

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**103948/0**

**APPROVABLE LETTER 1**

Our Reference Number: 99-0786

JUN 23 2000

Jacqueline J. Cinicola  
 Millennium & ILEX Partners, LP  
 75 Sidney Street  
 Cambridge, MA 02139

Dear Ms. Cinicola:

This letter is in regard to your biologics license application for Alemtuzumab submitted under section 351 of the Public Health Service Act. Reference is also made to our Information Request letter dated May 3, 2000.

The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this application. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

We have the following requests for additional information regarding study CAM-211:

1. Please provide, in tabular form, a **complete** follow-up for **all** patients enrolled on the study including the following: study site, patient number, Rai stage, objective response, date of initiation and completion of Alemtuzumab treatment, date of objective response if applicable, date of treatment failure if withdrawn from study for other than completion of therapy, date of progression if applicable, date of alternate treatment if applicable, date of death or date of last follow-up, and cause of death if dead. Please identify all values that are censored data points. Please provide a listing of all data changes made to the table as compared to the Follow-up Table in the 120 Day Safety Update. Please provide an electronic data set with this information that is SAS compatible, e.g., SAS transport file.
2. Please provide statistical analyses for the intent-to-treat (ITT) population, using the most recent information, for each of the following:
  - Complete, partial, and overall response rates and 95% confidence intervals for each rate;
  - Median time to response with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value;

(23)

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP	SUCKAPUPL		<del>GT</del>	<del>07/04</del>		DARP	DYON	6/23/00
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DARP	BRUCE	6-23-00	DUPA	WEIR	6/23			

- Median duration of response with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value;
- Median progression-free survival with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value;
- Median time to treatment failure analyses with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value; and,
- Median overall survival with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value.

Please include the results in a revised, updated clinical study report. For each analysis, clarify how you have handled missing data in the analysis.

3. Please provide a clinical benefit assessment, including the following information, for each patient identified as having a partial or complete response:

- Patient identifier;
- Rai stage at entry;
- Dates of Alemtuzumab therapy;
- Date of onset of response;
- Date of progression; and,
- Duration of response.

Include individual patient plots for:

- Performance status at baseline, during study, and during follow-up until progression;
- Hemoglobin (Hgb) at baseline, during study, and post-therapy until progression. The plot should be annotated to indicate the dose(s), dates, and duration of therapy with erythropoietin and the dates, type and number of units of blood products administered during and post therapy;

- Absolute neutrophil count (ANC) at baseline, during study, and post therapy until progression. The plot should be annotated to indicate the dose(s), dates, and duration of use of G-CSF or GM-CSF;
- Platelet counts at baseline, during study, and post therapy until progression. The plots should be annotated to indicate the date, number and type (i.e., random, single donor, HLA-matched) of platelet transfusions administered and the dose(s), dates and duration of platelet-growth factors administered;
- Absolute lymphocyte count (ALC) at baseline, during therapy, and post therapy until progression; and,
- CD4+ counts at baseline, during therapy, and post-therapy to the last available measurement.

Please provide information about all adverse events including infusion-related adverse events and all infections at baseline, during study, and post study until progression. Please include information on the use of parental or oral steroids. Please include a discussion of the clinical benefit for each patient after presentation of the above information and summarize the information for the entire group in a revised study report.

Please note that we differ in our determination of the individuals who have obtained a complete or partial response to Alemtuzumab therapy. The following patients are considered to have achieved an objective tumor response by the FDA: 001-005, 001-0041, 003-0049, 003-0095, 004-0055, 004-0092, 004-0097, 005-0013, 005-0035, 005-0039, 005-0099, 006-0023, 006-0027, 006-0032, 007-0003, 007-0006, 007-0007, 007-0029, 007-0091, 011-0014, 011-0037, 011-0042, 011-0047, 011-0048, 011-0050, 012-0011, 019-0065, 019-0069, 027-0062, and 027-0067.

4. We have identified instances where, based upon our review of the primary source documents, there are errors with regard to the reason for study drug discontinuation in the tabular listing of patients who have discontinued treatment. Please review this table and confirm that the reasons for study discontinuation listed in the table are consistent with the case report forms (CRFs) and primary source documents. If there are errors, this table must be revised and all relevant text and electronic data sets corrected.
5. Please provide a listing of all known hospitalizations for all study participants while on study and up to six months following Alemtuzumab therapy. Please include the patient identifier for all patients, indicate if hospitalizations occurred for each patient, and if so, provide the date(s) and reason(s) for the hospitalization(s). Please revise the study report to include a section that discusses hospitalization.

6. As you are aware, we have noted a number of errors in the information regarding transfusion information. Please provide accurate information for the type and number of transfusions during study. Please provide a corrected table for blood product usage and the reason for transfusion or other blood product use. Please revise the study report to include a discussion of the use of blood products.
7. Please provide an analysis of the change in the NCI CTC (version 2.0) Hgb toxicity grade from baseline during therapy (using two week intervals until the completion of therapy), and at 28 days post therapy for each objective response category (CR, PR, SD, PD, NE) for all patients and for the following subsets: patients who received transfusions during study and patients who did not receive transfusions during the study. Please provide a discussion of the results using descriptive statistics and include this information in the revised study report.
8. Please provide an analysis of the change in the NCI CTC ANC toxicity grade from baseline during therapy (using two week intervals until the completion of therapy), and at two months post therapy by objective response category for patients who received G-CSF or GM-CSF during the study. Please provide a separate analysis, done in the same manner, for patients who did not receive growth factors. Please provide a discussion of the results using descriptive statistics and include this information in the revised study report.
9. Please provide an analysis of the change in the NCI-CTC platelet toxicity grade from baseline during therapy (using two week intervals until the completion of therapy), and at two months post therapy for patients who received platelet transfusions during the study. Please provide a separate analysis for patients who did not receive platelet transfusions during the study. Please provide a discussion of the results using descriptive statistics and include this information in the revised study report.
10. Please provide a table that shows for every patient treated on this study, the date(s) of any omitted treatments and the reason(s) for the omission. Please discuss the results and revise the study report to include a section on treatment delays.
11. Please provide a tabulation of all infusion-related toxicities by one week intervals over the course of therapy according to the NCI-CTC scale for all patients who received systemic steroids and for those that did not. For each interval, provide the number of patients at risk (remaining on study) for that interval. Please discuss the results with regard to the incidence of infusion-related toxicities over the course of treatment and include this information in the revised study report.

12. Please revise the Patient Narratives (Deaths, Serious Adverse Events) to include the admitting complete blood count (CBC) including Hgb, white blood count (WBC), ANC, ALC, and platelet count and other pertinent laboratory information for any hospitalizations. Please review the narratives for accuracy and completeness and submit any narratives that are revised with a log of the changes made.
13. Please provide an analysis of the change in CD4+ counts by patient cohorts defined by the length of follow-up information (i.e. completion of study cohort, two month follow-up cohort, four month follow-up cohort, six-month follow-up cohort). Each cohort should include only those patients with complete information for all time points at which CD4+ was to be measured for that cohort. Each patient should be represented in only one cohort. Please provide a chronological listing of the information on lymphocyte subpopulations for each patient and indicate in that listing if the determination of lymphocyte subpopulations was not performed at the specified time points. Please discuss the results and include this information in the revised study report.

We have the following requests for additional information regarding study 005:

14. Please provide, in tabular form, complete follow-up for all patients with B-CLL treated on this study including the following: study site, patient number, Rai stage, objective response (independent review panel assessment), date of initiation and date of completion of Alemtuzumab treatment, date of objective response if applicable, date of alternative therapy if known, date of death or date of last follow-up, and cause of death if known. Please provide an electronic data set with this information that is SAS compatible.

Please note that the following patients included in the data set submitted for study 005 are considered by the FDA to have disease other than B-CLL: 002-009, 006-010, 007-005, 008-005, 015-001, 018-003, 018-005, and 008-016. If you consider these patients to have B-CLL and feel that they should remain in the data set, please provide source documentation that the disease at the time of study enrollment was B-CLL.

15. Please provide statistical analyses for the ITT population, using the most recent information, for each of the following:
  - Response rates for each category (CR, PR, stable disease, progressive disease and overall response rate) and 95% confidence intervals for each rate;
  - Median time to response with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value;

- Median duration of response with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value;
- Median progression-free survival with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value;
- Median time to treatment failure analyses with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value; and,
- Median overall survival with the range of values, 25% and 75% quartiles, and 95% confidence intervals around the median value.

Please include the results in a revised, updated clinical study report. For each analysis, clarify how you have handled missing data in the analysis.

16. Please review the tables in the BLA listing individual patient laboratory data and verify that all laboratory information for each patient is the same value as is reported in the CRF for that patient. For example, there are Hgb values in Table 16.2.8.1A that differ from the values cited in the CRFs.
17. This study does not provide any evidence of clinical benefit. Please provide a clinical benefit assessment, including the following information, for each patient identified as having a partial response:
  - Patient identifier;
  - Rai stage at entry (if < stage III, specify reason for treatment);
  - Dates of Alemtuzumab therapy;
  - Route of administration (subcutaneous, intravenous, or other) of Alemtuzumab therapy;
  - Dates of fludarabine treatment and the criteria met which satisfy the study definition of “refractoriness;”
  - Date of response;
  - Date of disease progression; and,
  - Duration of response.

Include individual patient plots for:

- Performance status at baseline, during study, and during follow-up until progression (or last follow-up);
- Hgb at baseline, during study, and post-therapy until progression with information about transfusion history and the use and duration of use of erythropoietin during and post therapy;
- ANC at baseline, during study, and post therapy until progression. Specify the dates, dosage and duration of use of G-CSF or GM-CSF on the plot;
- Platelet counts at baseline, during study, and post therapy until progression with platelet transfusion use clearly indicated and use of platelet-growth factors, if applicable; and
- ALC at baseline, during therapy, and post therapy until progression.

Please provide information about all adverse events including infusion-related adverse events and infections at baseline, during study, and post study until progression (or last follow-up) and include information on the use of parental or oral steroids. Please include a discussion of the clinical benefit for each patient after presentation of the above information and summarize the information for the entire group of objective responders.

18. Please revise the study report to include a thorough discussion of the use of blood products during the study. Please include information on pre-study transfusion requirements.
19. Provide an analysis of the change in WHO Hgb grade from baseline during therapy (using two-week intervals until the completion of therapy) and at 28 days post therapy for each objective response category (CR, PR, SD, PD, NE) for transfused patients. Please provide a separate analysis, done in the same manner, for patients who did not require transfusion. Please identify the patients who do not have baseline information. Please describe the data available for each patient, provide a discussion of the results using descriptive statistics, and include this information in the revised study report.
20. Please provide an analysis of the change in the WHO grade for ANC count from baseline during therapy (using two week intervals until the completion of therapy), and at 28 days post therapy by objective response category for patients who received G-CSF or GM-CSF during the study. Please provide a separate analysis done in the

same manner for patients who did not receive growth factors. Please provide a discussion of the results using descriptive statistics and include this information in the revised study report.

21. Provide an analysis of the change in WHO platelet grade from baseline during therapy (using two week intervals until the completion of therapy), and at two months post therapy by objective response category for patients who received platelet transfusions on study. Please provide a separate analysis using the same method for patients who did not receive platelet transfusions during the study. Please provide a discussion of the results using descriptive statistics and include this information in the revised study report.
22. Please provide a table that shows, for every patient treated on this study, the date(s) of any omitted treatments and the reason(s) for the omission and discuss the reasons for treatment delays.
23. Please revise the Patient Narratives (Deaths, Serious Adverse Events) to include the admitting CBC including Hgb, WBC, ANC, ALC, and platelet counts and other pertinent lab data at the time of any hospitalization or occurrence of any serious adverse event. Please review the narratives for accuracy and completeness. Please submit any narratives that are revised and provide a log of the changes made.
24. Revise all the Listings for Adverse Events and the Drug Related Adverse Events to accurately reflect the number of adverse events in the B-CLL patient population. We note that hematological toxicities are under-reported in the tables included in the original and updated submissions when compared to the data in the CRFs. Please revise the tables which report infections during, within 30 days, and at greater than 30 days post study to reflect the incidence in the B-CLL population.
25. Please provide documentation as to the site(s) of progression for the following patients who died from infection within 30 days of study drug discontinuation: 002-009, 009-004, 009-006, and 011-001.

We have the following requests for additional information regarding study 009:

26. Please provide a complete follow-up table for all patients enrolled on study including the following: study site, patient number, Rai stage, objective response, date of initiation and completion of Alemtuzumab treatment, date of objective response if applicable, date of treatment failure if withdrawn from study for other than completion of therapy, date of progression if applicable, date of alternate treatment if applicable,

date of death or date of last follow up, and cause of death if dead. Please indicate censoring and provide an electronic data set with this information that is SAS compatible.

27. Please provide a clinical benefit assessment, including the following information, for each partial responder:

- Patient identifier;
- Stage at entry (if < stage III, include the reason treatment was indicated);
- Dates of Alemtuzumab therapy;
- Criteria met which satisfy the study definition of fludarabine refractoriness;
- Date of response;
- Date of progression; and,
- Duration of response.

Please include individual patient plots for:

- Performance status at baseline, during study, and during follow-up until progression (or at last follow-up);
- Hgb at baseline, during study, and post-therapy until progression with information about transfusion history and the use and duration of use of erythropoietin during and post therapy;
- ANC at baseline, during study, and post therapy until progression with information about the use and duration of use of G-CSF or GM-CSF;
- Platelet counts at baseline, during study, and post therapy until progression with platelet transfusion use clearly indicated and use of platelet-growth factors if applicable;
- ALC at baseline, during therapy, and post therapy until progression; and,
- CD4+ counts at baseline, during therapy, and post-therapy to last measurement if available.

Please provide information about all adverse events including infusion-related adverse events and all infections at baseline, during study, and post study until progression. Please include information on the use of parental or oral steroids. Please include a discussion of the clinical benefit for each patient after presentation of the above information and summarize the information for the entire group.

28. Please provide a listing of all known hospitalizations for all study participants while on study and up to six months following Alemtuzumab therapy. Please include the patient identifier for all patients, indicate if hospitalizations occurred for each patient, and if so, provide the date(s) and reason(s) for the hospitalization(s). Please revise the study report to include a section that discusses hospitalization.
29. Please revise the study report to include a discussion of the use of blood products.
30. Provide an analysis of the change in NCI CTC (version 2.0) Hgb grade from baseline during therapy (using two week intervals until the completion of therapy), and at 28 days post therapy for each objective response category (CR, PR, SD, PD, NE) for transfused patients. Please provide a separate analysis, performed in the same manner, for non-transfused patients. Please identify the patients who do not have baseline information. Please describe the data available for each patient and provide a discussion of the results using descriptive statistics.
31. Please provide an analysis of the change in the NCI CTC grade for ANC count from baseline during therapy (using two week intervals until the completion of therapy), and at two months post follow up by objective response category for patients who received G-CSF or GM-CSF during the study. Please provide a separate analysis, done in the same manner, for patients who did not receive growth factors during the study. Please provide a discussion of the results using descriptive statistics and include this information in the revised study report.
32. Please provide an analysis of the change in NCI-CTC platelet grade from baseline over study (using two-week intervals until study completion), and at two months post therapy by each disease response category for patients who received platelet transfusions on study. Please provide a separate analysis, done in the same manner, for patients who did not receive platelet transfusions during the study. Please provide a discussion of the results using descriptive statistics and include this information in the revised study report.
33. Please provide a table that shows for every patient treated on this study the date(s) of any omitted treatments and the reason(s) for the omission.



withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, CBER may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

We acknowledge receipt of your amendment dated June 16, 2000. You may cross reference applicable sections of the amendment in your complete response to this letter and those sections will be reviewed as a part of your complete response.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Ms. Sharon\_Sickafuse, in the Division of Application Review and Policy at (301) 827-5101.

Sincerely yours,

Karen D. Weiss, M.D.  
Director  
Division of Clinical Trial Design  
and Analysis  
Office of Therapeutics  
Research and Review  
Center for Biologics  
Evaluation and Research

Kathryn E. Stein, Ph.D.  
Director  
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cc: HFM-515/P. Harris  
HFM-555/K. Webber  
HFM-555/K. Stein  
HFM-561/K. Brorson  
HFM-110/RIMS  
HFM-500/S. Risso  
HFM-500/J. Siegel  
HFM-585/G. Jones (Bimo comment 6-22-00)  
HFM-588/S. Sickafuse  
HFM-570/K. Weiss  
HFM-570/P. Keegan (Comments received 6-20-00 @ 5pm)  
HFM-573/G. Schechter (Comments received 6-20-00 @ 5pm)  
HFM-579/M. Green  
HFM-215/C. Gnecco  
HFM-650/L. Johnson  
HFM-675/W. Lange

OTRR:DARP:Sickafuse:6-20-00:6-21-00:dixon:6-21-00:69-23-00:sks:6-22-00:6-23-00  
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**MILESTONE: COMPLETE RESPONSE LETTER - (RL)**