2. STUDY SYNOPSIS.

Name of Sponsor: Biogen Idec Inc./ Biogen Idec Ltd.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: galiximab (IDEC-114)	**Name of Active Ingredient:** galiximab (IDEC-114)	**Study Indication:** Non-Hodgkin's Lymphoma

Title of Study: A Phase III, Randomized, Double-Blind Study of Galiximab in Combination with Rituximab Compared with Rituximab in Combination with Placebo for the Treatment of Subjects with Relapsed or Refractory, Follicular Non-Hodgkin's Lymphoma

Principal Investigator:

- [redacted]

Study Period: Date of first treatment: 28 November 2006 Date of early study termination: 19 October 2009 Date of last subject, last visit: 08 January 2010	**Phase of Development:** III

Study Objectives:

Primary objective:

- To compare the clinical benefit of galiximab in combination with rituximab with that of rituximab monotherapy for relapsed or refractory, follicular non-Hodgkin's lymphoma (NHL).

Secondary objectives:

- To further characterize the safety profile of galiximab in combination with rituximab.
- To further characterize the pharmacokinetics (PK) of 4 infusions of galiximab in combination with rituximab.

Study Design:

This was a Phase III, multicenter, global, randomized, double-blind study in subjects with relapsed or refractory, follicular NHL. Subjects were to be randomized in a 1:1 ratio to receive either galiximab in combination with rituximab or placebo in combination with rituximab. Subjects were to be stratified according to age (≤60 vs. >60 years), prior rituximab exposure (rituximab naïve vs. non-naïve), baseline tumor bulk (diameter of largest lesion ≤7 cm vs. >7 cm), and region (US sites vs. non-US sites).

The study period for each subject was to be approximately 4 years. On Study Days 1, 8, 15, and 22, subjects were to receive infusions of rituximab and galiximab (Group A, hereafter referred to as R + G group) or rituximab and placebo (Group B, hereafter referred to as R + P group). At these visits, the rituximab infusion was to be administered prior to the galiximab or placebo infusion. Subjects were to complete scheduled visits until Study Month 48, after which time they were to enter into the long-term, follow-up period of the study. Subjects were to be followed every 6 months for continuation of response (if applicable), disease progression, initiation of first subsequent lymphoma therapy, and survival, except

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in cases of death, if a subject was lost to follow up, or if a subject withdrew informed consent.

Subjects who had progressed after experiencing at least a partial response (PR) with time to progression (TTP) of 6 months or greater in either arm of this study were eligible for retreatment under a separate protocol (Protocol 114-NH-302).

The study was terminated early due to slow subject accrual.

Number of Subjects (Planned and Analyzed):

Planned: A total of 742 subjects were to be randomized.

Analyzed: A total of 337 subjects were randomized at 130 sites.

Study Population:

Main inclusion criteria:

- Must have given written informed consent and any authorizations as required by local law (e.g., Protected Health Information for North America)
- Aged ≥18 years old at the time of informed consent
- Histologically confirmed follicular Grade 1-3a NHL. If slides and/or tissue blocks from the most recent lymph biopsy were not available for Central Pathology Review, a repeat lymph node biopsy was to be required prior to enrollment. If there was any clinical evidence suggesting transformation (e.g., elevated lactate dehydrogenase >2 × upper limit of normal), a biopsy was to be required within 6 months prior to enrollment. Subjects with evidence of histologic transformation on a repeat biopsy were to be excluded from the study.
- Bidimensionally measurable disease with at least 1 lesion ≥2.0 cm in a single dimension
- Acceptable hematologic, hepatic, and renal function
- World Health Organization (WHO) Performance Status ≤2
- Recovered fully from any significant toxicity associated with prior surgery, radiation treatments, chemotherapy, biological therapy, autologous bone marrow or stem cell transplant, or investigational drugs
- Expected survival of ≥3 months
- Subjects of reproductive potential were to agree to follow accepted birth control methods during treatment and for 12 months after completion of treatment

Main exclusion criteria:

- Follicular lymphoma Grade 3b
- Previous exposure to galiximab or any anti-CD80 antibody

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- Known hypersensitivity to murine proteins
- Rituximab refractory or refractory to anti-CD20 radioimmunotherapy (no response to prior rituximab or prior rituximab-containing regimen, or a response with a TTP of less than 6 months)
- Cancer radiotherapy, biological therapy, or chemotherapy within 3 weeks prior to Study Day 1 (6 weeks if nitrosourea or mitomycin-C)
- Prior lymphoma vaccine therapy within 12 months prior to Study Day 1
- Chronic or intermittent corticosteroids for inflammatory or autoimmune disorders within 3 weeks prior to Study Day 1
- Prior antibody therapy for lymphoma (including radioimmunotherapy) within 6 months prior to Study Day 1
- Autologous bone marrow or stem cell transplant within 6 months prior to Study Day 1
- Prior allogeneic transplant
- Transfusion-dependent subjects
- Known history of hepatitis or hepatic disease. (Although testing for hepatitis B was not mandatory, this was to be considered for all subjects considered at high risk for hepatitis B infection and in endemic areas. Subjects with any serological evidence of current or past hepatitis B exposure were to be excluded unless the serological findings were clearly due to vaccination.)
- Presence of chronic lymphocytic leukemia, marginal zone lymphoma, mucosa associated lymphoid tissue
- Presence of central nervous system lymphoma
- Known history of human immunodeficiency virus infection or acquired immune deficiency syndrome
- Prior diagnosis of aggressive NHL or mantle cell lymphoma
- Histologic transformation
- Presence of pleural or peritoneal effusion with positive cytology for lymphoma
- Another primary malignancy requiring active treatment (except hormonal therapy)
- Serious nonmalignant disease (e.g., congestive heart failure, hydronephrosis); active uncontrolled bacterial, viral, or fungal infections; or other conditions, which would compromise protocol objectives in the opinion of the Investigator and/or the Sponsor
- New York Heart Association Class III or IV cardiac disease or myocardial infarction within 6 months prior to Study Day 1
- Major surgery, other than diagnostic surgery, within 4 weeks prior to Study Day 1
- History of alcoholism or substance abuse within the 2 years prior to Study Day 1

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- Pregnant or currently breastfeeding

Study Treatment, Dose, Mode of Administration, Lot Numbers:

Galiximab was to be administered weekly by intravenous (IV) infusion at a dose of 500 mg/m^2 for 4 weeks.

The following lot numbers were used during the study: [redacted]

Rituximab was to be administered weekly by IV infusion at a dose of 375 mg/m^2 for 4 weeks.

The following lot numbers were provided by the sponsor for use during the study: [redacted]

Placebo was to be administered weekly by IV infusion for 4 weeks.

Duration of Treatment and Follow-Up:

The study period was to consist of screening, randomization, treatment, follow-up, and long-term follow-up.

Screening period: Screening procedures to evaluate subject eligibility for the study were to be initiated within 6 weeks prior to Study Day 1.

Randomization period: Randomization was to be completed within 48 hours prior to Study Day 1.

Treatment period: Randomized subjects were to visit the study site to receive an infusion of study treatment (R + G or R + P) once a week for 4 weeks. Infusions were to be administered on Study Days 1, 8, 15, and 22.

Follow-up period: Subjects were to return to the study site for follow-up visits on Study Days 50 and Study Months 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, and 48.

Long-term Follow-up period: Following Study Month 48, subjects were to be entered into the long-term, follow-up period of the study, where they were to be followed by verbal or written contact every 6 months for continuation of response (if applicable), disease progression, initiation of first subsequent lymphoma therapy, and survival. Subjects were to be discontinued from the study and transitioned into long-term follow-up prior to Study Month 48 if they initiated a subsequent lymphoma therapy with or without disease progression. Long-term follow-up was to be continued until the subject died, was lost to follow-up, or withdrew informed consent.

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Criteria for Evaluation:

Efficacy:

The International Workshop Response Criteria for non-Hodgkin's lymphoma was to be used to assess response and time-to-event endpoints. Investigators at each site were to perform measurable lesion assessments based on CT scans and physical examination to determine response and progression.

The primary study endpoint was progression-free survival (PFS), defined as the time from the date of randomization to the date the subject progressed or died from any cause.

Secondary endpoints included the following:

- Event-free survival (EFS)
- TTP
- Duration of response (DR)
- Time-to-next lymphoma treatment (TTNT)
- Overall survival (OS)
- Overall response rate (ORR)
- Complete response (CR) rate
- Unconfirmed complete response (CRu) rate
- PR rate
- Change in the sum of the product of the perpendicular diameters of index lesions

Pharmacokinetics:

The following pharmacokinetic variables were to be assessed:

- Serum concentrations of galiximab
- Serum concentrations of rituximab, at select sites only

Pharmacodynamics:

Correlations of serum concentrations with response variables were to be performed. The appropriate PK/pharmacodynamic model was to be employed to describe these.

Quality of Life and Other Outcome Measurements:

The following assessments were to be performed:

- Quality of Life questionnaires
- Medical Resource Utilization
- Other outcome measurements, including changes in disease-related signs and symptoms

Safety:

The following clinical safety variables were to be assessed:

- Medical history

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- Physical examinations
- Vital sign measurements
  - pulse
  - blood pressure
  - respirations
  - temperature
- Weight
- Concomitant therapy and procedures
- Adverse events (AEs)
- Serious adverse events (SAEs)

The following laboratory safety variables were to be assessed:

- Hematology: hemoglobin, hematocrit, platelet counts, red blood cells, white blood cells, and absolute differential
- Blood chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, urea, uric acid, creatinine, lactate dehydrogenase, potassium, sodium, chloride, calcium, and phosphorous
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Quantitative serum immunoglobulins: IgG, IgA, and IgM
- Urine pregnancy test (female subjects of reproductive potential)

The following immunogenicity variables were to be assessed:

- Anti-galiximab antibody formation
- Human anti-chimeric antibody (HACA) formation

Statistical Methods:

The following analysis populations were defined for this study:

- Randomized Population – all subjects randomized into the study. This population was to be used for the analysis of subject disposition.
- Intent-to-Treat (ITT) Population – all subjects randomized into the study. This population was to be used for all efficacy analyses, and all analyses of demographic and baseline disease characteristics.
- Safety Population – a subset of subjects in the randomized population who received any part of study treatment.
- Pharmacokinetic Population – all randomized subjects who received at least 1 infusion of study treatment and had at least 1 sample collected for PK analysis.

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Subject Disposition:

Subject disposition was to be summarized using descriptive statistics for categorical variables using the Randomized Population.

Demographics, Baseline Disease Characteristics, and Prior Therapy Data:

Subject baseline demographics and disease status variables were to be summarized by treatment group for the Intent-to-Treat (ITT) Population. Other than visual inspection, no statistical tests to confirm homogeneity between treatment groups at baseline were to be performed. Descriptive statistics were to be used for continuous variables (n, mean, standard deviation, median, minimum, and maximum) and frequencies and percentages (n, %) for categorical variables.

Efficacy:

Analysis of efficacy endpoints was to be conducted on the ITT Population. The primary efficacy endpoint was PFS. The primary analysis for PFS was to use the investigator's assessment of response to determine the date of progression; the independent radiology review committee assessment was to be used in a confirmatory analysis. Secondary endpoints included EFS, TTP, DR, TTNT, OS, ORR, CR rate, CRu rate, and PR rate.

A difference in survival curves for the primary endpoint (PFS) was to be tested using a stratified log-rank test (with strata for age, prior rituximab use, and baseline tumor bulk), and evaluated using a group sequential testing design with stopping boundaries defined that ensure an overall 2-sided significance level of 0.01. Median PFS and the associated 2-sided 95% confidence interval (CI) were to be calculated using the Kaplan-Meier method. Analyses of secondary efficacy endpoints were to be evaluated only once, at the end of the study, using a 2-sided significance level of 0.01.

Interim Analyses:

Interim analyses were to be performed on the primary efficacy endpoint (PFS) using the ITT Population; all subjects randomized into the study at the time of an interim analysis were to be included.

Pharmacokinetics:

PK analyses were to be performed on data from the PK Analysis Population. Serum concentrations of galiximab were to be measured for all subjects. At select sites only, serum concentrations of rituximab were also to be measured. Population-based PK modeling was to be used to describe plasma concentrations. Standard PK parameters that were to be estimated included clearance, volume of distribution, and elimination half-life. PK parameters were to be presented with descriptive statistics by treatment group.

Pharmacokinetics/Pharmacodynamics:

Correlations of serum concentrations with response variables were to be evaluated. The appropriate PK/pharmacodynamic model was to be employed to describe these correlations.

Quality of Life and Other Outcome Measurements:

Quality of life analyses were to be performed on data from the ITT population. The FACT-lym domain scores (e.g., physical, social and family, emotional, functional well-being, and lymphoma) and total

score were to be summarized descriptively by scheduled visit. Change from baseline was also to be summarized by scheduled visit. The EQ-5D questionnaire was to be summarized using frequency of response for the 3 possible responses within each domain (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The visual analog scale for overall health from the EQ-5D was to be scored and summarized using descriptive statistics for a continuous variable.

Change in disease-related signs and symptoms was to be summarized by reporting the number and percentage of subjects whose disease-related signs and symptoms improved from baseline or resolved.

Detailed analyses of quality of life and other outcome measurements were to be reported separately from the CSR in a pharmacoeconomic report.

Safety:

Unless otherwise noted, safety variables were to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent) using the Safety Population.

Results:

Subject disposition:

- The study was terminated early on 19 October 2009. The last subject's last visit was on 08 January 2010.
- At the time of the last subject's last visit, 337 subjects had been enrolled at 130 study sites in 22 countries in North America and Rest of World and had completed a median of 13.8 months of follow-up.
- All 337 subjects were included in the Randomized Population and in the ITT Population: 175 in the R + G group and 162 in the R + P group.
- A total of 332 subjects received any part of study treatment and were included in the Safety Population: 172 in the R + G group and 160 in the R + P group.
- The first subject was treated on 28 November 2006.
- Two subjects in the R + G group and 5 subjects in the R + P group discontinued study treatment.
- Due to early study termination, all subjects are currently off study. The majority of subjects withdrew due to early study termination or disease progression requiring subsequent lymphoma therapy.

Demographics and baseline disease characteristics:

- Demographics and baseline disease characteristics were well balanced across the 2 treatment groups.
- Median age of subjects at study entry was 59 years (min. 27 years, max. 91 years).
- Study population was evenly balanced with regard to sex (49% male; 51% female).
- Ninety-four percent were Caucasian.

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- Median time since NHL diagnosis was 5.1 years (min. 0.2 years, max. 24.8 years).
- Twenty-three percent of subjects had Stage I/II and 77% had Stage III/IV disease at study entry.
- Median longest diameter of the largest lesion was 4.2 cm (min. 1.8 cm, max. 23.3 cm).
- Follicular Lymphoma International Prognostic Index risk group was divided evenly; 31% were classified as low risk; 34% were classifed as intermediate risk; 32% were high risk; and data were missing for 2% of subjects.
- WHO performance status was 0 in 62% of subjects, 1 in 36% of subjects, and missing in 2% of subjects.
- Thirty percent of subjects had bone marrow involvement; 11% had splenomegaly; and 6% had hepatomegaly.
- Thirty-five percent of subjects had received 1 prior lymphoma regimen; 25% had received 2 prior regimens; and 39% had received ≥3 prior regimens.
- Eighty-five percent and 88% of subjects in the R + G group and R + P group, respectively, had diagnosis of grade I-IIIa follicular lymphoma confirmed by retrospective, independent pathology review.

Efficacy:

- At data cut-off, 177 PFS events had been reported. This is approximately 28% of the originally planned 624 events. Forty-seven percent of subjects in the R + G group and 58% in the R + P group had experienced a PFS event. The Kaplan-Meier estimated median PFS was 12.02 months in the R + G group and 9.03 months in the R + P group. The observed hazard ratio (HR) was 0.738 (95% CI 0.543, 1.002; p = 0.050).
- Fifty-one percent of subjects in the R + G group and 48% of subjects in the R + P group responded to treatment (p = 0.455). In the R + G group, CR rate was 20%, unconfirmed CR rate was 6%, and PR rate was 25%. In the R + P group, CR rate was 15%, unconfirmed CR rate was 5%, and PR rate was 27% .
- Kaplan-Meier median EFS was 9.40 months in the R + G group and 9.03 months in the R + P group. The observed HR was 0.755 (95% CI 0.565, 1.010; p = 0.058).
- Kaplan-Meier median TTP was 12.02 months in the R + G group and 9.03 months in the R + P group. The observed HR was 0.743 (95% CI 0.546, 1.009; p = 0.056).
- Kaplan-Meier median DR was 14.95 months in the R + G group and 8.77 months in the R + P group. The observed HR was 0.644 (95% CI 0.411, 1.073; p = 0.092).
- Kaplan-Meier median TTNT was 18.92 months in the R + G group and 13.37 months in the R + P group. The observed HR was 0.756 (95% CI 0.542, 1.055; p = 0.099).
- Kaplan-Meier median OS has not yet been reached. The observed HR was 0.549 (95% CI 0.248, 1.217; p = 0.135). OS data were limited with only 27 deaths reported.

Pharmacokinetics/ Pharmacodynamics:

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- Based on rituximab concentration curves comparing the R + G group with the R + P group, no obvious differences in mean rituximab serum concentrations were observed between groups at all timepoints measured (Day 1 to Day 270). A complete assessment of pharmacokinetics for both galiximab and rituximab will be included as an addendum in a separate PK report.

Quality of Life and Other Outcome Measurements

- Overall, changes in quality of life measurements were small and no apparent difference was seen between galiximab and placebo.

Safety:

- Eighty-three percent of subjects in the R + G group and 81% of subjects in the R + P group experienced an AE.
- The most common (≥5% in the R + G group) AEs regardless of causality were pyrexia, fatigue chills, nausea, headache, cough, infusion-related reaction, back pain, vomiting, upper respiratory tract infection, diarrhea, insomnia, nasopharyngitis, abdominal pain, pruritus, neutropenia, asthenia, peripheral edema, hypertension, and muscle spasms.
- Eighteen percent of subjects in the R + G group and 19% in the R + P group experienced a ≥Grade 3 AE as their most severe AE. AEs ≥Grade 3 occurring in ≥1% of galiximab subjects included neutropenia, lymphopenia, back pain, pneumonia, leukopenia, febrile neutropenia, and neutrophil count decrease.
- Thirty-seven percent of subjects in the R + G group and 34% of subjects in the R + P group experienced a galiximab-related AE, defined as events classified as related or possibly related to galiximab/placebo.
- Galiximab-related AEs occurring in ≥3% of galiximab subjects included pyrexia, nausea, fatigue, headache, and chills.
- Galiximab-related Grade 3 or 4 AEs were reported in 7% of subjects in the R + G group, and 8% of subjects in the R + P group. There were no galiximab-related Grade 5 events in either group. Grade 3 or 4 galiximab-related AEs occurring in ≥1% of R + G subjects included neutropenia and neutrophil count decrease.
- Ten deaths were reported in the R + G group, all of which were considered not related to galiximab. Seventeen deaths were reported in the R + P group.
- Fourteen percent of subjects in the R + G group and 14% of subjects in the R + P group experienced SAEs. SAEs occurring in ≥1% of R + G subjects included pneumonia, pyrexia, and febrile neutropenia. In the R + G group, 2 SAEs were considered galiximab-related; these included Grade 1 pyrexia and Grade 4 neutrophil count decrease in 1 subject each.
- Two subjects discontinued study treatment and also withdrew from the study due to the following AEs: Grade 2 brain stem infarction (R + G) and Grade 1 left ventricular failure (R + P).
- One subject experienced Grade 4 atrial fibrillation (R + P) and discontinued study treatment but

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continued to participate in the study.

- Two subjects withdrew from the study after completing all 4 doses of treatment due to the following AEs: Grade 5 febrile neutropenia (R + P) and Grade 2 lymphadenopathy (R + P).
- Infections were reported in 31% of subjects in the R + G group and 27% of subjects in the R + P group. No infections led to discontinuation of treatment in either group.
- No cases of tumor lysis syndrome were identified.
- Infusion-related reaction (galiximab-related event) was reported in 1 subject in the R + G group (Grade 2) and 1 subject in the R + P group (Grade 1). Grade 3 serum sickness (galiximab-related event) was reported in 1 subject in the R + G group and Grade 2 drug hypersensitivity (galiximab-related event) was reported in 1 subject in the R + P group.
- On infusion Day 1, 51% of subjects in the R + G group and 50% of subjects in the R + P group experienced an AE. The incidence of infusion-related reactions progressively decreased over the second, third, and fourth infusions.
- Severe reductions in absolute neutrophil count were observed in a small number of subjects and there was no clear differences in the incidence of these events between the R + G and the R + P group. A contribution from galiximab was not clearly established.
- The vast majority of subjects in both groups had unchanged or improved chemistry results throughout the study for the following parameters: creatinine, alkaline phosphatase, albumin, and total bilirubin. One-grade shifts in ALT and AST were reported in approximately 20% of subjects in both groups.
- There were no clear differences between groups in the incidence or magnitude of urinalysis findings.
- There were no clear differences between groups in the incidence or magnitude of vital signs findings.
- Serum immunoglobulin concentrations were evaluated up to Study Day 380 and remained within the normal range during this time period for both groups.
- At baseline, 319 subjects were tested for anti-galiximab antibodies and found to be negative. A total of 324 subjects were tested while on study. All of these subjects remained negative throughout the study.
- At baseline, 305 subjects were tested for anti-chimeric antibodies. Two hundred ninety-six subjects were negative, 8 subjects were positive, and 1 had insufficient sample for testing. All positive results reported at baseline were transient. Three hundred twenty-two subjects had at least 1 post-baseline test result reported: each of the 8 subjects with a positive result at baseline had at least 1 negative result reported after baseline; 7 subjects who were negative at baseline had at least 1 positive result reported after baseline; 1 subject had only 1 post-baseline result and the sample was insufficient for testing; the remaining 306 subjects were negative at all timepoints where results were available.

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Conclusions:

- Galiximab in combination with rituximab was observed to have improved PFS compared with rituximab alone and was well tolerated in subjects with relapsed/refractory follicular NHL. Although the primary efficacy endpoint did not reach the originally planned, 2-sided, 0.01 level of significance, which may be largely due to the early termination of the trial, the results support further studies to more fully assess the potential of galiximab for the treatment of NHL.

Publications Based on the Study: None

Date of Report: 27 September 2010