2 STUDY SYNOPSIS

Name of Sponsor/Company: Biogen Idec Inc.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: IDEC-102 (rituximab)	**Name of Active Ingredient:** IDEC-102 (rituximab)	**Study Indication:** Relapsed or Refractory, Low-grade or Follicular, $CD20^+$, B-cell Non-Hodgkin's Lymphoma

Title of Study:
A Multicenter Study to Evaluate the Effect of Rituximab (IDEC-102) on Primary Humoral Response, Recall Response, and Maintenance of Acquired Immunity to Specific Antigens

Principal Investigator:
[redacted]

Study Period:	**Phase of Development:** 4
NHL Group: Date of first treatment: 13 January 2005 Date of completion: 13 June 2007 *Control Group:* Date of first treatment: 08 October 2003 Date of completion: 10 December 2004	

Study Objective(s):
The objective of this study was to determine whether therapy with rituximab alters the immune response in relapsed or refractory, low-grade or follicular, $CD20^+$, B-cell non-Hodgkin's lymphoma (NHL) subjects in comparison to untreated, age-matched control subjects (who do not have NHL).

Primary endpoint:
- To determine whether treatment with rituximab causes a clinically significant effect on immunological recall response to tetanus vaccine in NHL subjects.

Secondary endpoints:
- To determine whether NHL subjects can mount a primary immune response to key-hole limpet hemocyanin (KLH) after treatment with rituximab.
- To determine whether NHL subjects treated with rituximab experience clinically significant changes in antibody titers to a panel of specific antigens: *Streptococcus pneumoniae*, influenza A, mumps, rubella, and varicella.

Study Design:
This was an open-label, 2-arm, multicenter study. The NHL group comprised subjects with low-grade or follicular, CD20+ B-cell, relapsed, refractory NHL; the Control group comprised healthy volunteers. Treatment for the 2 groups was as follows:
- NHL group: rituximab (375 mg/m^2 once a week times 4) on Days 1, 8, 15, and 22; KLH (1 mg) immunizations on Days 252 and 259; and tetanus toxoid immunization (0.5 mL) on Day 252.
- Control group: KLH (1 mg) immunization on Days 1 and 8 and tetanus toxoid (0.5 mL) immunization on Day 1.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 160 NHL subjects. Approximately 100 control subjects.
Analyzed:
Safety Population: 173 NHL subjects. 98 Control subjects.
Per-protocol population: 110 NHL subjects. 84 Control subjects.

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Study Population:

NHL Group

Main inclusion criteria:

- Signed written informed consent form.
- Age ≥40 years.
- Relapsed (maximum of 5 relapses) or refractory, low-grade or follicular, $CD20^+$, B-cell NHL.
- Histologic confirmation of low-grade or follicular, B-cell NHL prior to study entry.
- Prestudy World Health Organization (WHO) performance status of 0, 1, or 2.
- Expected survival ≥1 year.
- Known history of tetanus toxoid immunization or positive tetanus titer at the screening visit.

Main exclusion criteria:

- Active autoimmune disease.
- Exposure to rituximab within 12 months prior to Day 1.
- Chemotherapy within 3 months prior to Day 1.
- Previous immunization with tetanus toxoid within 2 years prior to Day 1.
- Previous exposure to KLH.

Control Group

Main inclusion criteria:

- Signed written informed consent form.
- Age ≥40 years.
- Health status based on physical examination and laboratory safety tests that would not confound the results of the study or pose additional risk to the subject in the opinion of the Investigator.

Main exclusion criteria:

- Concurrent medical disease that could confound or interfere with evaluation of immune response including, but not limited to, rheumatoid arthritis, systemic lupus, spondyloarthropathy, and polymyalgia rheumatica.
- Prior exposure to rituximab.
- Immunization with tetanus toxoid within the 2 years prior to Day 1.
- Previous exposure to KLH.

Study Treatment, Dose, Mode of Administration, Lot Number(s):

Rituximab intravenous 375 mg/m^2 once weekly times 4:

100 mg lot numbers: [redacted]

500 mg lot numbers: [redacted]

Immunizations, Dose, Mode of Administration, Lot Number(s):

Tetanus toxoid intramuscular 0.5 mL. Lot numbers: [redacted].

KLH subcutaneous 1 mg. Lot number [redacted].

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Duration of Treatment and Follow-Up Period:

NHL Group

Treatment period: Study Day 1 through Day 22 and Days 252 and 259
Post-Treatment period: Study Days 84, 168, and 280

Control Group

Treatment and follow-up period: Study Day 1 through Day 8
Post-Treatment period: Study Day 28

Criteria for Evaluation:

Immunologic assessment variables:

- Recall response: Serum antibody titer to tetanus toxoid
- Primary humoral response: Serum antibody titer to KLH
- Maintenance of pre-existing acquired humoral immunity: Serum antibody titers to *Streptococcus pneumoniae*, influenza A, mumps, rubella, and varicella

Safety: NHL group and Control Group: Adverse events (AEs), physical examinations, vital signs, hematology, serum chemistry, urinalysis, and serum pregnancy test.
NHL group only: Rituximab human antichimeric antibody (HACA) concentrations.

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Statistical Methods:

Demographics and baseline disease characteristics: Demographic and baseline disease characteristics were summarized by descriptive statistics for continuous variables (n, mean, standard deviation [SD], median, min, max) and for categorical variables (n, %).

Extent of Exposure: The extent of exposure to rituximab, tetanus toxoid, and KLH was summarized using cumulative dose data.

Primary Immunologic Endpoint: Comparison of response proportions between the NHL group and the control group 28 days after tetanus toxoid immunization. A 2-sided 95% confidence interval for the difference in proportions was used. For subjects with tetanus antibody baseline titers <0.1 IU/mL, a response to the booster immunization is defined as an antibody titer ≥0.2 IU/mL measured 28 days after immunization. For subjects with tetanus antibody baseline titers ≥0.1 IU/mL, response to the booster immunization is defined as a 2-fold increase in antibody titers measured 28 days after immunization.

Secondary Immunologic Endpoints:

- The KLH response 28 days after immunization was summarized using descriptive statistics according to the number of fold increases in antibody titer (0 to 1-fold, 1-fold to 2-fold, and greater than 2-fold increase), by age category and total, for each treatment group.
- The maintenance of pre-existing acquired humoral immunity to *S. pneumoniae*, influenza A, mumps, rubella, and varicella was presented using descriptive statistics and by treatment group.

Additional Immunologic Endpoint: Comparison of response proportions, stratified by age, between the NHL group and the control group 28 days after tetanus toxoid immunization. A 2-sided 95% confidence interval for the weighted difference in proportions was used.

Safety

The safety variables analyzed for both the NHL group and the Control group included clinical AEs, medical history and physical examination findings, vital sign measurements, routine hematology CBC with differential and platelets, and serum chemistry panel.

AEs were summarized by treatment group, system organ class, preferred term, and grade. Hematology and chemistry were presented by shift table analysis. All other variables were provided by subject listing.

For the NHL group only, HACA concentrations were analyzed.

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Demographics and baseline disease characteristics:

- 173 NHL subjects were enrolled at 38 study sites; 129 completed the study. Two subjects were enrolled in the US and 171 were enrolled at non-US sites.
  - 173 NHL subjects (100%) received treatment (rituximab, tetanus, and KLH) and were included in the Safety Population and 110 subjects (63.6%) were in the Per-Protocol Population.
- A total of 103 control subjects were enrolled at 1 study site in the US; 96 control subjects completed the study.
  - 98 Control subjects (95.1%) received treatment (tetanus and KLH) and were included in the Safety Population and 84 subjects (81.6%) were included in the Per-Protocol Population.
- In the Safety Population, all NHL subjects were Caucasian; Control subjects were 49% Caucasian and 37% Asian.
- The median age in both groups was 59 years.
- NHL Group
  - The median time from diagnosis of NHL was 3 years (N = 161).
  - The median time since most recent relapse was 3.8 months (N = 158).
  - Five subjects had a change in histopathologic subtype since original diagnosis; 165 had no change; data are missing or unavailable on 3 subjects.
  - Histopathologic subtype was Grade I for 69 subjects (40%), Grade II for 43 subjects (25%), Grade III for 8 subjects (5%), and missing, not available or unknown for 53 subjects (30%).
  - Disease stage at study entry was Stage I for 21 subjects (12%), Stage II for 24 subjects (14%), Stage III for 53 subjects (31%), and Stage IV for 75 subjects (43%).
  - In the Safety Population, 169 of 172 subjects had received prior lymphoma therapy. The median number of prior regimens was 2 (minimum, 1; maximum 9).

Efficacy:

- In the NHL group, 18 of 110 (16%) subjects were classified as responders to the tetanus vaccine.
- In the age-matched control group, 68 of 84 (81%) subjects were classified as responders to the tetanus vaccine.
- There was a -0.65 difference in proportions between the groups with a 95% confidence interval of -0.77 to -0.53. Thus it was concluded that the response in the NHL group was not non-inferior to the Control group. Based on these results, the 2 groups do not respond similarly to tetanus vaccination.
- In the NHL group, 103 of 108 subjects (95%) demonstrated a less than 1-fold increase in antibody titer against KLH, and 4 of 108 subjects (4%) demonstrated a greater than 2-fold increase in antibody titer against KLH.
- In the control group, 15 of 84 subjects (18%) demonstrated a less than 1-fold increase in antibody titer, and 58 of 84 subjects (69%) demonstrated a greater than 2-fold increase in antibody titer.
- In both NHL and Control groups, mean antibody titers to a panel of specific recall antigens, *Streptococcus pneumoniae*, influenza A, mumps, rubella, and varicella, were similar after treatment to mean titers observed at screening.

Safety:

NHL Group

- 103 of 173 subjects (59.5%) experienced AEs during the study.
- The most common AEs were hypertension (8% of subjects), pyrexia, chills, and arthralgia (6.4% each), fatigue (5.8%), back pain and nausea (4.6% each), and headache (4.0%).
- Grade 3 or 4 AEs were reported in 17 of 173 subjects (9.8%).
- None of the subjects experienced study-related Grade 3 or 4 AEs.
- Thirteen (8%) subjects experienced serious adverse events (SAEs).
- One subject (448) did not complete the study due to an AE (post-thrombotic syndrome).

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- Forty five (26.0%) subjects experienced an infusion reaction to rituximab.
- All infusion reactions were mild or moderate.
- Two deaths occurred; neither was related to study treatment.
- Of the 173 treated subjects, human anti-chimeric antibody (HACA) samples were available on 170 subjects at screening and 130 subjects at Study Day 252. At screening, 168 subjects were below the limit of quantitation, 1 was positive, and 1 was not tested. At Study day 252, HACA concentrations were below the limit of quantitation in 126 subjects and positive in 4 subjects.

Control Group

- 43 of 98 (44%) subjects experienced AEs.
- The most common AEs were pruritus (8.2% of subjects), headache and peripheral edema (4.1% each).
- Grade 3 or 4 AEs were reported in 1 of 98 subjects (1%).
- None of the subjects experienced study-related Grade 3 or 4 AEs.
- One (1%) subject experienced an SAE, a skin ulcer and cellulitis caused by an infected cat scratch; it was considered "not related" to study treatment.

Conclusion(s):

These results demonstrate that previously-treated relapsed NHL subjects who received rituximab mount impaired antibody responses to tetanus toxoid and to KLH when compared with age-matched healthy volunteer, control subjects. Interpretation of this study is complicated by the inherent limitations of the study design i.e lack of control group with NHL, who were not treated with rituximab as it would have been unethical to withhold treatment from NHL patients. As a result, a conclusion of causality cannot be made as the effect of underlying disease or prior chemotherapy on blunted immune responses in lymphoma patients was not assessed. In addition, surrogate measures to evaluate protection (such as antibody titers, response to revaccination, and T-cell proliferative responses) have not always correlated with actual prevention of disease. In the absence of a proven surrogate for protection, the assumption must be that the ability for a given vaccine to prevent disease is blunted in patients with NHL who have received rituximab. Thus, for NHL patients, the benefits of primary or booster vaccinations should be weighed against the risks of delay in initiation of rituximab therapy

Publication(s) Based on the Study:
None.

Date of Report: 08 May 2008