincerely,



/Philantha M. Bowen/
Philantha M. Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted by: Seymour/March 16, 2011

Clearance: Barnes/March 16, 2011
Seymour/March 16, 2011

Finalized by: Bowen/March 16, 2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 18, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466
Subject: BLA 103705/5344 - FDA Labeling Information Request (IR) #1	

**Total no. of pages including
cover:** 41

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES XNO

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: March 18, 2011

Your submission dated October 15, 2010, to BLA 103705/5344, is currently under review and we have a request for labeling revisions. In the attached Package Insert and Medication Guide, the FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

We have the following recommendations regarding the labeling:

1. In Section 5.11, Laboratory Monitoring, include a statement regarding recommended laboratory monitoring in patients with WG and MPA.
2. Delete [REDACTED] ^{(b) (4)} from Table 3 as these are composite terms and the table otherwise contains preferred MedDRA terms.

Submit revised labeling incorporating the recommendations above and the changes shown in the attached marked up label for the Package Insert and Medication Guide. Submit a clean copy and a tracked change version of the label by March 28, 2011. Submit your response officially to the BLA and forward a courtesy copy to me via email.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,



/Philantha Montgomery Bowen/

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/March 18, 2011

Clearance: Barnes/March 18, 2011
Seymour/March 17, 2011
Seibel/March 17, 2011

Finalized: Bowen/March 18, 2011

Following this page, 39 pages withheld in full - (b)(4) Draft Labeling

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

March 24, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344
RITUXAN[®] (Rituximab)
sBLA Amendment: BL 103705/5344/0.005
Amendment to a Pending Application: Response to
BL 103705(5344)-Clinical Information Request

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b) (4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec. Reference is also made to BL 103705/5344/0.001, submitted on January 12, 2011, which included the 120 day safety update to this application.

The purpose of this submission is to provide responses to the BL 103705(5344)-Clinical Information Request for Information received by email from the Agency on March 16, 2011. This amendment includes the responses to these requests.

This submission is being submitted electronically via the FDA ESG (Approximate Size: 2 MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

Badrul A. Chowdhury, M.D., Ph.D.
March 24, 2011
Page 2

If you have any questions regarding this submission, please contact
Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michelle H. Rohrer".

Michelle H. Rohrer, Ph.D.
Vice President
Regulatory Affairs

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

March 25, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344.006
Rituxan[®] (Rituximab)
Amendment to a Pending Application: Revised Draft Label - Redlined and
Clean Draft Labeling

Dear Dr. Chowdhury

We refer to STN: BL 103705 for Rituxan[®] (rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b) (4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec. Reference is also made to the email from the Agency received on March 18, 2011 which included preliminary comments on the label.

The purpose of this submission is to provide proposed revisions in response to the proposed label received from the FDA on March 18, 2011. As requested by the Agency in the teleconference on March 16, this version also includes changes to the Rituxan label which have been approved while this sBLA has been under review, specifically changes approved in the "Changes Being Effected" Labeling Supplement 103705/5343 approved on January 6, 2011 and Prior Approval Supplement 103705/5332 approved on January 28, 2011. For ease of review, these approved changes are marked with gray highlight in the redlined draft label.

The submission contains two versions of the revised draft label in word format: one redlined version with changes tracked and one clean version incorporating the changes. Please note that the comment balloon feature has been utilized in the redlined version of the draft label to display the rationale for the Sponsor's proposed revisions.

Badrul A. Chowdhury, M.D., Ph.D.

March 25, 2011

Page 2

This submission is being submitted electronically via the FDA ESG (Approximate Size: 2MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus-free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Information at (650) 225-6508.

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michelle H. Rohrer".

Michelle H. Rohrer, Ph.D.
Vice President
Regulatory Affairs

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

March 25, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344
RITUXAN® (Rituximab)
sBLA Amendment: BL 103705/5344/0.007
Amendment to a Pending Application:
Proposed Postmarketing Commitment

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan® (rituximab), initially approved on November 26, 1997 and to the sBLA for (b) (4) submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec.

During a teleconference held with the Agency on March 16, 2011 the Agency requested that Genentech provide a proposal for an observational study to evaluate long term safety and retreatment with rituximab.

The purpose of this submission is to provide the Agency with the draft proposal and this study entitled, (b) (4)

Badrul A. Chowdhury, M.D., Ph.D.

March 25, 2011

Page 2

This submission is being submitted electronically via the FDA ESG (Approximate Size: 2 MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

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Michelle H. Rohrer, Ph.D.

Vice President

Regulatory Affairs

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

March 25, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344
RITUXAN[®] (Rituximab)
sBLA Amendment: BL 103705/5344/0.008
Amendment to a Pending Application: Correction to Response to
BL 103705/5344-Clinical Information Request

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b) (4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec. Reference is also made to BL 103705/5344/0.001, submitted on January 12, 2011, which included the 120 day safety update to this application.

The purpose of this submission is to provide a correction to the response submitted on March 24, 2011 (BL 103705/5344.005). The corrections are in Question 3 and are due to inadvertent errors in the prior version of the response document. For ease of review, appended to this cover letter is a redline version of the response document with changes tracked. The clean version of this document is submitted in Module 1, Section 1.11.3.

This submission is being submitted electronically via the FDA ESG (Approximate Size: 2 MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

Badrul A. Chowdhury, M.D., Ph.D.

March 25, 2011

Page 2

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michelle H. Rohrer", followed by a small square symbol.

Michelle H. Rohrer, Ph.D.

Vice President

Regulatory Affairs

EERs / Facility Inspections

Bowen, Philantha

From: CDER-TB-EER
Sent: Monday, April 04, 2011 2:47 PM
To: Bowen, Philantha
Cc: CDER-TB-EER; Pohlhaus, Timothy
Subject: Final TB-EER response - STN 103705/5344

Attachments: Final TB-EER response - STN 103705-5344.doc

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for STN 103705/5344. Please see the attached form for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.



Final TB-EER
response - STN 10...

Timothy J. Pohlhaus, Ph.D.
Interdisciplinary Scientist, Chemist
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 1333
Silver Spring, MD 20993
Phone - (301) 796-5224

From: Bowen, Philantha
Sent: Thursday, March 31, 2011 3:53 PM
To: CDER-TB-EER
Subject: BLA 103705(5344) - Final TB-EER w/in 30 days

Hi,

I am requesting a final TB-EER for BLA 103705(5344). The PDUFA date is April 19, 2011.

Thanks!

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
☎ 301-796-9718
✉ philantha.bowen@fda.hhs.gov

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: April 19, 2011

Applicant Name: Genentech
U.S. License #: 1048
STN(s): 103705/5344
Product(s): Rituxan® rituximab

Short summary of application: *Supplemental application for Rituxan® in the treatment of*
[REDACTED] (b) (4)

FACILITY INFORMATION

Firm Name: Genentech Inc
Address: South San Francisco, CA
FEI: 2917293

Short summary of manufacturing activities performed: DP manufacture, stability, and release testing, labeling and distribution; DS manufacture, stability and release testing

Inspected by SAN-DO June 18-21, 2009 and classified NAI. A comprehensive cGMP inspection, covering all six systems, was performed as part of this inspection. The CBI profile was updated as a result of this inspection and is considered acceptable. The SVS and TRP profiles were updated during SAN-DO's June 3- July 14, 2008 comprehensive inspection.

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Firm Name: Genentech Inc

Address: Vacaville, CA

FEI: 3002902534

Short summary of manufacturing activities performed: DS manufacture, stability and release testing

Inspected by SAN-DO, June 15-23, 2010 and classified NAI. The CBI and CTX profiles were covered and are acceptable.

Firm Name: Genentech Inc

Address: Oceanside, CA

FEI: 3006129086

Short summary of manufacturing activities performed: DS manufacture, stability, and release testing

Inspected by LOS-DO September 2-15, 2010 and classified NAI. The BTP and CTX profiles were covered and are acceptable.

Firm Name: Roche-Basel

Address: Basel, Switzerland

FEI: 3002807200

Short summary of manufacturing activities performed: DP manufacture, stability, and release testing.

Inspected by IOG August 24-28, 2009 and classified VAI. The SVS profile was covered and is acceptable.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 5, 2011

TO: Philantha Bowen, M.P.H., Regulatory Project Manager
Deborah Seibel, M.D., Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: 103705/5344

APPLICANT: Genentech

DRUG: Rituxan[®] (rituximab)

NME: No

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Treatment of [REDACTED] (b) (4) in
combination with glucocorticoids

CONSULTATION
REQUEST DATE: November 19, 2010

DIVISION ACTION
GOAL DATE: April 18, 2011

PDUFA DATE: April 19, 2011

I. BACKGROUND:

The applicant submitted this application for the use of Rituxan[®] to support an indication for the treatment of (b) (4) in combination with glucocorticoids. One pivotal study, Protocol ITN201A1, was submitted in support of the indication.

The conduct of Protocol ITN201A1 entitled "Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-associated Vasculitis" was inspected. The study was designed as a randomized, multicenter double-masked, placebo-controlled study of subjects with severe AAV who were randomized equally to the experimental and control arms of the study.

The primary efficacy analysis is the difference in the percentage of participants who attain complete remission in the experimental group versus the percentage of participants who attain complete remission in the control group.

Three domestic clinical investigator sites were selected for inspection. These sites were selected for inspection because of the enrollment of relatively large numbers of subjects. In addition, please note that the Mayo Clinic enrolled the largest number of subjects and had a remission rate [RTX (92.3%) vs CYC(61.5%)] significantly higher than that of the over all remission rate observed in the study [RTX 64.3% vs CYC (54.7%).

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site #08715 Peter A. Merkel, M.D. Boston University School of Medicine Vasculitis Center, E-533 715 Albany Street Boston, MA 02118	ITN021A1/ 43/	1 Feb-19 Mar 2011	VAI. Pending final classification.
Site #08772 Philip Seo, M.D. The Johns Hopkins Vasculitis Center 5501 Hopkins Bayview Circle, Room 1B.1A The Johns Hopkins Asthma and Allergy Center Baltimore, MD 21224	ITN021A1/ 35/	10-14 Feb 2011	NAI.
Site #08348 Ulrich Specks, M.D. Mayo Clinic 200 First Street, SW Rochester, MN 55905	ITN021A1/ 53/	7 Feb-4 Mar 2011	NAI. Pending final classification.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

1. Site #08715

Peter A. Merkel, M.D.

Boston University School of Medicine Vasculitis Center, E-533

715 Albany Street

Boston, MA 02118

- a. What was inspected:** At this site, 46 subjects were screened and 43 were enrolled. A total of 41 subjects completed the Common Closing Date Visit (Vccd). The records of 24 subjects were reviewed in depth with the records of all 43 subjects audited with respect to the first four infusions. The records audited included, but were not necessarily limited to, source documents and case report forms, efficacy endpoints, protocol deviations, IRB and monitor correspondence, and adverse event reporting.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. The inspection revealed that the site originally used paper CRFs then switched to electronic CRFs when CRO responsibilities were taken over by (b) (4) from (b) (4). There were 20 documented deviations noted that were not contained in the assignment data listings: 13 infusion dates out of window, 1 CYC dosing error, 2 hematology labs not processed, 1 premedication out of timeframe, and 3 prednisone dosing errors. It appeared that deviations were reported to the IRB but not to the sponsor. The primary efficacy endpoint data were verified as source documents corresponded with data listings and CRFs. Two deaths were reported. Subject 006-111 was reported to have pneumonia. Subsequent documentation indicated that the subject had pseudomonas bacteremia, ischemic stroke, and multi-organ failure. Data listings for this subject indicate only pneumonia as a serious adverse event. Other SAEs appear to have been reported appropriately.

The drug infusion process was inadequately documented and appeared problematic. There were two major issues involving infusion. First, though the study drug was ordered at a 2 mg/mL concentration, the study drug was prepared at a higher concentration but infused at the rate required for a 2 mg/mL concentration. As higher concentrations of the drug should have been delivered at slower rates, there were nine subjects over 28 infusions who were overexposed to study drug in a given timeframe. These subjects were #s 006, 007, 008, 009, 102, 103, 105, 106, and 107.

Second, the study drug was ordered and prepared at a 2 mg/mL final concentration but was infused at rates greater than that specified by protocol, resulting in overexposure to the study drug for a given timeframe for four subjects over six infusions. These subjects were #s 001, 003, 005, and 006.

The subjects identified above were exposed to the study drug in amounts greater than that specified by protocol. Discrepancies were observed between source data and CRFs with respect to infusions. Other infusion documentation deficiencies were observed as neither all study drug IV bag labels were available for review nor were all IV bags labeled with study drug concentrations. These unlabeled bags correlated with those subjects who were infused at higher concentrations than that specified by protocol.

Inspection revealed that worksheets used as source documentation have errors in that “pre-populated” calculations are incorrect with respect to the identification of dosages and volumes.

DSI Reviewer Note:

The unreported protocol deviations consist primarily of infusions or treatments taking place outside of the protocol-specified timeframe. The noted deviations would not appear to significantly affect data reliability. Detailed review of infusion records revealed a lapse in proper infusion practices as required by protocol. Drug infusions for a number of subjects were prepared at too high a concentration or infused too quickly resulting in overexposure to the study drug. These infusions did not appear to result in additional adverse events; however, the interpretation of data may be confounded given that drug exposure and infusion rates for a number of subjects did not comply with the protocol. The affected subjects are identified above. This issue of drug overexposure was discussed in a meeting on March 30, 2011, with Drs. Deborah Seibel and Sally Seymour of DPARP. After discussing possible scenarios that might have led to the instances of overexposure to the test article, it was agreed that the DSI Reviewer would identify the subjects involved for further review by DPARP. The identities of these subjects were then provided to the statistical reviewer for a revised analysis of the study excluding the data from these subjects. The review division may decide to exclude the data from these specific subjects from its overall analysis.

- c. **Assessment of data integrity:** Study data other than that from the small number of subjects overexposed to the test article appear adequate in support of the application. Overexposure to the test article of a subset of study subjects as described above suggests that the review division may wish to consider excluding data from these subjects from its overall analysis.

2. Site #08772

Philip Seo, M.D.
The Johns Hopkins Vasculitis Center
5501 Hopkins Bayview Circle, Room 1B.1A
The Johns Hopkins Asthma and Allergy Center
Baltimore, MD 21224

- a. **What was inspected:** At this site, 46 subjects were screened, 36 were enrolled, and 35 completed the study. The records of 30 of the 35 treated subjects were reviewed which included, but were not limited to, the following parameters: subject eligibility, randomization, treatment, and discontinuation, adverse events and protocol deviations, concomitant medications, IRB communications, primary efficacy endpoints, informed consent, randomization and blinding procedures, and test article accountability.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. In general, the study appeared to be conducted adequately. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

3. Site #08348

Ulrich Specks, M.D.
Mayo Clinic
200 First Street, SW
Rochester, MN 55905

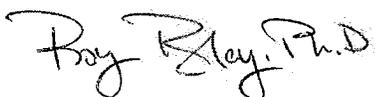
a. **What was inspected:** At this site, 59 subjects were screened and 53 were enrolled in the study. The records of 30 of the enrolled subjects were reviewed. The audit covered, but was not limited to, the following parameters: visit schedules, test article administration, concomitant medications, training documentation, financial disclosure, informed consent, drug accountability, adverse events, study endpoints, and sponsor and IRB communications.

b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. In general, the study appeared to be conducted adequately. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Merkel, Seo, and Specks were inspected in support of this NDA. Regulatory violations were noted at the site of Dr. Merkel, particularly with respect to infusion practices. The review division may wish to exclude the data from those subjects identified above from its overall analysis; however, the remaining data appears acceptable. The clinical sites of Drs. Seo and Specks appear to have conducted their studies adequately, and the data generated by these sites appear acceptable in support of the respective indication.



/Roy Blay, Ph.D./

Roy Blay, Ph.D.

Good Clinical Practice Branch II

Division of Scientific Investigations

CONCURRENCE:



/Tejashri Purohit-Sheth, M.D./

Tejashri Purohit-Sheth, M.D.

Branch Chief

Good Clinical Practice Branch II

Division of Scientific Investigations



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466
Subject: BLA 103705/5344 - FDA Labeling Information Request (IR) #2	

Total no. of pages including cover: 40

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES X NO

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: April 5, 2011

Your submissions dated October 15, 2010, and March 25, 2011, to BLA 103705/5344, are currently under review and we have a request for labeling revisions. In the attached Package Insert and Medication Guide, the FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

We have the following recommendations regarding the labeling:

1. Revise all 'IV' statements to 'intravenous' or 'intravenously' whichever is appropriate.
2. In the Geriatric Use section, provide some context for the statement that "SAEs were higher in patients over 65 years of age."
3. With regards to infusion reactions, evaluate whether any of the cases meet the definition of anaphylaxis as described in the following reference: Sampson HA, Munoz-Fulong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; (117)(2): 391-397.

Submit revised labeling incorporating the recommendations above and the changes shown in the attached marked up label for the Package Insert and Medication Guide. Submit a clean copy and a tracked change version of the label by April 8, 2011. Submit your response officially to the BLA and forward a courtesy copy to me via email.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,



/Philantha Montgomery Bowen/

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Following this page, 38 pages withheld in full - (b)(4) Draft Labeling

Drafted: Bowen/April 4, 2011

Clearance: Barnes/April 5, 2011
Seymour/April 4, 2011

Finalized: Bowen/April 5, 2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466
Subject: BLA 103705/5344 - FDA Information Request: PMC Proposal	

**Total no. of pages including
cover:** 2

Comments: Time-Sensitive: Please acknowledge Receipt

Document to be mailed: YES X NO

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: April 7, 2011

Your submission dated March 25, 2011, is currently under review and we have the following comments and/or requests for information:

Your proposal for a post-marketing clinical study is not adequate to fully address questions regarding retreatment with rituximab and concomitant medication use. While following the patients in RAVE will provide additional information, we request that you conduct a separate study to follow a broader group of patients with WG and MPA treated with rituximab. One option is a registry. Submit a proposal to address this post-marketing study. Include the general study design, number of patients, length of follow up, and proposed milestones.

Submit your response officially to the BLA and forward a courtesy copy to me via email by COB on Monday, April 11, 2011.

If you should have any questions, contact Philantha Bowen at 301-796-2466.

Sincerely,



/Carol F. Hill/

Carol F. Hill, M.S.

Regulatory Health Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/April 6, 2011

Clearance: Barnes/April 7, 2011

Finalized: Hill for Bowen/April 7, 2011

Genentech

A Member of the Roche Group

REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

April 8, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344.009
Rituxan® (Rituximab)
Amendment to a Pending Application:
Revised Draft Label - Redlined and Clean Draft Labeling
Responses to Agency's Labeling Information Request from April 5, 2011

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan® (Rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b)(4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec.. Reference is also made to the email received on April 5, 2011 which included comments on the label and a request for information.

The purpose of this submission is to provide a response to the Labeling Information Request received from the FDA on April 5, 2011. A rationale document which provides the Sponsors' responses to the Agency's recommendations is included with this submission in Section 1.14.1.2. This submission also contains two versions of the revised draft Rituxan label in Word format: one redlined version with changes tracked and one clean version incorporating the changes.

This submission is being submitted electronically via the FDA ESG (Approximate Size: 3MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

Badrul A. Chowdhury, M.D., Ph.D.

April 8, 2011

Page 2

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michelle H. Rohrer".

Michelle H. Rohrer, Ph.D.

Vice President

Regulatory Affairs



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REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

April 11, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344
RITUXAN[®] (Rituximab)
sBLA Amendment: BL 103705/5344/0.010
Amendment to a Pending Application:
Proposed Postmarketing Commitment

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b) (4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec.

Reference is also made to a submission on March 25, 2011, containing the Sponsors' proposed postmarketing commitment proposal based interactions with the Agency during a teleconference held on March 16, 2011 (BL 103705/5344/0.007). Reference is also made to a fax request from the Agency received on April 7, 2011 which indicated that the sponsor's proposal is not adequate to fully address questions regarding retreatment with rituximab and concomitant medication use and that a registry would be an option to address this PMC request.

The purpose of this submission is to provide the Agency with a proposal for a study, to fulfill the following proposed PMC:

Conduct a prospective, observational registry study of 100 rituximab-treated patients with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) followed for 4 years to evaluate long term safety and retreatment with rituximab or other therapies.

Badrul A. Chowdhury, M.D., Ph.D.

February 11, 2011

Page 2

This submission is being submitted electronically via the FDA ESG (Approximate Size: 2 MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michelle H. Rohrer".

Michelle H. Rohrer, Ph.D.

Vice President

Regulatory Affairs



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 13, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466
Subject: BLA 103705/5344 - FDA Labeling Information Request (IR) #3	

Total no. of pages including cover: 40

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: April 13, 2011

Your submissions dated October 15, 2010, and March 25 and April 8, 2011, to BLA 103705/5344, are currently under review and we have a request for labeling revisions. In the attached Package Insert and Medication Guide, the FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating the changes shown in the attached marked up label for the Package Insert and Medication Guide. Submit a clean copy and a tracked change version of the label by 10 AM EST April 15, 2011. Submit your response officially to the BLA and forward a courtesy copy to me via email.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,



/Eunice Chung-Davies, PharmD/

Eunice Chung-Davies for Philantha Bowen
Philantha Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert and Medication Guide

Following this page, 38 pages withheld in full - (b)(4) Draft Labeling

Drafted: Bowen/April 13, 2011

Clearance: Barnes/April 13, 2011
Seymour/April 12, 2011

Finalized: Bowen/April 13, 2011

Genentech

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REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

April 14, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344.011
Rituxan[®] (Rituximab)
Amendment to a Pending Application:
Revised Draft Label - Redlined and Clean Draft Labeling

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (Rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b) (4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec.

The purpose of this submission is to provide a response to the Labeling Information request received via email from the FDA on April 13, 2011. This submission contains two versions of the revised draft Rituxan label in Word format: one redlined version with changes tracked and one clean version incorporating the changes. Redlined version includes administrative changes only.

This submission is being submitted electronically via the FDA ESG (Approximate Size: 2MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

Badrul A. Chowdhury, M.D., Ph.D.

April 14, 2011

Page 2

If you have any questions regarding this submission, please contact
Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in black ink, appearing to read "Michelle H. Rohrer". The signature is stylized and includes a date "4/14/11" written to the right of the main signature.

Michelle H. Rohrer, Ph.D.

Vice President

Regulatory Affairs



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 15, 2011

To: Yasameen Qazen, Manager Regulatory Affairs	From: Philantha Montgomery Bowen Regulatory Project Manager
Company: Genentech, Inc	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 650-467-3198	Fax number: 301-796-9728
Phone number: 650-225-7952	Phone number: 301-796-2466

Subject: BLA 103705/5344 - FDA Labeling Information Request (IR) #4

Total no. of pages including cover: 40

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STN: BL 103705/5344
Rituxan® (rituximab)
Genentech, Inc.

DATE: April 15, 2011

Your submission dated April 15, 2011, to BLA 103705/5344, is currently under review and we have a request for labeling revisions. In the attached Package Insert and Medication Guide, the FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating the changes shown in the attached marked up label for the Package Insert and Medication Guide. Submit a clean copy and a tracked change version of the label by 10 AM EST April 18, 2011. Submit your response officially to the BLA and forward a courtesy copy to me via email.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,



/Colette Jackson/

Colette Jackson for Philantha Bowen
Philantha Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert and Medication Guide

Following this page, 38 pages withheld in full - (b)(4) Draft Labeling

Genentech

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REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

April 15, 2011

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Philantha Bowen

Subject: **License No. 1048**
STN: BL 103705/5344.012
Rituxan[®] (Rituximab)
Amendment to a Pending Application:
Revised Draft Label - Redlined and Clean Draft Labeling

Dear Dr. Chowdhury:

We refer to STN: BL 103705 for Rituxan[®] (Rituximab), initially approved on November 26, 1997 and to the sBLA for [REDACTED] ^{(b) (4)} submitted on October 15, 2010, a joint development project between Genentech, Inc. and Biogen Idec.

The purpose of this submission is to provide a response to the Labeling Information request received via email from the FDA on April 15, 2011. This submission contains two versions of the revised draft Rituxan label in Word format: one redlined version with changes tracked and one clean version incorporating the changes. The redlined version includes administrative changes only.

This submission is being submitted electronically via the FDA ESG (Approximate Size: 3MB). Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the files are virus free. For any technical issues regarding the electronic transmission of this submission, please contact James Layton, Manager, Regulatory Affairs at (650) 225-6508.

Badrul A. Chowdhury, M.D., Ph.D.

April 15, 2011

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If you have any questions regarding this submission, please contact Yasameen Qazen, Manager, Regulatory Affairs at (650) 225-7952.

Sincerely,

A handwritten signature in black ink, appearing to read "Michelle H. Rohrer", written over a horizontal line.

Michelle H. Rohrer, Ph.D.
Vice President
Regulatory Affairs

Post marketing Requirement Studies

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Conduct a prospective, observational registry study of 100 rituximab-treated patients with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) followed for 4 years to evaluate long term safety and retreatment with rituximab or other therapies.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>10/31/2011</u>
	Study/Clinical trial Completion Date:	<u>03/31/2018</u>
	Final Report Submission Date:	<u>3/31/2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The efficacy and safety of Rituxan for patients with WG and MPA was based upon a single clinical trial in which one course of rituximab was administered. This is sufficient for this orphan indication and unmet clinical need. Additional long term safety and potential retreatment data are necessary, but can be obtained post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In the clinical trial to support approval, only once course of Rituxan was pre-specified. In clinical practice, patients will relapse and likely need additional courses of Rituxan. In addition, the use of concomitant medications other than corticosteroids was limited. The safety of long term use of Rituxan, repeat courses of Rituxan and use with concomitant medications needs evaluation.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A observational registry in 100 Rituxan treated patients with WG or MPA.
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Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

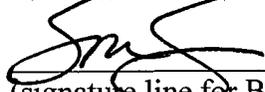
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.


(signature line for BLAs)


4/19/11

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA # 103705	NDA Supplement # BLA STN # 5344	If NDA, Efficacy Supplement Type:
Proprietary Name: Rituxan® Established/Proper Name: rituximab Dosage Form: intravenous infusion		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Philantha Montgomery Bowen		Division: DPARP
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 19, 2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request Comments: BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist³	
Officer/Employee List	
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP: 4/19/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	4/15/11
• Original applicant-proposed labeling	10/15/10
• Example of class labeling, if applicable	

Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4/15/11
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	10/15/10
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	None-original submission contained FPL
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	n/a
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 1/31/11 <input checked="" type="checkbox"/> DMEPA 3/17/11 <input checked="" type="checkbox"/> DRISK 3/14/11 <input checked="" type="checkbox"/> DDMAC 3/17/11 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews - OBP 4/13/11 Labeling Meeting: 3/2/11
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	11/18/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
<ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>orphan designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	11/12/10; 12/17/10; 2/1/11; 2/10/11; 2/18/11; 3/16/11; 3/18/11;

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	4/5/11; 4/7/11; 4/13/11; and 4/15/11
Internal memoranda, telecons, etc.	3/16/11
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 2/26/10
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg <i>Pre-sBLA</i> 4/6/10
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	
	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/19/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/5/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1
Clinical Information⁵	
Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Refer to CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	3/25/11; 12/3/10
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR	
If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	3/25/11 (pg 16)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	
	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	
	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	
	<input type="checkbox"/> None requested 4/5/11

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/8/10; 3/14/11
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/9/10; 3/25/11
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/30/10; 3/9/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/18/11
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	1/28/11
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: 4/4/11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

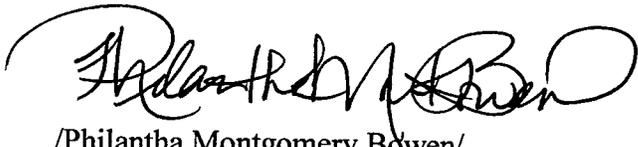
An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



/Philantha Montgomery Bowen/

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