2. STUDY SYNOPSIS

Name of Sponsor/Company: 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: Lumiliximab (IDEC-152)	**Name of Active Ingredient:** Lumiliximab (IDEC-152)	**Study Indication:** Chronic lymphocytic leukemia

Title of Study:

A Randomized, Open-Label, Multicenter, Phase 2 Study to Evaluate the Safety and Efficacy of Lumiliximab in Combination with Fludarabine, Cyclophosphamide, and Rituximab Versus Fludarabine, Cyclophosphamide, and Rituximab Alone in Subjects with Relapsed Chronic Lymphocytic Leukemia

Study Period:	**Phase of Development:**
Date of first treatment: 22 January 2007 Date of early study termination: 18 February 2010 Last subject last visit: 07 April 2010	2

Study Objectives:

Study 152CL201 (LUCID) was designed to assess lumiliximab in combination with fludarabine, cyclophosphamide, and rituximab (FCR) in the treatment of patients with relapsed chronic lymphocytic leukemia (CLL). Based on a lack of sufficient efficacy shown in the second interim analysis for LUCID, a decision was made not to proceed to the final analysis and the study was terminated early. Efficacy results based on the second interim analysis on the final data and safety results for all subjects in the Safety Population are provided in this study report.

Primary objective:

- To determine the efficacy of lumiliximab when used in combination with FCR compared with FCR alone for the treatment of subjects with relapsed CLL.

Secondary objective:

- To evaluate and compare the safety profile of subjects treated with lumiliximab in combination with FCR (FCR+L) versus FCR alone in subjects with relapsed CLL.

Name of Sponsor/Company: 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: Lumiliximab (IDEC-152)	**Name of Active Ingredient:** Lumiliximab (IDEC-152)	**Study Indication:** Chronic lymphocytic leukemia

Study Design:

Study 152CL201 (LUCID) was intended to support registration using both CR and PFS endpoints. The study sample size and analysis plan were updated through subsequent protocol amendments with up to 900 subjects planned. In late 2009 following the first interim analysis, an Independent Data Monitoring Committee determined that there was a risk of the study being underpowered for the planned CR endpoint analysis (n= 390); recruitment into the study was stopped; and the protocol was amended to update the primary analysis to CR rate only (n =630). The second interim analysis showed that there was no benefit of adding lumiliximab to FCR; therefore, the study terminated early and lumiliximab development was stopped. Details of the changes to the study design are described in Section 9.8.1 and an overview is provided in Figure 9-1. The final study design was a randomized, multicenter, global, open-label, Phase 2 study of FCR+L versus FCR alone in subjects with relapsed CLL (according to the 1996 National Cancer Institute-Working Group criteria). Approximately 630 subjects were to be enrolled into this study, and randomized into 2 treatment groups in a 1:1 ratio, stratified by Rai Stage at study entry (I/II versus III/IV) and number of prior CLL treatment regimens (1 versus 2). Approximately 200 sites worldwide were to participate in this study.

Up to 3 analyses were to be performed during the study (2 interims and a final) to compare efficacy with respect to complete response (CR) rate. The first interim analysis was to be based on CR rates confirmed by computed tomography (CT) scan as assessed by an Independent Review Committee; the second interim analysis and the final analysis were to be based on Investigator-assessed CR rates without the use of CT scans. At the first interim analysis of 195 subjects through at least Week 33 or withdrawal from the study, whichever came first, a decision was to be made 1) to continue to the second interim analysis of the study, 2) to stop the study if comparisons indicate futility in terms of the CR rate for FCR+L compared to that of FCR alone or 3) to stop or amend the protocol for safety reasons. The second interim analysis was to be used to determine if the study should proceed to the final analysis based on whether the prespecified stopping boundary demonstrated sufficient efficacy as indicated by a p-value $\leq$0.05. If the results met the prespecified criteria, the study was to continue to the final analysis of 630 (100%) subjects through at least Week 33 or withdrawal from the study, whichever came first, and a more thorough analysis of the data was to be performed. If the results indicate a lack of efficacy (p-value >0.05), the study may not have continued to the final analysis.

The study period for each subject was to be from date of enrollment until all subjects had passed at least the Week 33 visit or had withdrawn from the study, whichever came first. The study treatment was to be delivered over six 28-day cycles. Cycle 1 was to include 1 stepped-up dose of either rituximab and lumiliximab (Treatment Group A) or rituximab (Treatment Group B) and 3 days of fludarabine and cyclophosphamide. Cycles 2 to 6 were to include either rituximab and lumiliximab (Treatment Group A) or rituximab (Treatment Group B), without stepped-up dosing, and 3 days of fludarabine and cyclophosphamide. Subjects were to have completed scheduled visits until all subjects had passed at least the Week 33 visit or had withdrawn from the study, whichever came first.

Based on the outcome of the second interim analysis, the decision was made not to proceed to the final analysis and the study was terminated early.

Name of Sponsor/Company: 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: Lumiliximab (IDEC-152)	**Name of Active Ingredient:** Lumiliximab (IDEC-152)	**Study Indication:** Chronic lymphocytic leukemia

Results:

Subject disposition:

Six hundred twenty-seven subjects were randomized and 615 subjects were dosed in this study: 310 subjects received FCR+L and 305 subjects received FCR only.

Subjects who completed the Week 33 visit or who were prematurely withdrawn due to early study termination were considered to have completed the study. Four hundred twenty three subjects (67%) completed the study and 204 subjects withdrew from the study for the following reasons: subsequent CLL therapy (60 subjects), withdrew consent (39 subjects), death (38 subjects), adverse events (AEs; 27 subjects), Investigator judgement (16 subjects), lost to follow up (15 subjects), and personal reasons (9 subjects).

Demographics and baseline disease characteristics:

- Demographics were similar for both treatment groups. Most subjects were white (94%) and male (70%), and they ranged in age from 34 to 82 years of age.
- Baseline disease characteristics were similar for both treatment groups, including subject distribution of the 2 stratification factors, Rai stage at study entry and number of prior CLL treatments.

Efficacy:

Due to the study terminating early based on the results of the second interim analysis, the primary endpoint of complete response (CR) rate and the secondary endpoints of best response, overall response rate (ORR), and duration of response (DR), were evaluated for the Interim Analysis #2 Efficacy Population. This population was defined as the first 390 intent-to-treat (ITT) subjects who had passed the Week 33 visit or had withdrawn from the study, whichever came first due to the study terminating early based on these results.

The secondary endpoints of progression-free survival (PFS) and overall survival (OS) were evaluated for the ITT Population, defined as all subjects randomized into the study (N = 627).

- The primary endpoint for evaluating efficacy was CR rate, assessed by the Investigator without the use of CT scans for the Interim Analysis #2 Efficacy Population. The CR rate showed no significant difference between the treatment groups: 33 (16%) subjects in the FCR+L treatment group and 28 (15%) subjects in the FCR treatment group (p-value = 0.782).
- The secondary efficacy endpoints analyzed were best response (CR, nodular partial response [nPR], partial response [PR], stable disease, progressive disease, unevaluable, or not evaluated) and ORR without CT scans; DR; PFS, and OS. ORR was defined as any best response of CR, nPR, or PR.
- As with the primary efficacy endpoint, the best response did not show a difference between the treatment groups.

Name of Sponsor/Company: 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: Lumiliximab (IDEC-152)	**Name of Active Ingredient:** Lumiliximab (IDEC-152)	**Study Indication:** Chronic lymphocytic leukemia

- The median DR (for subjects with a best response of CR/nPR/PR) was 27 months for subjects in the FCR+L treatment group and 24.5 months for subjects in the FCR treatment group.
- The median PFS was 24.6 months for subjects in the FCR+L treatment group and 23.9 months for subjects in the FCR treatment group.
- The median OS was not met for either treatment group due to the lack of sufficient follow-up after the early termination of the study.

Safety:

- Six hundred three (98%) subjects experienced an AE: 307 (99%) subjects in the FCR+L treatment group and 296 (97%) subjects in the FCR treatment group.
- There was a slight increase in the incidence of prolonged cytopenia (prolonged was defined as duration greater than 28 days and cytopenia was defined into 4 broad categories with each category consisting of multiple Medical Dictionary for Regulatory Activities preferred terms consistent with that category; categories were anemia, leukopenia and neutropenia, pancytopenia, and thrombocytopenia) in the FCR+L versus FCR treatment groups. Prolonged serious leukopenia and neutropenia occurred in 7 (2%) subjects in the FCR+L treatment group and in 1 (<1%) subject in the FCR treatment group; prolonged serious thrombocytopenia was observed in 3 (<1%) subjects in the FCR+L treatment group and 0 in the FCR treatment group; and prolonged serious pancytopenia was observed in 3 (<1%) subjects in the FCR+L treatment group and 2 (<1%) subjects in the FCR treatment group.
- There was a slight increase in the incidence of tumor lysis syndrome, occurring in 6 (2%) subjects in the FCR+L treatment group compared to 2 (<1%) subjects in the FCR treatment group. None of the tumor lysis syndrome events led to discontinuation of study treatment.
- There were no apparent differences in infections or infusion reactions in the FCR+L and FCR treatment groups.
- Overall, the severity of AEs was similar between the treatment groups: Grade 1, 2, 3,4, and 5 events were reported in 11 (4%) subjects, 38 (12%) subjects, 117 (38%) subjects, 126 (41%) subjects, and 15 (5%) subjects in the FCR+L treatment group, respectively, and 13 (4%) subjects, 34 (11%) subjects, 103 (34%) subjects, 124 (41%) subjects, and 22 (7%) subjects in the FCR treatment group, respectively.

Name of Sponsor/Company: 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: Lumiliximab (IDEC-152)	**Name of Active Ingredient:** Lumiliximab (IDEC-152)	**Study Indication:** Chronic lymphocytic leukemia

- Five hundred eighty-seven (95%) subjects experienced a study-related AE: 301 (97%) subjects in the FCR+L treatment group and 286 (94%) subjects in the FCR treatment group. Events occurring in 10% or more of subjects in either treatment group were: neutropenia (226 [73%] subjects in the FCR+L treatment group and 220 [72%] subjects in the FCR treatment group), nausea (127 [41%] subjects in the FCR+L treatment group and 111 [36%] subjects in the FCR treatment group), thrombocytopenia (94 [30%] subjects in the FCR+L treatment group and 84 [28%] subjects in the FCR treatment group), anemia (86 [28%] subjects in the FCR+L treatment group and 88 [29%] subjects in the FCR treatment group), vomiting (71 [23%] subjects in the FCR+L treatment group and 49 [16%] subjects in the FCR treatment group), pyrexia (69 [22%] subjects in the FCR+L treatment group and 59 [19%] subjects in the FCR treatment group), leucopenia (65 [21%] subjects in the FCR+L treatment group and 46 [15%] subjects in the FCR treatment group), fatigue (63 [20%] subjects in the FCR+L treatment group and 57 [19%] subjects in the FCR treatment group), febrile neutropenia (45 [15%] subjects in the FCR+L treatment group and 32 [10%] subjects in the FCR treatment group), chills (42 [14%] subjects in the FCR+L treatment group and 29 [10%] subjects in the FCR treatment group), infusion-related reaction (35 [11%] subjects in the FCR+L treatment group and 36 [12%] subjects in the FCR treatment group), and diarrhea (28 [9%] subjects in the FCR+L treatment group and 39 [13%] subjects in the FCR treatment group).
- Two hundred thirty-five (76%) of the 310 subjects who received lumiliximab experienced a lumiliximab-related AE. Events occurring in 10% or more of subjects were: neutropenia (150 [48%] subjects), nausea (75 [24%] subjects), thrombocytopenia (66 [21%] subjects), anemia (56 [18%] subjects), fatigue (47 [15%] subjects), pyrexia (40 [13%] subjects), leukopenia (37 [12%] subjects), and vomiting (34 [11%] subjects).
- Sixty-seven subjects died. Of those, 1 subject did not receive study treatment. Thirty-seven subjects had deaths related to an AE and 30 subjects had deaths not related to an AE. Lumiliximab-related AEs leading to death were reported for 6 subjects.
- Two hundred forty-four (40%) subjects experienced a treatment-emergent serious AE: 125 (40%) subjects in the FCR+L treatment group and 119 (39%) subjects in the FCR treatment group. Events reported by more than 1% of subjects in both treatment groups combined were febrile neutropenia (33 [11%] subjects in the FCR+L treatment group and 29 [10%] subjects in the FCR treatment group), pneumonia (12 [4%] subjects in the FCR+L treatment group and 13 [4%] subjects in the FCR treatment group), neutropenia (12 [4%] subjects in the FCR+L treatment group and 8 [3%] subjects in the FCR treatment group), pyrexia (10 [3%] subjects in the FCR+L treatment group and 18 [6%] subjects in the FCR treatment group), anemia (8 [3%] subjects in the FCR+L treatment group and 6 [2%] subjects in the FCR treatment group), and pancytopenia (6 [2%] subjects in the FCR+L treatment group and 5 [2%] subjects in the FCR treatment group).

Name of Sponsor/Company: 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: Lumiliximab (IDEC-152)	**Name of Active Ingredient:** Lumiliximab (IDEC-152)	**Study Indication:** Chronic lymphocytic leukemia

- One hundred eighty-three (30%) subjects who were treated discontinued study treatment due to an AE: 95 (31%) subjects in the FCR+L treatment group and 88 (29%) subjects in the FCR treatment group. The majority of subjects discontinued study treatment due to neutropenia and thrombocytopenia.
- Fifty-nine (10%) subjects who were treated reported AEs that led to withdrawal from the study: 27 (9%) subjects in the FCR+L treatment group and 32 (10%) subjects in the FCR treatment group. Of these 59 subjects, 13 of the 27 subjects in the FCR+L treatment group and 21 of the 32 subjects in the FCR treatment group had AEs that also led to death. Ten subjects had lumiliximab-related AEs.

Conclusion(s):

- The second interim analysis results failed to show sufficient efficacy with FCR+L when compared with FCR alone and the final analysis was not performed due to the study being terminated.
- The addition of lumiliximab to the FCR regimen was well tolerated; however, there was a slight increased incidence of SAEs of prolonged cytopenia and AEs of tumor lysis syndrome. These increases did not appear to lead to differences in key outcomes such as infections or fatalities. There were no unexpected findings, e.g., no unexpected AEs in the FCR+L treatment group compared with the FCR treatment group.
- Biogen Idec has decided not to pursue further development of lumiliximab in CLL.

Date of Report: 13 August 2010