

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 103948/5070

Trade Name: Campath

Generic Name: Alemtuzumab

Sponsor: Genzyme Corp.

Approval Date: September 19, 2007

Indications: Campath is a CD52-directed cytolytic antibody indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 103948/5070

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 103948/5070

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103948/5070

SEP 19 2007

Genzyme Corporation
Attention: Katherine O'Keefe, M.P.H.
Associate Director, Regulatory Affairs
4545 Horizon Hill Boulevard
San Antonio, TX 78229-2263

Dear Ms. O'Keefe:

Your request to supplement your biologics license application for Alemtuzumab (Campath) to expand the indication to include use as a single agent for treatment of B-cell chronic lymphocytic leukemia (B-CLL) has been approved.

We approved your biologics license application for treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy, under the regulations at 21 CFR 601 Subpart E for accelerated approval of biological products for serious or life-threatening illnesses. Approval of this supplement fulfills your commitment made under 21 CFR 601.41 to verify the clinical benefit of Alemtuzumab by conducting protocol CAM 307.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We acknowledge your written commitment to conduct a postmarketing study as described in your letter of September 19, 2007, as outlined below:

Postmarketing Study Commitment subject to reporting requirements of 21 CFR 601.70:

1. To conduct a QT study according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in approximately 50 subjects receiving Alemtuzumab by the subcutaneous route of administration. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by December 31, 2008, and will be completed by September 30, 2010. A final study report will be submitted by June 30, 2011. A supplement with revised labeling, if applicable, will be submitted by September 30, 2011.

We request that you submit the clinical protocol to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103948. Please use the following designators to

label prominently all submissions, including supplements, relating to the postmarketing study commitment as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.fda.gov/cder/pmc/default.htm>). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/cder/guidance/5569fnl.htm>) for further information.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 103948/5070." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

Sincerely,

A handwritten signature in black ink that reads "Patricia Keegan". The signature is written in a cursive style with a large initial "P".

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 103948/5070

OTHER ACTION LETTERS



Our STN: BL 103948/5070

MAY 30 2007

Genzyme Corporation
Attention: Katherine O'Keefe
Associate Director, Regulatory Affairs
4545 Horizon Hill Boulevard
San Antonio, TX 78229-2263

Dear Ms. O'Keefe:

Please refer to the supplement to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated May 18, 2007. While conducting our filing review we identified the following potential review issues:

Clinical

1. There are missing or nonfunctional hyperlinks in Table 14.3.3 "Narratives of Deaths, SAEs, and Discontinuations Due to AEs (page 673 of 1228 in Section 5.3.5.1)." Site-PTIDs of concern are 1003-1054 to 1402-1285. Please submit as an amendment to the supplement Table 14.3.3 with functioning hyperlinks. In addition, please confirm that all other hyperlinks in the submission have been confirmed to be fully functional.
2. We refer to the May 14, 2007, teleconference between representatives of your firm and Dr. Jeff Summers and Ms. Suzanne Demko of this Division, during which our questions regarding the organization of the EFF1 primary efficacy analysis dataset and definition of key variables were discussed. As described in your emails of May 16 and 17, 2007, you identified an error in "a subsetting statement in the SAS program" that allowed for missing values from some subjects. You agreed to correct this error and resubmit the data from the relevant datasets. You also indicated that nine analysis datasets are affected, including EFF1.

It is unclear to us whether this error is limited to these nine datasets only or if other datasets are also affected. We are concerned that other programming errors may have occurred during the data compilation and analysis process and that other datasets may be compromised. We request that you conduct a thorough re-examination and quality control of the data and submit results of such analysis as an amendment to BL STN 103948/5070 along with the corrected datasets.

___3___ Page (s) Withheld

___ Trade Secret / Confidential (b4)

______ Draft Labeling (b4)

___ Draft Labeling (b5)

___ Deliberative Process (b5)

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 supplement 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 supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Amy Gomez, R.N., M.S., at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Attachment: redlined package insert with FDA comments

35 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



Our STN: BL 103948/5070

MAY 18 2007

Genzyme Corporation
Attention: Katherine O'Keefe
Associate Director, Regulatory Affairs
4545 Horizon Hill Boulevard
San Antonio, TX 78229-2263

Dear Ms. O'Keefe:

This letter is in regard to your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated March 19, 2007 for Alemtuzumab (Campath) to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your supplement today. The user fee goal date is September 19, 2007. 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.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before June 2, 2007.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Amy Gomez, R.N., M.S., at (301) 796-2320.

Sincerely,

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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APPLICATION NUMBER:

BLA 103948/5070

LABELING

Approved 9.19.2007

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Campath® (alemtuzumab)
Injection for intravenous use
Initial U.S. Approval: 2001

WARNING: CYTOPENIAS, INFUSION REACTIONS, and INFECTIONS

See full prescribing information for complete boxed warning.

Serious, including fatal, cytopenias, infusion reactions and infections can occur (5.1 – 5.3).

- Limit doses to 30 mg (single) and 90 mg (cumulative weekly); higher doses increase risk of pancytopenia (2.1).
- Escalate dose gradually and monitor patients during infusion. Withhold therapy for Grade 3 or 4 infusion reactions (5.2).
- Administer prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and herpes virus infections (2.2, 5.3).

RECENT MAJOR CHANGES

Indications and Usage: Previously untreated B-CLL patients (1) 9/2007

INDICATIONS AND USAGE

Campath is a CD52-directed cytolytic antibody indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) (1).

DOSAGE AND ADMINISTRATION

- Administer as an IV infusion over 2 hours (2.1).
- Escalate to recommended dose of 30 mg/day three times per week for 12 weeks (2.1).
- Premedicate with oral antihistamine and acetaminophen prior to dosing (2.2).

DOSAGE FORMS AND STRENGTHS

30 mg/1 mL single use vial (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

Cytopenias:

- Obtain complete blood counts (CBC) and platelet counts at weekly intervals during therapy and CD4 counts after therapy until recovery to ≥ 200 cells/ μ L (5.4).
- Discontinue for autoimmune or severe hematologic adverse reactions (5.1).

Infections:

- Campath induces severe and prolonged lymphopenia and increases risk of infection. If a serious infection occurs, withhold treatment until infection resolves (5.3).
- Do not administer live viral vaccines to patients who have recently received Campath (5.5).

ADVERSE REACTIONS

Most common adverse reactions ($\geq 10\%$): cytopenias, infusion reactions, cytomegalovirus (CMV) and other infections, nausea, emesis, diarrhea, and insomnia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 **FULL PRESCRIBING INFORMATION**

WARNING: CYTOPENIAS, INFUSION REACTIONS, and INFECTIONS

Cytopenias: Serious, including fatal, pancytopenia/marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia can occur in patients receiving Campath. Single doses of Campath greater than 30 mg or cumulative doses greater than 90 mg per week increase the incidence of pancytopenia [see **WARNINGS AND PRECAUTIONS (5.1)**].

Infusion Reactions: Campath administration can result in serious, including fatal, infusion reactions. Carefully monitor patients during infusions and withhold Campath for Grade 3 or 4 infusion reactions. Gradually escalate Campath to the recommended dose at the initiation of therapy and after interruption of therapy for 7 or more days [see **DOSAGE AND ADMINISTRATION (2)** and **WARNINGS AND PRECAUTIONS (5.2)**].

Infections: Serious, including fatal, bacterial, viral, fungal, and protozoan infections can occur in patients receiving Campath. Administer prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and herpes virus infections [see **DOSAGE AND ADMINISTRATION (2.2)** and **WARNINGS AND PRECAUTIONS (5.3)**].

2

3 **1 INDICATIONS AND USAGE**

4 Campath is indicated as a single agent for the treatment of B-cell chronic lymphocytic
5 leukemia (B-CLL).

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Dosing Schedule and Administration**

8 • Administer as an IV infusion over 2 hours. **Do not administer as intravenous push**
9 **or bolus.**

10 • Recommended Dosing Regimen

11 ○ Gradually escalate to the maximum recommended single dose of 30 mg.
12 Escalation is required at initiation of dosing or if dosing is held ≥ 7 days
13 during treatment. Escalation to 30 mg ordinarily can be accomplished in 3 - 7
14 days.

- 15 ○ Escalation Strategy:
- 16 ○ Administer 3 mg daily until infusion reactions are \leq grade 2 [*see*
- 17 *ADVERSE REACTIONS (6.1)*].
- 18 ○ Then administer 10 mg daily until infusion reactions are \leq grade 2.
- 19 ○ Then administer 30 mg/day three times per week on alternate days (e.g.,
- 20 Mon-Wed-Fri). The total duration of therapy, including dose escalation, is
- 21 12 weeks.
- 22 ● **Single doses of greater than 30 mg or cumulative doses greater than 90 mg per**
- 23 **week increase the incidence of pancytopenia.**

24 2.2 Recommended Concomitant Medications

- 25 ● Premedicate with diphenhydramine (50 mg) and acetaminophen (500-1000 mg) 30
- 26 minutes prior to first infusion and each dose escalation. Institute appropriate
- 27 medical management (e.g. steroids, epinephrine, meperidine) for infusion reactions
- 28 as needed [*see BOXED WARNING, WARNINGS AND PRECAUTIONS (5.2) and*
- 29 *ADVERSE REACTIONS (6.1)*].
- 30 ● Administer trimethoprim/sulfamethoxazole DS twice daily (BID) three times per
- 31 week (or equivalent) as *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis.
- 32 ● Administer famciclovir 250 mg BID or equivalent as herpetic prophylaxis.
- 33 Continue PCP and herpes viral prophylaxis for a minimum of 2 months after completion
- 34 of Campath or until the CD4+ count is \geq 200 cells/ μ L, whichever occurs later [*see*
- 35 *BOXED WARNING and WARNINGS AND PRECAUTIONS (5.3)*].

36 2.3 Dose Modification

- 37 ● Withhold Campath during serious infection or other serious adverse reactions until
 - 38 resolution.
 - 39 ● Discontinue Campath for autoimmune anemia or autoimmune thrombocytopenia.
 - 40 ● There are no dose modifications recommended for lymphopenia.
-

41
42**Dose Modification for Neutropenia or Thrombocytopenia**[see *WARNINGS AND PRECAUTIONS (5.1)*]

<u>Hematologic Values</u>	<u>Dose Modification*</u>
ANC < 250/ μ L and/or platelet count \leq 25,000/ μ L	
For first occurrence:	Withhold Campath therapy. Resume Campath at 30 mg when ANC \geq 500/ μ L and platelet count \geq 50,000/ μ L.
For second occurrence:	Withhold Campath therapy. Resume Campath at 10 mg when ANC \geq 500/ μ L and platelet count \geq 50,000/ μ L.
For third occurrence:	Discontinue Campath therapy.
\geq 50% decrease from baseline in patients initiating therapy with a baseline ANC \leq 250/ μ L and/or a baseline platelet count \leq 25,000/ μ L	
For first occurrence:	Withhold Campath therapy. Resume Campath at 30 mg upon return to baseline value(s).
For second occurrence:	Withhold Campath therapy. Resume Campath at 10 mg upon return to baseline value(s).
For third occurrence:	Discontinue Campath therapy.

43 *If the delay between dosing is \geq 7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then
 44 to 30 mg as tolerated [see *DOSAGE AND ADMINISTRATION (2.1)*].
 45

46 **2.4 Preparation and Administration**

47 Parenteral drug products should be inspected visually for particulate matter and
 48 discoloration prior to administration. If particulate matter is present or the solution is
 49 discolored, the vial should not be used. **DO NOT SHAKE VIAL.**

50 Use aseptic technique during the preparation and administration of Campath. Withdraw
 51 the necessary amount of Campath from the vial into a syringe.

- 52 • To prepare the 3 mg dose, withdraw 0.1 mL into a 1 mL syringe calibrated in
 53 increments of 0.01 mL.
- 54 • To prepare the 10 mg dose, withdraw 0.33 mL into a 1 mL syringe calibrated in
 55 increments of 0.01 mL.
- 56 • To prepare the 30 mg dose, withdraw 1 mL in either a 1 mL or 3 mL syringe
 57 calibrated in 0.1 mL increments.

58 Inject syringe contents into 100 mL sterile 0.9% Sodium Chloride USP or 5% Dextrose
 59 in Water USP. **Gently invert the bag to mix the solution.** Discard syringe.

60 **The vial contains no preservatives and is intended for single use only. DISCARD**
61 **VIAL including any unused portion after withdrawal of dose.**

62 Use within 8 hours after dilution. Store diluted Campath at room temperature (15-30°C)
63 or refrigerated (2-8°C). Protect from light.

64 **2.5 Incompatibilities**

65 Campath is compatible with polyvinylchloride (PVC) bags and PVC or polyethylene-
66 lined PVC administration sets. Do not add or simultaneously infuse other drug substances
67 through the same intravenous line.

68 **3 DOSAGE FORMS AND STRENGTHS**

69 30 mg/1 mL single use vial

70 **4 CONTRAINDICATIONS**

71 None

72 **5 WARNINGS AND PRECAUTIONS**

73 **5.1 Cytopenias**

74 Severe, including fatal, autoimmune anemia and thrombocytopenia, and prolonged
75 myelosuppression have been reported in patients receiving Campath.

76 In addition, hemolytic anemia, pure red cell aplasia, bone marrow aplasia, and hypoplasia
77 have been reported after treatment with Campath at the recommended dose. Single doses
78 of Campath greater than 30 mg or cumulative doses greater than 90 mg per week increase
79 the incidence of pancytopenia.

80 Withhold Campath for severe cytopenias (except lymphopenia). Discontinue for
81 autoimmune cytopenias or recurrent/persistent severe cytopenias (except lymphopenia)
82 [*see DOSAGE AND ADMINISTRATION (2.3)*]. No data exist on the safety of Campath
83 resumption in patients with autoimmune cytopenias or marrow aplasia [*see ADVERSE*
84 *REACTIONS (6.1)*].

85 **5.2 Infusion Reactions**

86 Adverse reactions occurring during or shortly after Campath infusion include pyrexia,
87 chills/rigors, nausea, hypotension, urticaria, dyspnea, rash, emesis, and bronchospasm. In
88 clinical trials, the frequency of infusion reactions was highest in the first week of

89 treatment. Monitor for the signs and symptoms listed above and withhold infusion for
90 Grade 3 or 4 infusion reactions [see *ADVERSE REACTIONS (6.1)*].

91 The following serious, including fatal, infusion reactions have been identified in post-
92 marketing reports: syncope, pulmonary infiltrates, acute respiratory distress syndrome
93 (ARDS), respiratory arrest, cardiac arrhythmias, myocardial infarction, acute cardiac
94 insufficiency, cardiac arrest, angioedema, and anaphylactoid shock.

95 Initiate Campath according to the recommended dose-escalation scheme [see *DOSAGE*
96 *AND ADMINISTRATION (2)*]. Premedicate patients with an antihistamine and
97 acetaminophen prior to dosing. Institute medical management (e.g., glucocorticoids,
98 epinephrine, meperidine) for infusion reactions as needed [see *DOSAGE AND*
99 *ADMINISTRATION (2.2)*]. If therapy is interrupted for 7 or more days, reinstitute
100 Campath with gradual dose escalation [see *DOSAGE AND ADMINISTRATION (2.3)* and
101 *ADVERSE REACTIONS (6)*].

102 **5.3 Immunosuppression/Infections**

103 Campath treatment results in severe and prolonged lymphopenia with a concomitant
104 increased incidence of opportunistic infections [see *ADVERSE REACTIONS (6.1)*].
105 Administer PCP and herpes viral prophylaxis during Campath therapy and for a
106 minimum of 2 months after completion of Campath or until the CD4+ count is ≥ 200
107 cells/ μL , whichever occurs later [see *DOSAGE AND ADMINISTRATION (2.2)*].
108 Prophylaxis does not eliminate these infections.

109 Routinely monitor patients for CMV infection during Campath treatment and for at least
110 2 months following completion of treatment. Withhold Campath for serious infections
111 and during antiviral treatment for CMV infection or confirmed CMV viremia (defined as
112 polymerase chain reaction (PCR) positive CMV in ≥ 2 consecutive samples obtained 1
113 week apart) [see *ADVERSE REACTIONS (6.1)*]. Initiate therapeutic ganciclovir (or
114 equivalent) for CMV infection or confirmed CMV viremia [see *DOSAGE AND*
115 *ADMINISTRATION (2.3)*].

116 Administer only irradiated blood products to severely lymphopenic patients to avoid
117 Graft versus Host Disease (GVHD), unless emergent circumstances dictate immediate
118 transfusion.¹

119 In patients receiving Campath as initial therapy, recovery of CD4+ counts to ≥ 200
120 cells/ μL occurred by 6 months post-treatment; however at 2 months post-treatment, the

121 median was 183 cells/ μ L. In previously treated patients receiving Campath, the median
122 time to recovery of CD4+ counts to \geq 200 cells/ μ L was 2 months; however, full recovery
123 (to baseline) of CD4+ and CD8+ counts may take more than 12 months [see *BOXED*
124 *WARNING and ADVERSE REACTIONS (6)*].

125 **5.4 Laboratory Monitoring**

126 Obtain complete blood counts (CBC) at weekly intervals during Campath therapy and
127 more frequently if worsening anemia, neutropenia, or thrombocytopenia occurs. Assess
128 CD4+ counts after treatment until recovery to \geq 200 cells/ μ L [see *WARNINGS AND*
129 *PRECAUTIONS (5.3) and ADVERSE REACTIONS (6)*].

130 **5.5 Immunization**

131 The safety of immunization with live viral vaccines following Campath therapy has not
132 been studied. Do not administer live viral vaccines to patients who have recently received
133 Campath. The ability to generate an immune response to any vaccine following Campath
134 therapy has not been studied.

135 **6 ADVERSE REACTIONS**

136 The following adverse reactions are discussed in greater detail in other sections of the
137 label:

- 138 • Cytopenias [see *WARNINGS AND PRECAUTIONS (5.1)*]
- 139 • Infusion Reactions [see *WARNINGS AND PRECAUTIONS (5.2)*]
- 140 • Immunosuppression/Infections [see *WARNINGS AND PRECAUTIONS (5.3)*]

141 The most common adverse reactions with Campath are: infusion reactions (pyrexia,
142 chills, hypotension, urticaria, nausea, rash, tachycardia, dyspnea), cytopenias
143 (neutropenia, lymphopenia, thrombocytopenia, anemia), infections (CMV viremia, CMV
144 infection, other infections), gastrointestinal symptoms (nausea, emesis, abdominal pain),
145 and neurological symptoms (insomnia, anxiety). The most common serious adverse
146 reactions are cytopenias, infusion reactions, and immunosuppression/infections.

147 **6.1 Clinical Trials Experience**

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

151 The data below reflect exposure to Campath in 296 patients with CLL of whom 147 were
152 previously untreated and 149 received at least 2 prior chemotherapy regimens. The
153 median duration of exposure was 11.7 weeks for previously untreated patients and 8
154 weeks for previously treated patients.

155 *Lymphopenia:* Severe lymphopenia and a rapid and sustained decrease in lymphocyte
156 subsets occurred in previously untreated and previously treated patients following
157 administration of Campath. In previously untreated patients, the median CD4+ was 0
158 cells/ μ L at one month after treatment and 238 cells/ μ L [25-75% interquartile range 115
159 to 418 cells/ μ L at 6 months post-treatment [see *WARNINGS AND PRECAUTIONS*
160 (5.3)].

161 *Neutropenia:* In previously untreated patients, the incidence of Grade 3 or 4 neutropenia
162 was 42% with a median time to onset of 31 days and a median duration of 37 days. In
163 previously treated patients, the incidence of Grade 3 or 4 neutropenia was 64% with a
164 median duration of 28 days. Ten percent of previously untreated patients and 17% of
165 previously treated patients received granulocyte colony stimulating factors.

166 *Anemia:* In previously untreated patients, the incidence of Grade 3 or 4 anemia was 12%
167 with a median time to onset of 31 days and a median duration of 8 days. In previously
168 treated patients, the incidence of Grade 3 or 4 anemia was 38%. Seventeen percent of
169 previously untreated patients and 66% of previously treated patients received either
170 erythropoiesis stimulating agents, transfusions or both.

171 *Thrombocytopenia:* In previously untreated patients, the incidence of Grade 3 or 4
172 thrombocytopenia was 14% with a median time to onset of 9 days and a median duration
173 of 14 days. In previously treated patients, the incidence of Grade 3 or 4
174 thrombocytopenia was 52% with a median duration of 21 days. Autoimmune
175 thrombocytopenia was reported in 2% of previously treated patients with one fatality.

176 *Infusion reactions:* Infusion reactions, which included pyrexia, chills, hypotension,
177 urticaria, and dyspnea, were common. Grade 3 and 4 pyrexia and/or chills occurred in
178 approximately 10% of previously untreated patients and in approximately 35% of
179 previously treated patients. The occurrence of infusion reactions was greatest during the
180 initial week of treatment and decreased with subsequent doses of Campath. All patients
181 were pretreated with antipyretics and antihistamines; additionally, 43% of previously
182 untreated patients received glucocorticoid pre-treatment.

183 *Infections:* In the study of previously untreated patients, patients were tested weekly for
184 CMV using a PCR assay from initiation through completion of therapy, and every 2
185 weeks for the first 2 months following therapy. CMV infection occurred in 16% (23/147)
186 of previously untreated patients; approximately one-third of these infections were serious
187 or life threatening. In studies of previously treated patients in which routine CMV
188 surveillance was not required, CMV infection was documented in 6% (9/149) of patients;
189 nearly all of these infections were serious or life threatening.

190 Other infections were reported in approximately 50% of patients across all studies. Grade
191 3 - 5 sepsis ranged from 3% to 10% across studies and was higher in previously treated
192 patients. Grade 3 - 4 febrile neutropenia ranged from 5 to 10% across studies and was
193 higher in previously treated patients. Infection-related fatalities occurred in 2% of
194 previously untreated patients and 16% of previously treated patients. There were 198
195 episodes of other infection in 109 previously untreated patients; 16% were bacterial, 7%
196 were fungal, 4% were other viral, and in 73%, the organism was not identified.

197 *Cardiac:* Cardiac dysrhythmias occurred in approximately 14% of previously untreated
198 patients. The majority were tachycardias and were temporally associated with infusion;
199 dysrhythmias were Grade 3 or 4 in 1% of patients.

200 *Previously Untreated Patients*

201 Table 1 contains selected adverse reactions observed in 294 patients randomized (1:1) to
202 receive Campath or chlorambucil as first line therapy for B-CLL. Campath was
203 administered at a dose of 30 mg intravenously three times weekly for up to 12 weeks.
204 The median duration of therapy was 11.7 weeks with a median weekly dose of 82 mg
205 (25-75% interquartile range: 69 mg – 90 mg).

Table 1

Per Patient Incidence of Selected ¹ Adverse Reactions in Treatment Naive B-CLL Patients					
		Campath (n=147)		Chlorambucil (n=147)	
		All Grades ² %	Grades 3-4 %	All Grades %	Grades 3-4 %
Blood and Lymphatic System Disorders	Lymphopenia	97	97	9	1
	Neutropenia	77	42	51	26
	Anemia	76	13	54	18
	Thrombocytopenia	71	13	70	14
General Disorders and Administration Site Conditions	Pyrexia	69	10	11	1
	Chills	53	3	1	0
Infections and Infestations	CMV viremia ³	55	4	8	0
	CMV infection	16	5	0	0
	Other infections	74	21	65	10
Skin and Subcutaneous Tissue Disorders	Urticaria	16	2	1	0
	Rash	13	1	4	0
	Erythema	4	0	1	0
Vascular Disorders	Hypotension	16	1	0	0
	Hypertension	14	5	2	1
Nervous System Disorders	Headache	14	1	8	0
	Tremor	3	0	1	0
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	14	4	7	3
Gastrointestinal Disorders	Diarrhea	10	1	4	0
Psychiatric Disorders	Insomnia	10	0	3	0
	Anxiety	8	0	1	0
Cardiac Disorders	Tachycardia	10	0	1	0

207 ¹Adverse reactions occurring at a higher relative frequency in the Campath arm

208 ²NCI CTC version 2.0 for adverse reactions; NCI CTCAE version 3.0 for laboratory values

209 ³CMV viremia (without evidence of symptoms) includes both cases of single PCR positive test results and of
210 confirmed CMV viremia (≥ 2 occasions in consecutive samples 1 week apart). For the latter, ganciclovir (or
211 equivalent) was initiated per protocol.

212 Previously Treated Patients

213 Additional safety information was obtained from 3 single arm studies of 149 previously
214 treated patients with CLL administered 30 mg Campath intravenously three times weekly
215 for 4 to 12 weeks (median cumulative dose 673 mg [range 2 – 1106 mg]; median duration
216 of therapy 8.0 weeks). Adverse reactions in these studies not listed in Table 1 that

217 occurred at an incidence rate of > 5% were fatigue, nausea, emesis, musculoskeletal pain,
218 anorexia, dysesthesia, mucositis, and bronchospasm.

219 **6.2 Immunogenicity**

220 As with all therapeutic proteins, there is potential for immunogenicity. Using an ELISA
221 assay, anti-human antibodies (HAHA) were detected in 11 of 133 (8.3%) previously
222 untreated patients. In addition, two patients were weakly positive for neutralizing activity.
223 Limited data suggest that the anti-Campath antibodies did not adversely affect tumor
224 response. Four of 211 (1.9%) previously-treated patients were found to have antibodies
225 to Campath following treatment.

226 The incidence of antibody formation is highly dependent on the sensitivity and specificity
227 of the assay. Additionally, the observed incidence of antibody (including neutralizing
228 antibody) positivity in an assay may be influenced by several factors including assay
229 methodology, sample handling, timing of sample collection, concomitant medications,
230 and underlying disease. For these reasons, comparison of the incidence of antibodies to
231 Campath with the incidence of antibodies to other products may be misleading.

232 **6.3 Postmarketing Experience**

233 The following adverse reactions were identified during post-approval use of Campath.
234 Because these reactions are reported voluntarily from a population of uncertain size, it is
235 not always possible to reliably estimate their frequency or establish a causal relationship
236 to Campath exposure. Decisions to include these reactions in labeling are typically based
237 on one or more of the following factors: (1) seriousness of the reaction, (2) reported
238 frequency of the reaction, or (3) strength of causal connection to Campath.

239 Fatal infusion reactions: [see *WARNINGS AND PRECAUTIONS (5.2)*].

240 Infections: Epstein-Barr Virus (EBV), Progressive Multifocal Leukoencephalopathy
241 (PML).

242 Immune disorders: Goodpasture's syndrome, Graves' disease, aplastic anemia, Guillain
243 Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, serum
244 sickness.

245 Cardiovascular: cardiomyopathy, decreased ejection fraction (in patients previously
246 treated with cardiotoxic agents).

247 Metabolic: Tumor lysis syndrome

248 Neurologic: Optic neuropathy

249 **7 DRUG INTERACTIONS**

250 No formal drug interaction studies have been performed with Campath.

251 **8 USE IN SPECIFIC POPULATIONS**

252 **8.1 Pregnancy**

253 **Pregnancy Category C**

254 Animal reproduction studies have not been conducted with Campath. IgG antibodies,
255 such as Campath, can cross the placental barrier. It is not known whether Campath can
256 cause fetal harm when administered to a pregnant woman or can affect reproduction
257 capacity. Campath should be given to a pregnant woman only if clearly needed.

258 **8.3 Nursing Mothers**

259 Excretion of Campath in human breast milk has not been studied; it is not known whether
260 this drug is excreted in human milk. IgG antibodies, such as Campath, can be excreted in
261 human milk. Because many drugs are excreted in human milk and because of the
262 potential for serious adverse reactions in nursing infants from Campath, a decision should
263 be made whether to discontinue nursing or to discontinue the drug, taking into account
264 the elimination half-life of Campath and the importance of the drug to the mother.

265 **8.4 Pediatric Use**

266 Safety and effectiveness have not been established in pediatric patients.

267 **8.5 Geriatric Use**

268 Of 147 previously untreated B-CLL patients treated with Campath, 35% were \geq age 65
269 and 4% were \geq age 75. Of 149 previously treated patients with B-CLL, 44% were \geq 65
270 years of age and 10% were \geq 75 years of age. Clinical studies of Campath did not include
271 sufficient number of subjects age 65 and over to determine whether they respond
272 differently than younger subjects. Other reported clinical experience has not identified
273 differences in responses between the elderly and younger patients.

274 **10 OVERDOSAGE**

275 Across all clinical experience, the reported maximum single dose received was 90 mg.
276 Bone marrow aplasia, infections, or severe infusions reactions occurred in patients who
277 received a dose higher than recommended.

278 One patient received an 80 mg dose by IV infusion and experienced acute bronchospasm,
279 cough, and dyspnea, followed by anuria and death. Another patient received two 90 mg
280 doses by IV infusion one day apart during the second week of treatment and experienced
281 a rapid onset of bone marrow aplasia.

282 There is no known specific antidote for Campath overdose. Treatment consists of drug
283 discontinuation and supportive therapy.

284 **11 DESCRIPTION**

285 Campath (alemtuzumab) is a recombinant DNA-derived humanized monoclonal antibody
286 (Campath-1H) directed against the 21-28 kD cell surface glycoprotein, CD52. Campath-
287 1H is an IgG1 kappa antibody with human variable framework and constant regions, and
288 complementarity-determining regions from a murine (rat) monoclonal antibody
289 (Campath-1G). The Campath-1H antibody has an approximate molecular weight of 150
290 kD. Campath is produced in mammalian cell (Chinese hamster ovary) suspension culture
291 in a medium containing neomycin. Neomycin is not detectable in the final product.

292 Campath is a sterile, clear, colorless, isotonic solution (pH 6.8-7.4) for injection. Each
293 single use vial of Campath contains 30 mg alemtuzumab, 8.0 mg sodium chloride, 1.44
294 mg dibasic sodium phosphate, 0.2 mg potassium chloride, 0.2 mg monobasic potassium
295 phosphate, 0.1 mg polysorbate 80, and 0.0187 mg disodium edetate dihydrate. No
296 preservatives are added.

297 **12 CLINICAL PHARMACOLOGY**

298 **12.1 Mechanism of Action**

299 Campath binds to CD52, an antigen present on the surface of B and T lymphocytes, a
300 majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. A
301 proportion of bone marrow cells, including some CD34⁺ cells, express variable levels of
302 CD52. The proposed mechanism of action is antibody-dependent cellular-mediated lysis
303 following cell surface binding of Campath to the leukemic cells.

304 **12.3 Pharmacokinetics**

305 Campath pharmacokinetics were characterized in a study of 30 previously treated B-CLL
306 patients in whom Campath was administered at the recommended dose and schedule.

307 Campath pharmacokinetics displayed nonlinear elimination kinetics. After the last 30 mg
308 dose, the mean volume of distribution at steady-state was 0.18 L/kg (range 0.1 to 0.4
309 L/kg). Systemic clearance decreased with repeated administration due to decreased
310 receptor-mediated clearance (i.e., loss of CD52 receptors in the periphery). After 12
311 weeks of dosing, patients exhibited a seven-fold increase in mean AUC. Mean half-life
312 was 11 hours (range 2 to 32 hours) after the first 30 mg dose and was 6 days (range 1 to
313 14 days) after the last 30 mg dose.

314 Comparisons of AUC in patients ≥ 65 years (n=6) versus patients < 65 years (n=15)
315 suggested that no dose adjustments are necessary for age. Comparisons of AUC in female
316 patients (n=4) versus male patients (n=17) suggested that no dose adjustments are
317 necessary for gender.

318 The pharmacokinetics of Campath in pediatric patients have not been studied. The effects
319 of renal or hepatic impairment on the pharmacokinetics of Campath have not been
320 studied.

321 **13 NONCLINICAL TOXICOLOGY**

322 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

323 No long-term studies in animals have been performed to establish the carcinogenic or
324 mutagenic potential of Campath, or to determine its effects on fertility in males or
325 females.

326 **14 CLINICAL STUDIES**

327 **14.1 Previously Untreated B-CLL Patients**

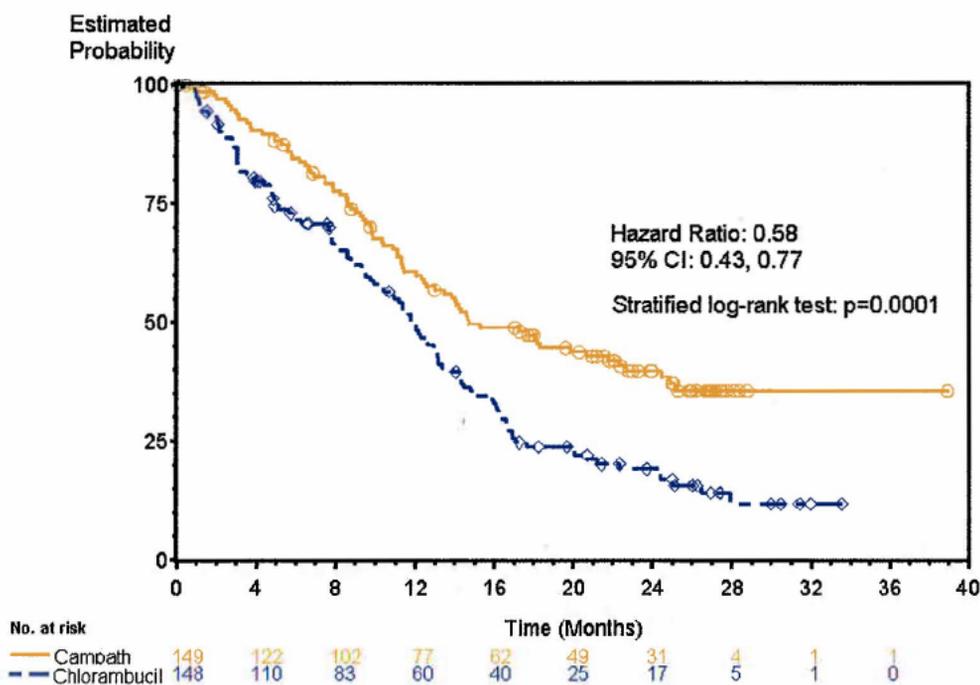
328 Campath was evaluated in an open-label, randomized (1:1) active-controlled study in
329 previously untreated patients with B-CLL, Rai Stage I-IV, with evidence of progressive
330 disease requiring therapy. Patients received either Campath 30 mg IV 3 times/week for a
331 maximum of 12 weeks or chlorambucil 40 mg/m² PO once every 28 days, for a maximum
332 of 12 cycles.

333 Of the 297 patients randomized, the median age was 60 years, 72% were male, 99% were
334 Caucasian, 96% had a WHO performance status 0-1, 23% had maximum lymph node

335 diameter ≥ 5 cm, 34% were Rai Stage III/IV, and 8% were treated in the U.S.
 336 Patients randomized to receive Campath experienced longer progression free survival
 337 (PFS) compared to those randomized to receive chlorambucil (median PFS 14.6 months
 338 vs. 11.7 months, respectively). The overall response rates were 83% and 55% ($p <$
 339 0.0001) and the complete response rates were 24% and 2% ($p < 0.0001$) for Campath and
 340 chlorambucil arms, respectively. The Kaplan-Meier curve for PFS is shown in **Figure 1**.

341 **Figure 1**

342 **Progression Free Survival in Previously Untreated B-CLL Patients¹**



344 ¹ Log-rank test adjusted for Rai Stage (I-II vs. III-IV).

345 **14.2 Previously Treated B-CLL Patients**

346 Campath was evaluated in three multicenter, open-label, single arm studies of 149
 347 patients with B-CLL previously treated with alkylating agents, fludarabine, or other
 348 chemotherapies. Patients were treated with the recommended dose of Campath, 30 mg
 349 intravenously, three times per week for up to 12 weeks. Partial response rates of 21 to
 350 31% and complete response rates of 0 to 2% were observed.

351 **15 REFERENCES**

352 ¹ American Association of Blood Banks, America's Blood Centers, American Red Cross.
 353 Circular of Information for the Use of Human Blood and Blood Components. July 2002.

354 **16 HOW SUPPLIED/STORAGE AND HANDLING**

355 Campath (alemtuzumab) is supplied in single-use clear glass vials containing 30 mg of
356 alemtuzumab in 1 mL of solution. Each carton contains three Campath vials (NDC
357 50419-357-03) or one Campath vial (NDC 50419-357-01).

358 Store Campath at 2-8°C (36-46°F). Do not freeze. If accidentally frozen, thaw at 2-8°C
359 before administration. Protect from direct sunlight.

360 **17 PATIENT COUNSELING INFORMATION**

361 *Cytopenias:* Advise patients to report any signs or symptoms such as bleeding, easy
362 bruising, petechiae or purpura, pallor, weakness or fatigue [see *WARNINGS AND*
363 *PRECAUTIONS (5.1)* and *ADVERSE REACTIONS (6.1)*].

364 *Infusion Reactions:* Advise patients of the signs and symptoms of infusion reactions and
365 of the need to take premedications as prescribed [see *WARNINGS AND PRECAUTIONS*
366 *(5.2)* and *OVERALL ADVERSE REACTIONS (6.1)*].

367 *Infections:* Advise patients to immediately report symptoms of infection (e.g. pyrexia)
368 and to take prophylactic anti-infectives for PCP (trimethoprim/sulfamethoxazole DS or
369 equivalent) and for herpes virus (famciclovir or equivalent) as prescribed [see
370 *WARNINGS AND PRECAUTIONS (5.3)* and *ADVERSE REACTIONS (6.1)*].

371 Advise patients that irradiation of blood products is required until adequate lymphocyte
372 recovery [see *WARNINGS AND PRECAUTIONS (5.3)*].

373 Advise patients that they should not be immunized with live viral vaccines if they have
374 recently been treated with Campath [see *WARNINGS AND PRECAUTIONS (5.5)*].

375 Advise male and female patients with reproductive potential to use effective
376 contraceptive methods during treatment and for a minimum of 6 months following
377 Campath therapy [see *NONCLINICAL TOXICOLOGY (13.1)*].

378 U.S. Patents: 5,846,534; 6,569,430

379 Manufactured by: Genzyme Corporation, Cambridge, MA 02142

380 Distributed by: Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ 07470

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 103948/5070

OFFICE DIRECTOR MEMO

Division Director Decisional Review

Date	September 17, 2007
From	Patricia Keegan, M.D. <i>Patricia Keegan</i> 9-19-2007
Subject	Division Director Decisional Review
BLA Supp #	BL STN 103948/5070
Proprietary / Established (USAN) names	Campath® /alemtuzumab
Dosage forms / strength	30 mg/1 mL single use vial
Proposed Indication(s)	Campath is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL).
Action	Approval

1. Introduction to Review

This supplement to the Biologics Application License (BLA) for Alemtuzumab seeks to expand labeling to include initial (first-line) treatment of chronic lymphocytic leukemia (CLL) and to provide verification of the clinical benefit of alemtuzumab in support of conversion from accelerated to regular approval. The primary data supporting this supplement is obtained from the CAM 307 Study, a commercially sponsored, multinational, 297- patient, randomized (1:1), open-label study of Campath versus chlorambucil in patients with progressive, previously untreated B-cell CLL. Patients randomized to receive Campath experienced significantly longer progression-free survival (PFS) compared to those randomized to receive chlorambucil (median PFS 14.6 months vs. 11.7 months, respectively). Patients randomized to Campath also demonstrated significantly better outcomes on secondary endpoints of tumor response rates. The overall response rates were 83% and 55% ($p < 0.0001$) and the complete response rates were 24% and 2% ($p < 0.0001$) for Campath and chlorambucil arms, respectively. The results of this study were highly significant and the direction of the effects (superior PFS) was consistent across major subgroups, although not statistically significantly different in all subgroups (e.g., age \geq 65 yrs).

Given the robustness of the results and consistency across major subgroups, including significant differences within subgroups defined by gender and Rai stage, as well as the data supporting the initial accelerated approval, a single study is deemed sufficient to establish efficacy for the initial treatment of B-cell CLL and to verify clinical benefit. Issues to be discussed in subsequent sections of this review memo raised in the review include:

- the relevance of the control arm, single agent chlorambucil
- the use of progression-free survival as the primary efficacy endpoint, with lack of long-term survival data

- Extrapolation of the results to the United States (U.S.) population, given that only 10% of the study population was enrolled in the U.S.

(b) (4)

- (b) (4)

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2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Alemtuzumab (Campath[®]) was approved on May 7, 2001 as a single agent for the treatment of chronic lymphocytic leukemia, following treatment with alkylating agents and fludarabine. The approval was based on the surrogate endpoint of durable overall response rates. The magnitude of the response rate (approximately 30% in one primary and two supportive single arm studies) and durability of effect were similar to that used to support accelerated approval of fludarabine, a drug approved in 1991 for the palliative treatment of patients with B-cell lymphocytic leukemia (CLL) who have not responded or have progressed during treatment with at least one standard alkylating agent containing regimen.

Alemtuzumab is the first agent in several decades to be considered for approval for the initial treatment of B-cell CLL. Fludarabine, while widely used in the U.S. for the initial treatment of B-cell CLL, does not have an approved indication for this use. Similarly, Rituximab, which is approved for the treatment of low-grade, follicular, and CD20+ diffuse large cell lymphoma, is commonly used in the US as a component of initial therapy for the treatment of B-cell CLL but is not labeled for this use. Until the approval of newer agents in 1990s, alkylating agents, particularly chlorambucil, were the primary treatment option for B-cell CLL.

3. CMC/Microbiology/Device

CMC information in the application was limited to a request for categorical exclusion for environmental assessment [under 21 CFR 25.31 (b)] and validation data for assays used to detect immune responses (binding and neutralizing anti-Campath antibodies) and to measure CD52 expression. The claim for categorical exclusion was accepted. The assay methodology was determined to be acceptable and the results from these assays valid for inclusion in product labeling.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies or relevant information (literature reports) provided in the supplement and none were deemed necessary for review of this supplement.

5. Clinical Pharmacology/Biopharmaceutics

The application contained no new information on pharmacokinetics of the product, thus there was no opportunity to evaluate the pharmacology of Campath in special populations, effects on QT, or impact of anti-Campath antibodies on pharmacology. Evaluations of safety, of pharmacodynamic effects (circulating lymphocyte counts), and of efficacy did not reveal important differences among subgroups defined by age, gender, or presence of an immune response and the effects on PFS as determined by the hazard ratio, while differing in magnitude and level of statistical significance, were in the same direction consistently favoring the Campath arm.

Serial sampling for anti-alemtuzumab antibodies (screening for binding antibodies and, in those patients whose serum was seropositive for binding antibodies, an assessment for neutralizing antibodies) was performed at baseline and at 1, 2, and 6 months post-completion of Campath administration for patients randomized to the alemtuzumab in Study CAM 307. Samples were tested for $\geq 75\%$ of patients in the Alemtuzumab arm at 1 and at 2 months post-treatment and samples were assessed for nearly 70% of patients in the Alemtuzumab arm at 6 months post-treatment. The results demonstrated that the incidence of anti-Campath antibodies were 0.8% at baseline (0.8%) and 8.3% post-treatment. The incidence of anti-Campath antibody development in previously untreated patients with CLL (CAM 307 participants) is than that observed in the 211 heavily pre-treated patients with CLL enrolled in the studies supporting original licensure. The lower incidence in heavily pretreated patients may be a reflection on a more severely immunocompromised state either due to more advanced CLL stage and/or prior anti-cancer therapy.

In comparing outcomes of patients enrolled in CAM 307 and randomized to Alemtuzumab, there were no apparent differences in safety, pharmacodynamic outcomes or activity (as assessed by achievement of objective tumor responses) in patients with and those without anti-alemtuzumab antibodies. The data were reviewed under BL STN 103948.5072, which is the final study report for PMC #4 in the approval letter of May 7, 2001 (below). The clinical pharmacology, medical, and CMC reviewers all concur that these data are sufficient to fulfill PMC #4.

PMC 4

"[to conduct] A quantitative analysis of the incidence and magnitude of HAHA and anti-idiotypic antibodies at study entry and following exposure to Alemtuzumab."

In addition, serial sampling to determine the qualitative presence of CD52 expression of circulating lymphocytes was performed at 1, 2, and 6 months post-completion of Campath administration among patients randomized to the either arm in Study CAM 307. This sampling was conducted to assess the mechanism of loss of responsiveness to Campath

and to determine whether this was correlated with CD52-negative status at the time of progressive disease. Because the natural history of CD52 expression (and loss of expression) in relapsed/refractory B-cell CLL is not known, CD52 expression was assessed in both study arms. Since sampling occurred at fixed intervals rather than following disease progression, assessments for CD52 expression at the time of disease progression, defined post-hoc by FDA as within 30 days preceding or following IRRP-confirmed disease progression, was available in fewer than half the patients with disease progression in the Campath arm. There was differential ascertainment in the two treatments arms for CD52 determination at relapse. At the time of disease progression, CD52 expression data were provided for 31 patients among the 82 patients with a PFS event (38%) in the Alemtuzumab arm compared to CD52 expression data for 75 patients among the 109 patients with a PFS event (69%) in the chlorambucil arm.

(b) (4)

(b) (4)

The applicant has not provided information at the time of initial approval or within this supplement to the BLA regarding the impact of alemtuzumab on the QT interval. The Agency has requested and Genzyme has agreed to conduct a study to assess such effects in approximately 50 patients receiving alemtuzumab as a post-marketing commitment to this approval. Further discussion will consider the optimal route of administration for such a study (IV vs. SC routes), sample size, and number of sampling time points; these will be addressed by the division in consultation with the IRT at the time of protocol submission.

6. Clinical/Statistical

6.1. General Discussion

The primary efficacy endpoint of the CAM 307 trial was progression-free survival, which has been accepted by the Agency as an appropriate measure of clinical benefit in the initial treatment of indolent B-cell lymphomas as well as the related disease, B-cell CLL, because of the long survival times of such patients. Given the open-label nature of the study, the Agency asked for independent verification of the endpoints of PFS and response rates. The applicant constituted an independent endpoint review panel (IRRP), which determined endpoints through a review of certain primary source documents (bone marrow histology reports, laboratory data including flow cytometry) and investigator-generated tumor measurements. This hybrid review is not a truly

independent assessment because of the reliance on investigator-reported tumor measurements and presence/absence of B-symptoms (fever, night sweats, weight loss), however the IRRP review of objective measures of hematologic parameters was a critical component of the assessment and more important to disease status determinations than in other cancers.

Comparative assessments of survival were requested to evaluate for potential drug toxicity resulting in adverse survival. Longer-term survival studies were requested to assess for potential survival benefit, however the applicant has declined to extend follow-up and no data regarding the long-term effects on alemtuzumab on survival are expected from this study. The Agency's thinking on the need for long-term survival data has evolved since the design of the study and, given the magnitude of the effect on PFS and lack of impact on survival in the short-term, the need to demonstrate effects on overall survival are not required for determination of net benefit in this supplement.

As noted above, there was agreement on the primary (PFS) and key secondary endpoints (response rate, duration of response, and overall survival). The applicant identified two additional secondary endpoints which were not acceptable to the Agency: time to treatment failure and time to alternative therapy. The statistical analysis plan for the protocol did not contain adjustments for testing of these latter two secondary endpoints, which were nonetheless reported by the applicant in the clinical study report. Time to treatment failure has not been accepted as a valid measure of benefit because it is a composite endpoint combining events that measure efficacy (progression) with those that are measures of safety (drug discontinuation for adverse events). Time to alternative therapy, which under carefully controlled circumstances is felt by experts in the treatment of CLL to be a measure of clinical benefit, was not considered a valid endpoint in this study for several reasons. These reasons include the open label nature of the study (lack of control for investigator and patient bias in determining timing of next treatment) and the failure to pre-specify for uniform criteria for initiation of next treatment (to minimize the subjectivity of initiation of subsequent therapy). Since this endpoint was measured from time of randomization, the differences in duration of treatment between the two study arms (12 weeks vs. 1 year) would have been predicted to favor the control rather than the treatment arm, although effective alemtuzumab exposures persist for months following the last dose, as demonstrated by pharmacodynamic effects on lymphocyte counts.

6.2. Efficacy

(b)

(4)



6.2.2. Phase 3/essential clinical studies, including design and analytic features

At the time of approval, a post-marketing commitment to verify clinical benefit was required; the study design was agreed upon in concept at approval although the protocol was not finalized until several months following approval. One area of particular concern to the Agency was the control arm selected by the applicant, single agent chlorambucil, which represented an appropriate and clinically relevant standard. The Agency recommended that fludarabine be used as the control based on its increasing acceptance in the medical community as the standard treatment for previously untreated CLL at the time of the Campath approval. Although the choice of the control may not have been optimal, the design of the study was determined by the Agency as acceptable to isolate the effects of alemtuzumab and provide direct comparisons to an active agent for treatment of CLL. The results of CAM 307 clearly establish that this is an effective drug with an acceptable toxicity profile.

The control arm posed by the applicant (at that time, not Genzyme) impacted study accrual in the United States where fludarabine, initially as a single agent and subsequently as a component of combination chemotherapy with cyclophosphamide with or without rituximab, became widely adopted in the U.S. in that first-line setting. The design of CAM 307 does not permit direct comparisons of the safety and efficacy of single agent alemtuzumab to these more commonly used agents and combination treatment regimens. Such data will be obtained in ongoing, Genzyme-sponsored or supported clinical trials, which may also provide data on the safety and efficacy of introduction of alemtuzumab into combination chemotherapy regimens.

Although conducted primarily outside of the US, the results of the CAM 307 trial can be extrapolated to the US population as there are no regional differences in the disease diagnosis or prognosis which would preclude such extrapolation.

An additional area, which will also be assessed in ongoing clinical trials, is the safety and efficacy of alemtuzumab administration by the subcutaneous route, which has become widely adopted in the United States.

6.2.3. Other efficacy studies

The supplement contained the results of a single clinical study. No additional studies were reviewed or considered by the Agency in the review of this application.

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions
The medical and statistical review team (primary and secondary reviewers) recommended approval and there were no differences of opinion on this recommendation across the review team.

6.2.5. Pediatric use/PREA waivers/deferrals
Campath was granted orphan drug designation for the treatment of chronic lymphocytic leukemia. Therefore, the provisions of PREA are not applicable. B-cell CLL is a disease primarily of the 5th-7th decades of life, however is has also been reported in younger adults. Because this disease does not occur in children, the Agency has not requested that the applicant voluntarily agree to conduct studies in pediatric patients.

6.2.6. Notable issues

(b) (4)



6.3. Safety

6.3.1. General safety considerations

The safety experience from this study was an advance over prior single arm studies and post-marketing experience in terms of carefully collected assessments and internal controls. The sample size was not adequate to detect adverse reactions occurring in up to 1% of patients but is sufficient to detect events occurring in up to 5% of patients, which is an acceptable level of characterization given the magnitude of the benefit observed, to conclude that there is net clinical benefit. There were no previously unidentified safety signals identified in this study, although the CAM 307 study provided better characterization of infusion reactions, particularly with respect to cardiac instability and dysrhythmias.

6.3.2. Safety findings from submitted clinical trials

No new safety signals were identified in CAM 307. The study design (randomized, internal control) allowed an assessment of alemtuzumab toxicity against the background of the disease setting and an active agent with a fairly low level of toxicity for an anti-cancer agent. The most common toxicities were those noted in the prior single-arm, single agent studies of alemtuzumab in relapsed/refractory CLL; these were infusion reactions (pyrexia, chills, hypotension, urticaria, nausea, rash, tachycardia, dyspnea), cytopenias (neutropenia, lymphopenia, thrombocytopenia, anemia), infections (CMV viremia, CMV infection, and a mixture of bacterial, viral, and other infections), gastrointestinal symptoms (nausea, emesis, abdominal pain), and neurological

symptoms (insomnia, anxiety). The most common serious adverse reactions were cytopenias, infusion reactions, and infections. There were 27 patients (18%) in the alemtuzumab arm and 11 patients (7%) in the chlorambucil arm who discontinued study treatment for an adverse reaction. The most common reasons for treatment termination in the Alemtuzumab arm were CMV reactivation (6%), infusion reactions (5%), cardiac events (3%), and cytopenias (3%).

As noted in trials of previously treated patients with CLL, the incidence and severity of infusion reactions was highest during the first week of treatment and while generally managed by control of the infusion rate and premedication, in at least 5% of patients, it was the primary reason for terminating treatment prematurely.

Cytopenias were both more frequent and more severe than in the control (chlorambucil) arm in this population of treatment-naïve CLL patients, although less common and less often severe than in heavily pre-treated CLL. The clinical course of alemtuzumab-induced cytopenias is characterized by later onset and more prolonged duration than that seen with either for alkylating agents or fludarabine. In particular, severe lymphopenia occurs within hours to days of the first dose of Alemtuzumab and persists for an average of 6 months post-treatment. Despite the frequent nature, cytopenias resulting in hospitalization, transfusions, or inpatient medical intervention was uncommon (<10% of patients) in patients with previously untreated CLL.

The overall incidence of infections was 50% across all studies, with a higher incidence among heavily pretreated patients. With the exception of CMV infection identified by serology, the causative organism was not identified in the majority of cases of infection in CAM 307. It should be noted that all patients in the alemtuzumab arm received prophylactic antibiotics for PCP and Herpes virus throughout the active treatment period until recovery from severe lymphopenia. The incidence of CMV infection and confirmed viremia (both of which required treatment with ganciclovir or an equivalent agent and interruption or termination of alemtuzumab) was 16%; such events were serious in nature in approximately 5% of patients. This incidence should be judged in the context of the clinical trial (in which all patients were monitored weekly for CMV with qualitative PCR testing during treatment and every other week for two months after termination of alemtuzumab treatment).

6.3.3. Safety update

No new findings were provided in the safety update which impacted the assessment of Alemtuzumab's net clinical benefit.

6.3.4. Immunogenicity

Serial serum samples were collected, at baseline, during and at multiple time points following alemtuzumab administration, as part of the prespecified

monitoring plan for the CAM 307 studies. These data were intended to fulfill post-marketing commitment #4 cited in the May 7, 2001 approval letter for alemtuzumab (BL STN 103948/0). The PMC 4 was "[to conduct] A quantitative analysis of the incidence and magnitude of HAHA and anti-idiotypic antibodies at study entry and following exposure to Alemtuzumab". While the clinical data were collected and provided in this supplement and incorporated into the final product labeling resulting from the approval, the data are also being reviewed under a separate submission for the final study report for this PMC (103948/5072), which cross-references the data in this supplement.

There were no apparent differences in efficacy, adverse event profile, or pharmacodynamic activity of Campath among those with a documented immune response compared to those without such a response, however due to the small numbers of patients with immune responses, a definitive conclusion cannot be made regarding the impact (or lack of impact) of immune responses on patient outcomes. The incidence of anti-Campath binding antibodies was 0.8% at baseline and 8.3% within 6 months after the last dose of treatment. This rate (8.3%) of anti-product antibody responses is higher than has been reported for other humanized monoclonal antibodies and within the range of anti-product antibody responses typically observed with chimeric antibodies. Because the incidence of anti-product immune responses is a function of the co-morbid medical conditions and the nature of concomitant therapy (both of which may suppress immune responses) and the route of administration (subcutaneous route being associated with the higher rates of immunogenic responses compared with intravenous routes for the same product). (b) (4)

6.3.5. Special safety concerns: none

6.3.6. Discussion of primary and secondary reviewers' comments and conclusions

The review staff concluded that the adverse reactions observed were manageable and tolerable when alemtuzumab is administered in accordance with product labeling. The toxicity profile of alemtuzumab is dominated by infusion reactions, for which the incidence and severity are greatest during the first week of treatment, cytopenias, and infectious complications, most notably CMV viremia and infection. Physicians who treat patients with cancer are experienced in diagnosis, management and supportive care of cytopenias. The atypical aspects of cytopenias from Campath are the time to onset and duration of cytopenias, which are adequately described in product labeling. Similarly, infections are a common toxicity of chemotherapeutic agents and of other agents used to treat CLL; specifically, the incidence, type, and severity of infections resulting from alemtuzumab are also seen with fludarabine, and to a lesser extent with Rituximab. These risks are also adequately described in product labeling.

6.3.7. Notable issues: None

6.4. Clinical Microbiology

No clinical microbiology data were contained within the application nor was such data considered necessary for the review of the application.

7. Advisory Committee Meeting

This supplement was not presented to the Oncologic Drugs Advisory Committee because of the robust findings of the effects on PFS in light of the generally acceptable toxicity profile. The general design of this study was discussed in two ODAC meetings held on the general topic of required Phase 4 post-marketing commitments for cancer drugs granted accelerated approval. Slow accrual to the Phase 4 study and issues raised at the second of these meetings (choice of control arm, relevance of the data given current first-line treatment approaches in the US) were considered by the Agency and discussed in section 6 of this review memo.

8. Risk Minimization Action Plan

At this time, a Risk Minimization Action Plan is not required. There are three issues for which a risk minimization plan might be considered: minimization of the risks of overdosage, of the risks of CMV infection, and the potential risks of subcutaneous administration with increased immunogenicity. All of these issues are being addressed by other mechanisms than a Risk-MAP, as discussed below.

In review of post-marketing reports submitted to update product labeling with regard to drug overdosage section, multiple reports of overdosage have been reported since 2002. The majority of these consisted of a medication error resulting in a single dose administered at 3-fold higher (90 mg rather than 30 mg) than intended. The next most common error consisted of failure to gradually escalate to the 30 mg dose. Because of these reports, special attention was directed towards revision of the Dosage and Administration section of the package insert for greater clarity. The effectiveness of this will be monitored through post-marketing reports.

The risks of CMV infection have been addressed through product labeling, including recommendations for routine CMV surveillance and directions for prophylactic and therapeutic anti-viral administration as utilized in the CAM 307 trial. The applicant

(b) (4)

The final issue is the potential for increased immunogenic responses to Campath with off-label routes of administration. The applicant has stated that clinical studies evaluated the safety (including immunogenicity) (b) (4)

(b) (4)

9. Other Regulatory Issues

There are no outstanding regulatory issues, including concerns regarding the Application Integrity Policy (AIP) or exclusivity/patent issues

10. Financial Disclosure

Information regarding financial disclosures was provided for the majority of the ~~investigators and statements of conflicts of interest from the IRRP members.~~ There was no evidence of financial conflicts and given the small number of patients accrued at most clinical sites, little ability of one or a small number of investigators to affect the clinical study results. The two clinical sites with the largest number of patients accrued were inspected by the BioResearch Monitoring staff, who concluded that the data were reliable.

11. Labeling

11.1. Proprietary name: No concerns or new issues were identified

11.2. Physician labeling:

The following is a brief listing of major issues that were ultimately resolved and the reasons for the FDA recommendations for product labeling.

- (b) (4)

- (b) (4)

- (b) (4)

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

11.3. Carton and immediate container labels: No problems noted

11.4. Patient labeling/Medication guide:
Neither patient labeling nor medication was considered necessary at this time.

(b) (4)

12. DSI Audits

Bioresearch monitoring audits were conducted at two of the highest accruing sites. The inspections revealed errors which were deemed to warrant voluntary action only. Both the FDA field auditor, DSI, and the medical officer considered the violations identified to be minor and not to affect the overall conclusions of the study.

13. Conclusions and Recommendations

13.1. Regulatory action:

All members of the review team recommended approval and there were no areas of disagreement between review team members or between primary and secondary reviewers. Approval is based on demonstration of a clinically important and highly significant (robust) prolongation in progression-free survival with an acceptable level of toxicity in the clinical setting of previously untreated B-cell CLL.

13.2. Safety concerns to be followed post-marketing: None

13.3. Risk Minimization Action Plan: None

13.4. Post-marketing studies

13.4.1. Required studies: none

13.4.2. Commitments (PMCs):

The Agency requested, and the applicant agreed, to conduct a study intended to assess the effects, if any, of alemtuzumab on the QT interval. This study is requested as a routine part of drug development and characterization of product safety and is not requested due to specific concerns regarding product safety.

13.4.3. Other agreements: None

13.5. Summary of reviewers' comments:

All reviewers recommended approval for the reasons documented above.

(b) (4) [REDACTED]. Evaluation of post-marketing commitment #4, which appears to have been fulfilled, will be completed under the cross-referenced supplement.

13.6. Comments to be conveyed to the applicant:

None. See approval Sept. 19, 2007 approval letter and attached final draft product labeling.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 103948/5070

MEDICAL REVIEW



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

CLINICAL REVIEW

Application Type: BLA
Submission Number: 103948/5070
Submission Code: PAS

Letter Date: March 19, 2007
Stamp Date: March 20, 2007
PDUFA Goal Date: September 19, 2007

Reviewer Name: Suzanne G. Demko, P.A.-C., Senior Clinical Analyst, DBOP, OODP
Through : Jeff Summers, M.D., Team Leader, DBOP, OODP
Through: Patricia Keegan, M.D., Division Director, DBOP, OODP

Review Completion Date: September 12, 2007

Established Name: Alemtuzumab
Trade Name: Campath®
Therapeutic Class: Humanized Monoclonal Antibody
Applicant: Genzyme Corporation

Priority Designation: P

Formulation: Single-use 1 mL vials containing 30 mg alemtuzumab

Dosing Regimen: Initial dose/dose escalation: 3 mg IV over 2 hours on day 1 as tolerated, then increase to 10 mg IV over 2 hours on day 2 as tolerated, then increase to 30 mg IV over 2 hours on day 3 as tolerated. Target dose is 30 mg IV per day 3 times per week on alternate days for a maximum of 12 weeks.

Indication: Single agent treatment of B-cell chronic lymphocytic leukemia (B-CLL)

Intended Population: Patients with B-cell chronic lymphocytic leukemia

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer to grant the approval of this Biological License Application efficacy supplement, STN 103948/5070, for conversion of Campath® to regular approval as a single agent for treatment of B-cell Chronic Lymphocytic Leukemia (B-CLL). Confirmation of clinical benefit in this application is based on analyses of data from a Phase III, open label, international, multicenter, randomized trial of Campath versus chlorambucil for subjects with B-CLL, Rai stage I-IV, who were previously untreated and experiencing progression of disease requiring treatment at time of study entry.

Assessment of benefit is based on a primary endpoint of progression free survival (PFS) in an intent-to-treat population as determined by an independent response review panel (IRRP). Review of the clinical data indicated a statistically significant improvement in PFS for Campath compared to chlorambucil. Campath prolonged the median progression free interval by 88 days (2.9 months) with an log-rank p-value adjusted for Rai stage group of 0.0001. Campath also demonstrated increased overall and complete response rates when compared to chlorambucil. The overall response rate was 83% for subjects treated with Campath and 55% for subjects treated with chlorambucil ($p < 0.0001$). The complete response rate was 24% for subjects treated with Campath and 2% for subjects treated with chlorambucil ($p < 0.0001$). No survival benefit was demonstrated.

The safety profile for Campath was based on analyses of the experiences of 147 subjects treated. Results were consistent with current product labeling. No new safety signals were identified. The most common and serious adverse reactions associated with Campath were cytopenias, infusion reactions, and infections.

A determination of clinical benefit in this subject population was based on response to treatment, a prolonged treatment free interval and symptom control.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

Pharmacovigilance/Safety Reporting: The Applicant will continue to provide annual progress reports as required under 21CFR§ 601.70.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Campath (Alemtuzumab) is a recombinant DNA-derived humanized IgG1 kappa monoclonal antibody (Campath-1H) specific for the cell surface glycoprotein CD52 expressed on normal and malignant human peripheral blood B and T lymphocytes as well as NK cells, monocytes, macrophages, and other tissues. The mechanism of action for Campath is not completely understood, but involves a number of effects including complement-mediated cell lysis, antibody-dependent cellular toxicity and induction of apoptosis.

FDA granted Campath accelerated approval on May 7, 2001 for the treatment of patients with B-cell chronic lymphocytic leukemia who had been treated with alkylating agents and who had failed fludarabine therapy. The approval was contingent upon post-marketing commitments by the applicant, including a trial to confirm clinical benefit. CAM 307, "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Campath (alemtuzumab) versus Chlorambucil in Patients with Progressive B-cell Chronic Lymphocytic Leukemia" was submitted as the confirmatory efficacy trial and is the subject of this supplemental Biological License Application.

CAM 307 was a Phase III, open label, international, multicenter, randomized (1:1), comparative trial for patients with previously untreated, Rai stage I-IV B-CLL experiencing progression of their disease requiring treatment. The primary endpoint for the study was progression free survival (PFS) and the primary analysis was based upon intent-to-treat, defined as all randomized patients. The study randomized 297 patients.

1.3.2 Efficacy

The primary efficacy endpoint for CAM 307 was progression free survival (PFS) as determined by an independent response review panel (IRRP). Analyses were performed on an intent-to-treat (ITT) population. Based upon the primary analysis, Campath demonstrated increased efficacy by prolonging the median progression free interval by 88 days (2.9 months) when compared to chlorambucil (medians: 445 days/14.6 months vs. 357 days/11.7 months). The log-rank p-value adjusted for Rai stage group was 0.0001 with an estimated hazard ratio of 0.58 (95% CI 0.43, 0.77). Campath also demonstrated increased overall and complete response rates when compared to chlorambucil. The overall response rate was 83% for subjects treated with Campath and 55% for subjects treated with chlorambucil ($p < 0.0001$). The complete response rate was 24% for subjects treated with Campath and 2% for subjects treated with chlorambucil ($p < 0.0001$). No survival benefit was demonstrated.

For a full discussion of FDA's efficacy analyses, please refer to the Office of Pharmacoepidemiology and Statistical Science, Office of Biostatistics Review.

1.3.3 Safety

The safety profile for Campath was described in detail in BLA STN 103948/0. Included in the analyses were three single arm clinical trials in 149 subjects with previously treated B-cell chronic lymphocytic leukemia (B-CLL). Synopses of these legacy data were submitted with the current application and re-examined during this review cycle. New clinical data

was submitted from 294 previously untreated B-CLL subjects who received either Campath (147) or chlorambucil (147) during the conduct of CAM307, a randomized, multi-center trial. These data were reviewed and analyzed to assess safety. No new safety signals were identified. The results were consistent with current product labeling.

Key safety findings:

For subjects receiving Campath, 95.9% experienced one or more adverse events and 18.3% of these subjects discontinued treatment as a result. For subjects receiving chlorambucil, 75.5% experienced one or more adverse events and 7.4% discontinued treatment as a result.

Infusion reactions associated with Campath were common in spite of subject premedication with diphenhydramine and acetaminophen. Most common were pyrexia (69.4%), chills (53.1%), nausea (17.7%), headache (14.3%), hypotension (16.3%), urticaria (15.6%), dyspnea (13.6%), rash (12.9%), vomiting (10.9%), and tachycardia (9.5%).

CMV infection was reported in 15.6% of subjects. CMV viremia was reported in 55.8% of subjects treated with Campath and 44% of these subjects were treated with antivirals.

There was an increase in incidence rates for cytopenias in subjects treated with Campath. Decrease to NCI CTCAE version 3 grade 3 or 4 absolute lymphocyte count (ALC) was reported in 98.6% of subjects treated with Campath and 2.8% treated with chlorambucil. Lymphocyte subsets during Campath treatment fell to zero. CD4+ lymphocyte recovery after treatment with Campath was prolonged with a median recovery time of six months. Decrease to grade 3 or 4 absolute neutrophil count (ANC) was reported in 44.5% of Campath treated subjects and 27.1% of subjects treated with chlorambucil. White blood cell counts (WBC) were decreased to grade 3 or 4 in 62.6% of subjects treated with Campath and 1.4% treated with chlorambucil.

Cardiac events related to Campath infusion were clinically meaningful. Within two days of receiving Campath 13.6% of subjects experienced one or more cardiac events. The majority were rhythm disturbances, specifically tachycardia, sinus tachycardia and supraventricular extrasystole. There was one grade 4 cardiac arrest, one grade 4 sinus bradycardia, one grade 2 angina pectoris, and one grade 1 cyanosis reported on the date of Campath infusion.

Anti-human antibodies (HAHA) were detected in 11 of 133 subjects (8.3%) tested. Two subjects with detectable anti-Campath antibody titers were also weakly positive when analyzed for neutralizing antibodies.

1.3.4 Dosing Regimen and Administration

The recommended dosing scheme for Campath is an initial dose of 3 mg as an intravenous (IV) infusion administered over 2 hours daily until infusion-related side effects are tolerated then increasing to 10 mg IV over 2 hours daily until infusion-related side effects are tolerated. The target dose is 30 mg IV over 2 hours 3 times per week on alternate days for a total of 12 weeks. As a result of side effects associated with Campath infusion, current approved labeling recommends patients receive pre-medication with an antihistamine and acetaminophen prior to Campath dosing, and be monitored closely for infusion reactions.

1.3.5 Drug-Drug Interactions

No data are available concerning the incompatibility of Campath with other drug

substances. No formal drug interaction studies were performed during the conduct of the study submitted in support of this application.

1.3.6 Special Populations

Pediatric

Information from the published medical literature is available on the treatment of children with Campath. However, the indication supported in this application occurs almost exclusively in adults.

Age

In legacy studies of subjects with previously treated B-CLL age 65 and older compared to subjects less than 65, there were no substantial differences in safety and efficacy observed. In subgroup analyses of the 53 previously untreated subjects \geq age 65 treated with Campath during CAM 307, PFS was not significantly different when compared to subjects \geq age 65 treated with chlorambucil. A median PFS of 381 days/12.7 months was observed for subjects \geq age 65 treated with Campath versus 380 days/12.66 months for chlorambucil. The log-rank p-value was 0.1187 with a hazard ratio of 0.68 (95% CI: 0.418, 1.107). No new safety signals were identified during CAM 307 for subjects \geq age 65 treated with Campath.

Clinical studies of Campath did not include sufficient number of subjects age 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between older and younger subjects.

Gender

There were 213 male and 84 female subjects treated during CAM 307. There were 105 male and 43 female subjects treated with Campath and 107 male and 41 female subjects treated with chlorambucil. The ratio of male to female subjects enrolled was not dissimilar to the demographic distribution of the B-CLL population where the ratio of males to females with the disease is 2:1. There was an unequal distribution of censoring for females on the study (Campath 58% and chlorambucil 24.4%). The median PFS for females treated with Campath was 758 days (25.3 months) versus 357 days (11.9 months) for chlorambucil with a p-value of 0.0129 by log-rank test and a hazard ratio of 0.482 (95% CI: 0.268, 0.868). For males, the median PFS for Campath was 428 days (14.3 months) versus 364 days (12.1 months) for chlorambucil with a p-value of 0.0046 by log-rank test and a hazard ratio of 0.621 (95% CI: 0.445, 0.866).

With regard to safety, males experienced higher rates of common Campath related adverse events than females for pyrexia (65.4% vs. 60.5%), CMV viremia (58.7% vs. 41.9%), neutropenia (10.6% vs. 4.7%), and chills (51.9% vs. 46.5%) while females experienced higher rates of CMV infection (18.6% vs. 10.6%), hypotension (18.6% vs. 12.5%), and urticaria (20.9% vs. 12.5%).

Race

The small number of subjects enrolled in CAM 307 who were not Caucasian (one in each treatment arm) did not allow for informative efficacy or safety analyses to be performed in this subpopulation.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

For detailed product information, please refer to the original BLA (STN 103948/0)

Generic Name:	alemtuzumab
Trade Name:	Campath [®]
Pharmacological Category:	Cytolytic antibody-CD52 directed
New Molecular Entity:	No
Drug Class:	Recombinant humanized monoclonal antibody
Route of Administration:	Intravenous
Dose and Regimen:	Initiate at a dose of 3 mg IV over 2 hours daily until tolerated then 10 mg IV over 2 hours daily until tolerated, then at a target dose of 30 mg IV over 2 hours 3 times per week on alternate days for up to 12 weeks
Population Studied:	Adult patients with previously untreated progressive B-cell Chronic Lymphocytic Leukemia

2.2 Currently Available Treatment for Indications

Chronic lymphocytic leukemia (CLL) is a clonal malignancy of mature lymphocytes exhibiting prolonged cell survival and leading to an expanded mature lymphocyte compartment. In 95% of cases the cell affected is of B-cell lineage. Chronic lymphocytic leukemia is the most common adult leukemia in Western countries accounting for approximately 25% of all diagnosed cases. In the United States alone there are over 10,000 new diagnoses per year. The median age at diagnosis is 70 years. The ratio of males to females who develop CLL is 2:1. The estimated death rate per year from CLL is 1.6:100,000. CLL is not curable with current available therapies and has an overall median survival from diagnosis of approximately six years.

Progressive CLL is defined as one or more of the following: an increase of 50% or more in the size of lymph nodes, spleen, or liver; an increase of 50% or more in the total lymphocyte count; Richter's transformation (i.e., development of an aggressive large-cell lymphoma in the setting of CLL or small lymphocytic lymphoma). Treatment has consisted historically of chlorambucil plus corticosteroids; although there is no evidence for the additive benefit from corticosteroids and the risk of steroid toxicity may outweigh the benefits of use. Administration of combination chemotherapy regimens containing alkylating agents such as COP and CHOP offers no survival advantage. Treatment with purine analogs (fludarabine, 2-chlorodeoxyadenosine and pentostatin) used as single agents or in combination with other agents increase response rates when compared to alkylating agents. However, overall survival is not prolonged. Rituximab, a CD 20-directed monoclonal antibody, has been used in progressive CLL with limited success. In addition, biologic response modifiers such as recombinant interferon alpha and interleukin-2 have been used to treat progressive CLL with variable results.

(b) (4)

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

The U.S. Food and Drug Administration (FDA) granted alemtuzumab accelerated approval on May 7, 2001 for "the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL) who have been treated with alkylating agents and who have failed fludarabine therapy." Alemtuzumab is marketed in the United States under the trade name Campath® by Genzyme Corporation.

2.4 Important Issues With Pharmacologically Related Products

There are no pharmacologically related products or equivalents to Campath.

2.5 Presubmission Regulatory Activity

The regulatory activity associated with this application is summarized in Table 1.

Table 1 Regulatory History

12MAR-01	Type C Teleconference to discuss Phase 4 confirmatory study (CAM 307)
16MAR-01	IND 004294 (CAM307) submitted
20APR-01	CAM 307 amendment submitted
07MAY-01	BLA 103948 accelerated approval granted; CAM307 accepted as confirmatory trial for efficacy to satisfy PMC#1
29OCT-02	Type C Teleconference to discuss delay in study completion
11FEB-04	CAM 307 final amendment submitted
04MAR-05	Statistical analysis plan (SAP) submitted
24MAY-05	Type C Teleconference to discuss CAM 307 statistical analysis plan
13JUL-05	Facsimile letter comments from FDA regarding SAP revisions
20JUL-05	Revised SAP submitted
12OCT-06	Type B Meeting to discuss the submission of sBLA 103948/5064
07DEC-06	Discuss overview of CAM 307 database

CAM 307 Major Clinical Regulatory Agreements

The following major clinical regulatory agreements were made regarding the conduct of the CAM 307 trial:

12MAR-01 Type C Teleconference

FDA and the applicant agreed:

- CAM 307 with modifications is acceptable as the confirmatory study for PMC#1
- The sample size is 284 subjects

- The primary analysis is intent-to-treat, defined as all randomized subjects
- For the purposes of the interim analyses, if the alemtuzumab arm has a higher rate of progression free survival than the chlorambucil arm and excess mortality, the trial will not be considered a success
- For the purposes of the interim analyses, if there is no difference in survival between the two treatment arms, the trial will not be considered a success

29OCT-02 Type C Teleconference

FDA and the applicant agreed:

- The stratified log rank test specified in the protocol is the primary analysis for regulatory purposes
- Any analysis using the Cox proportional hazard model having pre-specified covariates and/or strata is regarded as supportive analysis
- Any adjusted or weighted analysis not based on pre-specified covariates and strata is considered exploratory
- In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints cannot result in an efficacy claim
- (b) (4)
- Duration of response should not be compared between treatment arms

13JUL-05 Letter Comments From FDA Regarding Statistical Analysis Plan Revisions

FDA informed the applicant:

- The primary analysis method for response rate is the chi-square test
- Cochran-Mantel-Haenzsel test is to be used as a supportive analysis
- Analysis of duration of response will include responders only

12OCT-06 (Type B) Pre-sBLA Meeting

FDA informed the applicant:

- Improvement in progression-free survival for patients in the alemtuzumab treatment arm supports the filing of an sBLA
- The Genzyme plan to include unconfirmed progressions as events in the primary analysis supported by a sensitivity analysis censoring these patients is acceptable
- A decision on priority review status will be made at the time the efficacy supplement is filed
- PMC final study reports are to be submitted to FDA separately. The data may not be included as part of the efficacy supplement
- (b) (4)
- The case report forms intended for submission with the sBLA are acceptable
- Submission of the efficacy supplement in electronic CTD format is acceptable

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

2.6 Other Relevant Background Information

In November, 2005 FDA issued an alert to inform the public and health care professionals about three cases of idiopathic thrombocytopenic purpura (ITP) and one death in a clinical study of Campath for the treatment of Multiple Sclerosis (MS). Campath is not approved to treat MS.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

This efficacy supplement was reviewed by the Office of Oncology Drug Products, Division of Biologic Oncology Products (DBOP); the Office of Pharmacoepidemiology and Statistical Science, Office of Biostatistics Review; the Office of Clinical Pharmacology; and the Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies. Separate archived reviews for divisions other than DBOP are available in the FDA document file and are referenced where appropriate in this review.

3.1 CMC

To fulfill postmarketing commitments made at the time of accelerated approval, final study reports for assays utilized to evaluate CD52 expression, anti-Campath antibodies, and neutralizing antibodies were submitted for review as amendments to this application. The assays were analyzed and deemed adequate and appropriately validated. For a full analysis of the assays, see the Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies review.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Genzyme submitted CAM 307 clinical data in electronic CTD format as discussed in a Type B meeting held on October 12, 2006. Study reports and SAS datasets were also provided. A side-by-side comparison of safety results from CAM 307 and CAM 211 was submitted; however, the safety and efficacy data from CAM 307 were not integrated with the CAM 211 data. Study synopses were provided for legacy studies CAM 211, CAM 005, CAM 009, and CAM 213.

Case Report Forms (CRFs) for CAM 307 were submitted for each subject who died while receiving drug, after cessation of drug but with persistent toxicity, or without confirmation of disease progression by the independent evaluators. CRFs were also submitted for each subject who discontinued study drug as a result of an adverse event, and who discontinued for any reason other than toxicity or independent response review panel (IRRP) documented disease progression.

Additionally, in response to FDA's request, the applicant submitted both adverse event and demographic data in CDISC/SDTM format along with details of the conversion process.

4.2 Tables of Clinical Studies

CAM 307 is the sole new study presented in support of this application. Synopses of single arm legacy studies were also provided. The clinical studies submitted or referenced in this application are listed in **Table 2** which was reproduced from the original study protocol (CSR Appendices 16.1.1, CAM 307 protocol, Mar 16, 2001, Table 5-3).

Table 2 sBLA 103948/5070 Listing of Clinical Studies¹

Study Identifier	Objective(s) of Study	Study Design and Type of Control	Test product(s) Dosage regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Studies of alemtuzumab							
CAM307	Safety and Efficacy	Phase 3, open-label, multicenter, randomized, comparative study	alemtuzumab, 3mg-10mg-30mg dose escalation; 30mg/day maintenance dose, 3 times per week on alternate days; IV Chlorambucil, (comparator study drug); 40mg/m ² once every 28 days; PO	297 total (enrolled/ treated) 149/147-alemtuzumab arm; 148/147-Chlorambucil arm	Adults, 18 years of age or older with progressive B-CLL, not previously treated with chemotherapy	alemtuzumab, 12 weeks of therapy inclusive of escalation period ^{b,c} Chlorambucil, repeated monthly (every 28 days) for a maximum of 12 cycles.	Completed CSR: 25 JAN 2007
CAM211	Safety and Efficacy	Phase 2, open-label, multicenter, non-comparative	alemtuzumab; 3mg-10mg-30mg/day maintenance dose, 3 times per week on alternate days; IV	94/93 (enrolled/ treated)	Adults, 18 years of age or older with B-CLL who received an alkylating agent and for whom there was documentation of failure to fludarabine therapy	4 - 12 weeks ^d	Completed CSR: 27 NOV 1999 ^e Updated CSR: 10 AUG 2000
125-005-C92	Safety and Efficacy	Phase 2, open-label, multicenter (EU), non-comparative	alemtuzumab; 3mg or 10mg IV, or 10mg SC dose escalation, 30mg/day or 80mg/day (with sponsor approval), 3 days per week; IV or SC	125 total; 60/NHL, 53/CLL, 12/other	Adults, 18 years of age or older; NHL or CLL patients who failed to respond to or relapsed following conventional first-line or subsequent therapy	6 - 12 weeks ^d	Completed CSR: 11 NOV 1999 ^e Updated CSR: 11 AUG 2000
125-009-C92	Safety and Efficacy	Phase 2, open-label, multicenter (US), non-comparative	alemtuzumab; initiated daily dose of 10mg/day until well tolerated (up to 5 days per week if needed); 30mg/day 3 times per week, or 80mg/day (with sponsor approval), 3 days per week; IV	24 total	Adults, 18 years of age or older; CLL patients who failed to respond to or relapsed following first-line treatment with fludarabine or other chemotherapy regimens followed by second- or third-line fludarabine	8 - 16 weeks ^d	Completed CSR: 28 OCT 1999 ^e Updated CSR: 11 AUG 2000
CAM213	Safety, Efficacy, and PK Analysis	Phase 2, open-label, multicenter (UK), single-arm, non-comparative	alemtuzumab; 3mg-10mg-30mg dose escalation; 30 mg/day maintenance dose 3 times per week for 12 weeks; IV	30 total	Adults 18 years of age or older with B-CLL who had previously failed to respond to, relapsed following treatment with, or indicated tolerance to purine analogues.	12 weeks of therapy (maximum of 12 weeks)	Completed CSR: 21 SEPT 2001

4.3 Review Strategy

The clinical review focused on data submitted from study CAM 307 in order to confirm the primary efficacy endpoint progression free survival and to assess safety. In addition, single arm legacy studies and postmarketing safety updates were reviewed during the safety analyses. Electronic datasets and case report forms were used to verify the applicant's

¹ See Appendix 10.3 for footnotes within table

analyses and claims. Throughout the review process, consistency between SAS dataset entries and case report forms was examined. In addition, a consult for the inspection of two study sites was submitted to the Division of Scientific Investigations (DSI). This is discussed further in section 4.4.

4.4 Data Quality and Integrity

The CAM 307 study database was locked on August 7, 2006. The database was re-locked on October 11, 2006 after a significant SAE report, received after the initial data lock, was added. As the result of a data audit performed in November, 2006, it was discovered that an error had occurred involving lymph node measurements. Specifically, protocol guidelines directed that when a lymph node was reported as "normal" or "not palpable" a value of "0 x 0" was to be assigned in the database. In cases where responses from investigators to audit queries reported lymph nodes as "normal" or "not palpable", "0.5 x 0.5" was entered into the database erroneously. Where these errors occurred, the values were corrected and the database was again re-locked in December, 2006.

As a result of a teleconference initiated by FDA on May 14, 2007 to discuss certain design elements of the primary efficacy analysis dataset, it became evident that the applicant and FDA were referencing two different datasets. FDA requested an audit of the data to confirm that the data submitted to FDA was the same data upon which study conclusions were based. Upon completion of the audit, the applicant reported that a SAS subsetting error was discovered which affected nine datasets including the primary efficacy datasets. The applicant reported further that only four subjects were at issue and that the study conclusions were in no way affected by the error. All datasets containing errors were corrected and re-submitted as an amendment to the application on May 25, 2007. As a result of this interaction, FDA became concerned that other such errors may have occurred with the data and requested a complete quality control of all data from CAM 307. FDA also requested that a report of the applicant's findings be submitted to the application in the form of an amendment. In response, the applicant indicated that their original audit was exhaustive, all database errors were corrected, the corrected datasets were submitted to the application, there were no substantive changes to the Clinical Study Report (CSR), and errata would be prepared and submitted with updates to the CSR.

On August 24, 2007 the applicant submitted amendment 0012 to the application containing CSR errata in the form of narrative, tables and data listings. These errata were updates to the CAM 307 CSR and database resulting from the May 25, 2007 submission of corrected datasets. In the August submission, additional errors in certain summary statistics and listings not previously noted by the applicant were identified. These were the result of another programming error which led to using the August, 2006 database to generate the listings rather than the December, 2006 final locked database. The errors were first called to the applicant's attention as a result of FDA's inspection of site 4001 in Lodz, Poland (discussed further below). Data requiring corrections were in summaries 14.3.2-1: Listing of All Serious Adverse Events (Safety Population) and 14.3.2-2: Listing of All Drug Related Serious Adverse Events (Safety Population). In addition, three other data listing summaries were affected, but these did not require correction.

In general, entries in the case report forms (CRFs) contained multiple errors, corrections and retrospective revisions. There was minor discordance between final CRFs and SAS

dataset entries noted in a review of approximately 10% of CRFs.

Discrepancies were also identified between incidence totals compiled by the applicant and by FDA in a number of the safety analyses. These discrepancies did not change the overall conclusions of the review.

Inspections of two study sites in Lodz (site 4001) and Lublin (site 4006), Poland were performed by the Division of Scientific Investigations (DSI). The Clinical Inspection Summary was added to the file for this application on August 15, 2007. The summary reports similar findings at each site inspected, most relating to instances of failure to follow protocol procedures. At the Lodz, Poland site, where 26 subjects were enrolled, the following observations were made: there were at least three study subjects who received four maintenance doses of Campath per week instead of the three doses per week specified in the protocol; there were SAEs not reported to the applicant within the 24 hour window required by the protocol; there were at least five study subjects who did not meet entry requirement criteria regarding the timing of imaging studies prior to randomization; two study subjects did not begin treatment within seven days of randomization. At the Lublin, Poland site, where 24 subjects were enrolled, the following observations were made: two study subjects received four treatments per week instead of three during two weeks of the 12 week dosing schedule; six SAEs experienced by four study subjects were not reported to the applicant within the 24 hour window required by the protocol; adverse events (i.e., nausea, vomiting, diarrhea, fever, rigors, hives, tingling) were unreported in eight subjects; 40 ampoules of the study drug were shipped below the recommended storage temperature range (2-8 ° C) and used in the study without the applicant being notified.

The preliminary conclusion reached from the inspections was, overall, there were no significant findings that would impact the validity or reliability of the submitted data from these study sites.

Although the integrity and quality of the data appear adequate to support study conclusions, overall quality control of the data from this study was suboptimal.

4.5 Compliance with Good Clinical Practices

The applicant asserts that study CAM 307 was conducted in accordance with the Declaration of Helsinki and ICH guidelines for Good Clinical Practice (GCP). The protocol and its amendments were approved by independent ethics committees and the requisite authorities according to ethical requirements and laws governing the conduct of clinical trials in each country where the study enrolled subjects.

4.6 Financial Disclosures

As required by 21 CFR 54.4(a)(1), the applicant provided a listing of investigators who participated in CAM 307 attesting that financial disclosure forms were received from each investigator. The applicant also attests that there have been no financial interests or arrangements made with the listed investigators linking compensation with the outcome of the study.

Lists of financial disclosure information were submitted and reviewed. There were 44 investigators listed as having participated in CAM 307. No source financial information from these investigators was submitted. The applicant's list of financial disclosure forms received from investigators (CSR section 1.3.4) was compared to another list of investigators for CAM 307 located in the clinical study report (CSR section 16.1.4, Table

16-2). There is one investigator whose name appears on the CSR list of investigators, but not on the financial disclosure forms received from investigators list.

Comment: This investigator's site accrued only (b) (6) subjects, making it highly unlikely that bias would have been introduced into the study results were this investigator found to have a financial interest in any of the companies involved with this study.

5. CLINICAL PHARMACOLOGY

Pharmacokinetic studies were not conducted as a part of CAM 307. Pharmacodynamic studies were reviewed by CMC and clinical pharmacology reviewers and are discussed briefly in other sections of this review (see sections 3.1, CMC and 7.1.10, Immunogenicity). For a full discussion of the pharmacodynamic studies, please see the Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies, and Office of Clinical Pharmacology reviews.

6. INTEGRATED REVIEW OF EFFICACY

The review of efficacy described in this section is based on a single Phase III, multinational, randomized (1:1), open label trial of Campath versus chlorambucil in 297 subjects with histopathologically confirmed B-CLL, RAI stage I through IV, previously untreated with evidence of progressive disease and in need of treatment at the time of study entry. The study fulfills a postmarketing commitment made at the time of accelerated approval to confirm clinical benefit attributed to Campath and supports conversion to regular approval based on a demonstration of superior progression-free survival when compared to standard first-line treatment (chlorambucil) for progressive B-CLL.

For a full discussion of the efficacy analyses performed by FDA, see the Office of Pharmacoepidemiology and Statistical Science, Office of Biostatistics review. A discussion of the study design and efficacy findings follows.

6.1 Indication

Campath is approved currently "for the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and who have failed fludarabine."

The applicant's proposed indication submitted with this application was (b) (4)

FDA's proposed indication is "as a single agent for the treatment of B-cell chronic lymphocytic leukemia."

6.1.1 Methods

The efficacy review is focused on data submitted for study CAM 307. Synopses of all legacy studies (CAM 211, 005, 009 (b) (4)) submitted with this application were also reviewed. The legacy studies were designed as single arm trials; therefore no formal comparisons to CAM 307 were performed nor were data from these studies pooled as a part of the efficacy analyses.

6.1.2 General Discussion of Endpoints

The primary endpoint for CAM 307 was progression free survival (PFS), defined as time from the date of randomization to the date of first objective documentation of disease

progression or death due to any cause. An independent response review panel (IRRP) was utilized to assess both response and onset of disease progression for all subjects. The IRRP-defined assessment was used in the calculation of each subject's PFS. PFS has been accepted as a measure of clinical benefit for subjects with CLL and is an appropriate primary endpoint.

Secondary endpoints included in the statistical analysis plan were overall survival, overall response rate, duration of response, time to treatment failure and time to alternative treatment. It is noted that although time to alternative treatment was included as a secondary endpoint in the study, it was not among the endpoints identified in the multiple endpoints adjustment; that is, there was no pre-specified adjustment proposed for this secondary endpoint. In addition, CAM 307 survival data were immature and the study was not powered to detect a difference in survival. There were not enough events or long enough follow up to detect a difference in overall survival. In addition, there was no plan for continued follow-up of subjects in this study.

Subgroup analyses included age group, maximum lymph node size, gender, performance status, percent marrow involvement at baseline, beta-2 microglobulin at baseline, and cytogenetic abnormalities at baseline.

6.1.3 Study Design CAM 307

Protocol title: "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Alemtuzumab vs. Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia"

Study sites: There were forty-four study centers in the following countries: Czech Republic, Croatia, Estonia, France, Ireland, Italy, Lithuania, Netherlands, Poland, Serbia, Slovakia, United Kingdom, United States

Study period: Date first subject randomized: December 5, 2001
Date last subject randomized: July 15, 2004
Date last subject completed: May 4, 2005
Date of data cut off: June 1, 2006

Primary objective: To assess whether Campath is superior to chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival.

Secondary objectives: To compare overall survival time, complete response, overall response rate, duration of response, time to treatment failure, time to alternative treatment and safety between patients treated with Campath and patients treated with chlorambucil.

Study design: CAM 307 was a Phase III, open label, multicenter, randomized, comparative trial of 297 subjects with histopathologically confirmed progressive B-CLL (CD5, CD19, or CD23 positive clone). Subjects were required to be RAI stage I through IV, treatment naïve with evidence of progressive disease and in need of treatment at the time of study entry. There was a 1:1 randomization to one of two treatment arms. Subjects were to receive either Campath (at a starting dose of 3 mg IV over 2 hours daily until tolerated then increased to 10 mg IV over 2 hours daily until tolerated, then at a target dose of 30 mg IV over 2 hours 3 times per week on alternate days for a total of 12 weeks) or chlorambucil (40 mg/m² PO once every 28 days for up to 12 cycles). Treatment was to be discontinued upon investigator-determined disease progression using 1996 National Cancer Institute

Working Group (NCIWG) criteria for CLL, unacceptable toxicity, a complete remission, or response plateau. Subjects were stratified by study center, RAI stage, WHO performance status, age, gender, and maximum lymph node size. Subjects who did not progress at the 18 month point after their initial dose were to be followed every three months until time of progression or requirement for alternative therapy. Subjects who progressed were to be followed every three months for survival.

Study population:

Inclusion criteria

- Histopathologically confirmed diagnosis of B-CLL with CD5, CD19, or CD23 positive clone
- Rai stage I through IV; evidence of progressive disease defined as one or more of the following:
 - o Disease-related B symptoms
 - o Marrow failure manifested by: decreased hemoglobin to $< 11\text{g/dL}$, or platelet count $< 100 \times 10^9/\text{L}$ within the prior six months, or absolute neutrophil count $< 1.0 \times 10^9/\text{L}$ within the prior six months
 - o Progressive splenomegaly $> 2\text{ cm}$ below the left costal margin or other organomegaly with progressive increase over two clinic visits ≥ 2 weeks apart
 - o Progressive lymphadenopathy, at least 5 sites of involvement with either two nodes at least 2 cm in longest diameter or one node $\geq 5\text{ cm}$ in longest diameter with progressive increase over two consecutive clinic visits ≥ 2 weeks apart
 - o Progressive lymphocytosis, an increase of $> 50\%$ over a two month period or an anticipated doubling time of less than six months
- Life expectancy of at least 12 weeks
- No previous chemotherapy for B-CLL
- WHO performance status 0, 1 or 2
- 18 years of age or older
- Renal function: creatinine $\leq 2.0 \times$ institutional upper limit of normal (ULN)
- Hepatic function: total bilirubin, AST, ALT $\leq 2 \times$ institutional ULN
- Not pregnant
- Agree to practice an effective contraceptive method
- Sign written informed consent

Exclusion criteria

- ANC $< 0.5 \times 10^9/\text{L}$ or platelet count $< 10 \times 10^9/\text{L}$
- Chronic use of oral corticosteroids
- Autoimmune thrombocytopenia
- Prior bone marrow transplant
- Investigational agent in past 30 days
- HIV positive
- History of anaphylaxis to rat or mouse-derived humanized monoclonal antibodies
- Active infection
- Serious cardiac or pulmonary disease
- Active tuberculosis (TB) in past 2 years or current antibiotics for TB
- Active secondary malignancy

- Central nervous system CLL
- Other severe, concurrent diseases or mental disorders
- Pregnant or lactating
- Quantitative PCR positive for CMV
- Diagnosis of mantle cell lymphoma

Treatment plan: Campath was to be administered for a maximum of 12 weeks, which included the dose escalation period. Subjects were eligible to receive a second treatment course of Campath if a CR or PR was achieved with the initial treatment course and there was disease progression at greater than six months. Chlorambucil was to be administered once every 28 days for a maximum of 12 months.

Dose modification and delay:

Campath was to be interrupted or discontinued for the following:

- Serious infection
- Disease progression
- \geq CTC grade 3 pulmonary, renal, or hepatic toxicity
- A positive qualitative PCR assay for CMV
- Autoimmune anemia or autoimmune thrombocytopenia
- $ANC \leq 0.25 \times 10^9/L$
- Platelets count $\leq 50\%$ of baseline value in subjects with a baseline $\leq 0.25 \times 10^9/L$
- Interruption of Campath therapy for > 4 weeks

Campath dosing was modified and re-initiated as set out in **Table 3** which was reproduced from the original study protocol (CSR Appendices 16.1.1, CAM 307 protocol, Mar 16, 2001, Table 5-3).

Table 3 CAM 307 Campath Dose Modification and Reinitiation of Therapy

Hematological Toxicity	Dose Modification and Reinitiation of Therapy
For first occurrence of $ANC < 250/\mu L$ and/or platelet count $< 25,000/\mu L$	Withhold Campath® therapy. When $ANC > 500/\mu L$ and platelet count $> 50,000/\mu L$, resume Campath® therapy at same dose. If delay between dosing is > 7 days, initiate therapy at Campath® 3 mg and escalate to 30 mg.
For second occurrence of $ANC < 250/\mu L$ and/or platelet count $< 25,000/\mu L$	Withhold Campath® therapy. When $ANC > 500/\mu L$ and platelet count $> 50,000/\mu L$, resume Campath® therapy at 10 mg. If delay between dosing is > 7 days, initiate therapy at Campath® 3 mg and escalate to 10 mg only.
For third occurrence of either toxicity	Discontinue Campath® therapy permanently.

Chlorambucil was to be interrupted or discontinued for the following:

- Disease progression
- \geq CTC grade 3 pulmonary, renal, hepatic, or non-hematologic toxicity
- Serious infection
- Autoimmune anemia or autoimmune thrombocytopenia
- Complete remission
- Response plateau

Concomitant therapy:

- Subjects treated with Campath were to receive trimethoprim/sulfamethoxazole for PCP

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- prophylaxis or, if allergic, a therapeutic equivalent
- Prophylactic antibiotics to prevent recurrence of an infection were allowed
 - Premedication for Campath treatment consisting of diphenhydramine, acetaminophen or paracetamol was to be given.
 - Hydrocortisone or its equivalent, meperidine, and other supportive measures were permitted as clinically indicated for Campath infusion reactions
 - Allopurinol for Campath treatment was to be given prior to the first treatment and for 14 days thereafter
 - Allopurinol for chlorambucil treatment was to be given prior to the first day of treatment and for 8 days thereafter for the first three treatment cycles

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Study schedule:

Study schedules reproduced from the original protocol are represented in **Table 4** and **Table 5**. (CSR Appendices 16.1.1 CAM 307 protocol, Mar 16, 2001, Table A-1 and A-2)

Table 4 Schedule of Events Standard Assessments²

Activity	Screening ^a	After Randomi- zation and Prior to Treatment ^b	During Treatment		End of Therapy ^f	Post Treatment Follow-up	
			Weekly	Monthly		Once a Month	Every 3 Months
						<18 Months After 1 st Dose ^f	>18 Months After 1 st Dose ^g
Informed consent	X						
Medical history	X						
Disease Assessment:							
Physical exam ^h	X			X	X	X	X
RAI stage	X						
Disease related symptoms	X			X	X	X	X
Weight, temperature	X			X	X	X	X
CBC, differential, platelets	X		Months 1-2: ^{c,d}	> 2 Months ^g	X	X	X
NCIWG Response					X ^r	X ^r	
WHO performance status	X			X	X	X	
β ₂ microglobulin	X			X	X		
Serum chemistry panel ⁱ	X			X ^j	X ^j		
Urine dip stick (leukocyte esterase)	X						
Direct & Indirect Coombs	X			X ^j	X ^j		
Cytogenetic analysis ^k		X					
CMV antibody by ELISA	X						
PCR for CMV	X		X ^p	X ^q	X ^r	X ^v	
IgA, IgG, IgM	X			X	X		
Serum pregnancy test	X						
Chest x-ray (PA)	X ^s			X ^t	X ^t		
Imaging studies	X ^s				X ^t		
Campath [®] dosing				X ^u			
Chlorambucil dosing				X ^m			
Concomitant medications, transfusions, growth factors	X			X	X ⁿ	X ⁿ	
Infections				X	X	X ^o	
Adverse Events				X	X	X ^{o,a}	
Alternative Therapy, Disease progression				X	X	X	X
Survival, Diagnosis of 2 nd malignancy				X	X	X	X

²See Appendix 10.4 for footnotes from table

Table 5 Schedule of Events Treatment Associated Assessments³

Activity	Screening ^a	After Randomization and Prior to Treatment ^b	Time After Treatment Start		End of Treatment ^c	Time After Treatment End			
			Months 1 and 2	Months 3 to 11		Month 1	Month 2	Month 6	Month 24
BM aspirate/biopsy ^a	X		X		X	X	X	X	X
Flow cytometry BM aspirate ^d	X		X		X	X	X	X	X
Flow cytometry peripheral blood	X		X	X ^h	X	X	X	X	X
Antigen-specific immune function assay ^e		X				X	X	X	
Anti-Campath antibody test ^f		X				X	X	X	
Tetanus antibody titer and tetanus toxoid booster								X ^g	

Evaluation Criteria: Evaluation for subject response was to be performed monthly during treatment and at the completion of treatment or early discontinuation. Investigators were to use 1996 National Cancer Institute Working Group (NCIWG) criteria to assess response to study treatment. A Data and Safety Monitoring Board was to review all data pertaining to efficacy and safety.

Special Laboratory Variables: In order to satisfy post-marketing commitments, two areas with clinical pharmacology implications were to be assessed as a part of CAM 307. An assessment was to be made of the incidence of loss of CD52 expression at the time of relapse or disease progression during or following Campath therapy. In addition, a quantitative analysis was to be performed of the incidence and magnitude of HAMA and anti-idiotypic antibodies at study entry and following exposure to Campath. The results pertaining to these assessments and the assays utilized to obtain them are discussed in the safety section of this review as well as the Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies, and Office of Clinical Pharmacology reviews of this data. A full clinical review of these data is ongoing.

Efficacy Endpoints:

Primary:

- Progression free survival (time from date of randomization to date of first IRRP documentation of PD or death)

Secondary:

- Overall survival (time from randomization to date of death from any cause)
- Response rate (number of CRs plus PRs divided by total number of ITT population)
- Duration of response (determined from date of first documented objective response to the date of documented disease progression)
- Time to treatment failure (time from randomization to date of disease progression,

³ See Appendix 10.5 for footnotes from table

death or discontinuation resulting from an AE, whichever is earliest)

- Time to alternative treatment (time from randomization to date of alternative tx or death)

Statistical and Analysis Plan: The planned sample size of the study was 284 subjects (actual sample size was 299 subjects). This sample size assumed a median PFS of 14 months for subjects treated with chlorambucil and 21 months for subjects treated with Campath. The study was powered at 80% with a two-sided alpha of 0.05 and a hazard ratio of 0.667. It was assumed that 5% of subjects would not have a confirmed diagnosis of B-CLL and 190 PFS events were targeted for the analysis.

The primary analysis of PFS was to be performed for the ITT population (n=297) utilizing a stratified log-rank test. A blinded independent response review panel (IRRP) was to evaluate all responses and progression events. Duration of PFS was to be calculated from date of subject randomization to the IRRP documented date of progression, relapse, or date of death from any cause, whichever occurred earlier.

Exploratory subgroup analyses of PFS as related to stratification factors (Rai stage, age, gender, performance status and maximum lymph node size) between treatment arms were to be defined prospectively and performed. Censoring rules were also to be applied as follows: in cases of unconfirmed CLL or where no study drug was given, subjects would be censored at the date of randomization; inevaluable responses would be considered progressive disease and censored at the date of last evaluation; in cases where subjects were alive and without evidence of progressive disease at last evaluation, they would be censored at the date of last evaluation. Analyses of the secondary endpoints were to be performed using summary statistics based on IRRP and investigator assessments. Comparisons between treatment arms were to be conducted.

Additional detail regarding the statistical analyses and methods utilized for CAM 307 can be found in the Office of Pharmacoepidemiology and Statistical Science, Office of Biostatistics review.

IRRP Charter: The IRRP was chosen by the applicant and consisted of three reviewers who were experts in the diagnosis and treatment of B-CLL. Each reviewer provided a CV demonstrating their expertise and non-affiliation with the applicant, and signed a confidentiality agreement and financial disclosure statement. The reviewers were compensated for their time and expenses. Data for review were organized by patient and included database summaries with calculations of change from baseline for certain parameters. The database (including unlocked data) was the primary source for information reviewed, however, source documentation would be provided if necessary. Central bone marrow and flow cytometry results were included for evaluation and no radiology films were evaluated.

Comment: IRRP evaluation of source documents, including bone marrow slides and radiology films, would have resulted in a more rigorous review and enhanced the study results accordingly.

Protocol Amendments: Key modifications from amendments to the protocol are summarized in **Table 6**.

Table 6 CAM 307 Amendments

Version	Date	Enrolled	Modifications
0	Mar. 16, 2001	0	Original protocol
1	Jun. 4, 2001	4	<ul style="list-style-type: none"> hemoglobin to <11 g/dL sufficient evidence of disease progression time needed between assessments in determining disease progression for splenomegaly and lymphadenopathy at least 2 weeks patients had to be chemotherapy naïve
			<ul style="list-style-type: none"> effective contraception use on Campath arm 6 months baseline + CMV PCR ineligible stopping rules for + CMV PCR Campath retreatment allowed if CR or PR > 6 mos weekly and repeat CBC during Campath tx weekly CMV assay during Campath tx primary stat analysis ITT
2	Nov. 20, 2001	293	<ul style="list-style-type: none"> Campath duration of tx 12 weeks total including dose escalation period CD23 + clone eligible mantle cell lymphoma not eligible SAE reporting to continue for 6 months after last tx
3	Feb. 9, 2004	0	<i>Intentionally left blank</i>

Supporting Efficacy Studies:

- CAM 211: Ph 2, open label, multicenter, single arm, 94 subjects enrolled, B-CLL treated w/ alkylating agents and failed fludarabine, safety & efficacy
- 125-005-C92: Ph 2, open label, multicenter, single arm, 125 subjects enrolled, NHL (60)/CLL (53)/other (12) failed to respond or relapsed after conventional first-line tx, safety & efficacy
- 125-009-C92: Ph 2, open label, multicenter, single arm, 24 subjects, CLL failed to respond or relapsed after fludarabine or other chemo followed by 2nd or 3rd line fludarabine, safety & efficacy
- [REDACTED] (b) (4)

6.1.4 Efficacy Findings

Subject Demographics, Baseline Characteristics and Disposition

Two hundred and ninety-seven subjects were randomized during CAM 307 from December, 2001 to July, 2004. The last patient received drug in May, 2005. The data cutoff date was June 1, 2006. Data lock was completed on August 7, 2006. However a re-lock on October 11, 2006 was necessary to add an SAE report received after the initial data lock. In November 2006, an audit uncovered an error in the database involving lymph node measurements. This required another re-lock of the data in December, 2006.

There was a 1:1 randomization to either Campath (n = 149) or chlorambucil (n = 148). Subjects were enrolled in 44 sites in Europe and the United States. There were 24 subjects enrolled in the United States. An adaptive randomization method was utilized to achieve balance between treatment arms for study center, Rai stage group (Rai I/II vs. Rai III/IV),

age (< 65 vs. ≥ 65), WHO performance status (0,1 vs. 2), gender, and maximum lymph node size (non palpable or < 5cm vs. ≥ 5 cm). Balance between treatment arms was achieved and all randomized subjects received the study treatment to which they were randomized. Two hundred and ninety-four subjects received treatment and their data were included in the safety database.

Table 7 summarizes subject demographics. Gender stratification was similar to that seen in B-CLL where there is a 2:1 ratio of male to female. There were 295/297 subjects who were caucasian and 192/297 were <65 years of age. The majority of subjects enrolled in the study were RAI stage I/II (188/297 IRRP assessed) with WHO grade 0,1(285/297) and lymphadenopathy measures <5 cm (229/297).

Table 7 CAM 307 Subject Demographics

GENDER	Campath	Chlorambucil
Female	43	41
Male	105	107
AGEGRP		
< 65	96	96
≥ 65	52	52
MXLYGP		
< 5 cm	115	114
≥ 5 cm	33	34
WHO GRADE		
0, 1	142	142
2	5	5
RAI GROUP per IRRP		
I/II	92	96
III/IV	50	48
RAI GROUP per INV		
I/II	97	95
III/IV	50	50
MONTHS FROM DX TO RANDOMIZATION Mean (SD)	20.54 (27.78)	19.72 (27.76)

Disposition of study subjects at the end of treatment is summarized in **Table 8**. The number of subject deaths represented in this table are those occurring within 30 days of treatment. Specific adverse events and the reasons given for investigator decision will be discussed later in this review.

Table 8 CAM 307 Subject Disposition

Disposition	Campath	Chlorambucil
Completed Protocol	101	61
Adverse Event	18	2
Deceased	1	3
Disease Progression	2	37
Infection	8	5
Investigator Decision	10	29
Autoimmune Anemia/Thrombocytopenia	1	5
Protocol Violation	1	1
Refused Further Treatment	7	5

Protocol Deviations

The Division of Scientific Investigations (DSI) conducted bioresearch monitoring clinical investigator inspections of two investigator sites in Poland. These sites enrolled a total of

50 subjects, 17% of all subjects enrolled. Preliminary results of the inspections revealed similar findings at each site, most relating to instances of failure to follow protocol procedures. Dosing maintenance in seven subjects were contrary to protocol specifications. In addition, adverse events (i.e., nausea, vomiting, diarrhea, fever, rigors, hives, tingling) were unreported in eight subjects and there were SAEs not reported to the applicant within the 24 hour window required by the protocol. There were at least five subjects at one site who did not meet entry requirement criteria regarding the timing of imaging studies prior to randomization. Overall, the audit of these sites revealed no significant findings that would impact data validity and data reliability for this application. A final DSI report will be included in the file for this application.

Table 9 summarizes the major protocol violations for the CAM 307 intent-to-treat population. It should be noted that four subjects who did not meet eligibility criteria received waivers from the applicant, three randomized to Campath and one to chlorambucil. Other categories of protocol deviations were:

- Physical exams, chest x-rays, or other radiographic imaging, and laboratory testing were not done or not reported at protocol-specified time points
- Protocol specified directions for scheduled dosing were not followed
- Disease/response assessments and/or tumor measurements were not done at protocol-specified time points
- Protocol specified premedications were missed or the dosing was unreported
- SAEs were not reported to the applicant within the appropriate time frame
- Errors were made in eligibility criteria

Table 16-5 of the Clinical Study Report is a 15 page listing of protocol deviations by subject. An analysis of the efficacy, hematology and chemistry datasets revealed that all 297 subjects in the safety population (100%) had at least one protocol deviation during the conduct of CAM 307.

Table 9 Major Protocol Violations

REASON	Campath® n = 149	Chlorambucil n = 148
ANC was $<0.5 \times 10^9$ at study entry	1(.67%)	0
Active infection at study entry	0	1(.68%)
Diagnosis of BCLL was not confirmed per IRRP	2(1.3%)	2(1.4%)
Ineligible, Rai 0 per IRRP	4(2.7%)	1(.68%)
Insufficient evidence of progressive disease	7(4.7%)	3(2.0%)
Randomized, but did not receive study drug	2(1.3%)	1(.68%)
Uncompliant, dose delay during treatment over 3 months	1(.67%)	0
TOTAL (8.4%)	17(11.4%)	8(5.4%)

Analysis of Response

The primary efficacy endpoint for CAM 307 was progression free survival (PFS). Duration of PFS was calculated from the date of subject randomization to an independent response review panel (IRRP) documented date of progression, relapse, or death from any cause, whichever occurred earlier. Subjects not progressed and alive on the date of last evaluation were considered censored at that time point. Subjects with missing response assessments were considered to have progressed on the date of the inevaluable response plus one day. An interim efficacy analysis was performed after 95 subjects had progressed. The final efficacy analysis used a pre-specified significance

level of 0.048 and was based on 191 PFS events. The efficacy analyses were performed on the 297 subject intent-to-treat population (Campath = 149, chlorambucil = 148). Subjects with unconfirmed B-CLL (Rai stage I – IV) as determined by the IRRP were censored at day one. There were eleven such subjects (Campath = 7, chlorambucil = 4). The difference in PFS between the Campath and chlorambucil treatment arms after adjustment by Rai stage group was highly statistically significant with a p-value of 0.0001 and an estimated hazard ratio of 0.58 (95% CI: 0.43, 0.77). Campath prolonged the median progression free interval by 88 days (2.9 months). The median PFS for subjects treated with Campath was 445 days (14.6 months), and for subjects treated with chlorambucil 357 days (11.7 months).

In subgroup analyses for PFS in subjects with Rai stage III/IV (n=98) treated with Campath as compared to those treated with chlorambucil, a hazard ratio of 0.651 (95% CI: 0.411, 1.033) with log rank p-value of 0.0663 were observed. In addition, in subgroup analyses for subjects \geq age 65 treated with Campath as compared to subjects treated with chlorambucil, a hazard ratio of 0.68 (95% CI: 0.418, 1.107) with log rank p-value of 0.1187 were observed. The results of these analyses suggest a diminished treatment effect for these populations.

Because of the limited number of study subjects with WHO performance status 2 (n=10), lymph node size \geq 5 cm (n=67), and treated in the United States (n=24), analyses of PFS in these subject populations were not meaningful.

Figure 1 represents the Kaplan-Meier curves for the primary analysis.

Analyses of secondary endpoints detected a higher overall response rate, 83% vs. 55%, for Campath treated subjects compared to those treated with chlorambucil with a p-value $<$ 0.0001 and an estimated odds ratio of 3.99 (95% CI: 2.33, 6.84). These results indicate that the odds of an improved treatment response is four times more likely to occur with Campath than with chlorambucil. Campath also demonstrated a superior complete response rate of 24% vs. 2% when compared to chlorambucil ($p <$ 0.0001).

In the analyses of time to alternative treatment, Campath was superior to chlorambucil with a log-rank test p-value of 0.0001 prolonging time to alternative treatment by 261 days (8.6 months) when compared to chlorambucil with medians of 708 days (23.3 months) vs. 447 days (14.7 months). However, subgroup analyses by Rai stage suggested no difference for time to alternative treatment between Campath and chlorambucil for Rai stage III/IV patients. It is noted that although time to alternative treatment was included as a secondary endpoint in the study, it was not among the endpoints identified in the multiple endpoints adjustment; that is, there was no pre-specified adjustment proposed for this secondary endpoint.

The CAM 307 protocol defined duration of response as the interval between the date of first documented objective response to the date of documented progressive disease or death from any cause as determined by the IRRP. The CRF design did not make it clear that the intended date of response was the date of initial response. As a result, the IRRP provided the date of best response and the duration of response analysis was performed using this time point and the censoring rules from the primary PFS analysis (The primary analysis censored subjects with unconfirmed Rai stage I-IV as determined by the IRRP at day 1). The median duration of response for subjects treated with Campath was 492 days (16.4

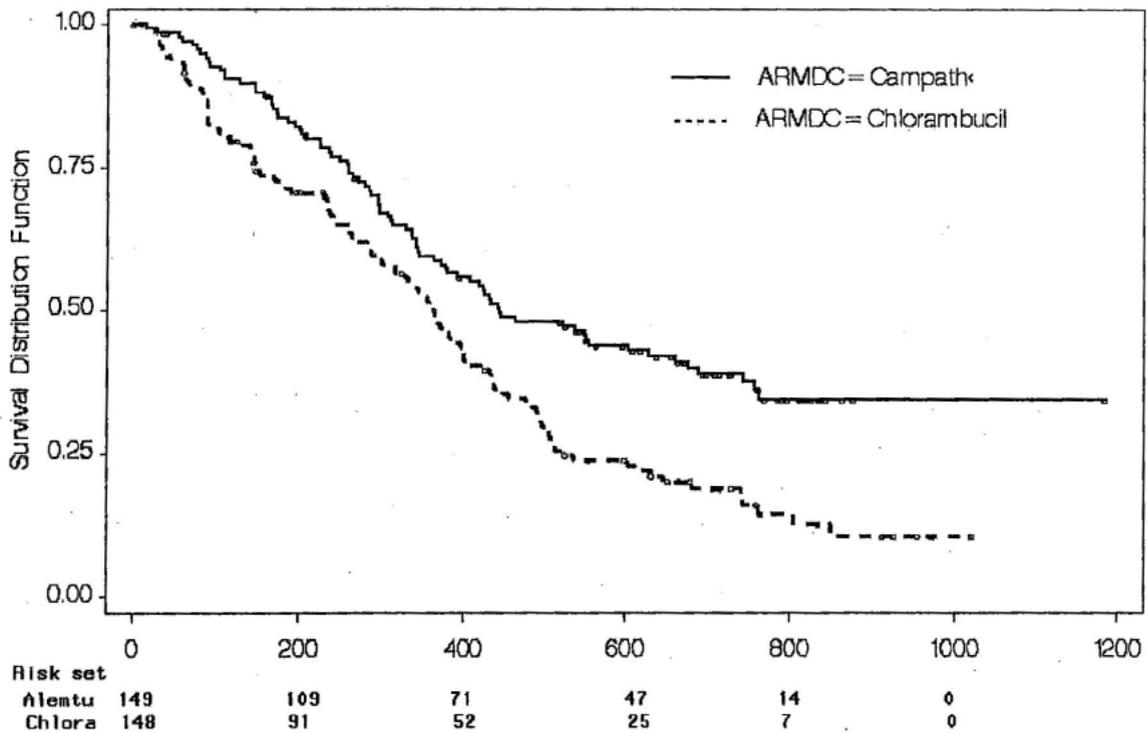
months) and 386 days (12.9 months) for subjects treated with chlorambucil.

Analysis of time to treatment failure defined this event as the time from randomization to the date of progression, death from any cause, or study discontinuation due to adverse event, whichever was earliest. Treatment interruption due to an adverse event resulting in treatment delay over 4 weeks from the last dose for chlorambucil, or 4 weeks from the last scheduled dose for Campath were considered discontinuation of treatment for the purpose of between arm comparison. The median time to treatment failure for Campath was 299 days (10 months) and for chlorambucil 344 (11.5 months) with a log-rank test p-value of 0.1551 (95% CI: 0.627, 1.082).

There was no difference detected in overall survival between treatment arms. The study was not powered to detect a difference in overall survival, and there were not enough events, or long enough follow up to detect a difference. In addition, there was no plan for continued follow-up of subjects in this study.

For a full discussion of all efficacy analyses performed by FDA, please refer to the Office of Pharmacoepidemiology and Statistical Science, Office of Biostatistics review.

Figure 1. CAM 307 Kaplan-Meier Curves for PFS



Prog. Free Surv2 (IRRP) Rai I-IV patient

6.1.5 Clinical Microbiology

This section is not addressed intentionally.

6.1.6 Efficacy Conclusions

In a randomized (1:1), multi-center trial of previously untreated subjects with B-CLL, Rai stage I to IV with progressive disease and in need of treatment, Campath demonstrated greater efficacy when compared to chlorambucil for progression free survival (PFS). Campath prolonged the median progression free interval by 88 days (2.9 months) when compared to chlorambucil (medians: 445 days/14.6 months vs. 357 days/11.7 months). The log-rank p-value was 0.0001 after adjustments for Rai stage group with an estimated hazard ratio of 0.58 (95% CI 0.43, 0.77).

There was an increased overall response rate, 83% vs. 55%, for Campath treated subjects compared to those treated with chlorambucil with a p-value < 0.0001 and an estimated odds ratio of 3.99 (95% CI: 2.33, 6.84). These results indicate that the odds of an improved treatment response is four times more likely to occur with Campath than with chlorambucil. Campath also demonstrated an increased complete response rate of 24% vs. 2% when compared to chlorambucil (p < 0.0001).

There was no survival benefit demonstrated.

In subgroup analyses for PFS in subjects with Rai stage III/IV (n=98) treated with Campath as compared to those treated with chlorambucil, a hazard ratio of 0.651 (95% CI: 0.411, 1.033) and log rank p-value of 0.0663 were observed. In addition, in subgroup analyses for subjects \geq age 65 treated with Campath as compared to subjects treated with chlorambucil, a hazard ratio of 0.68 (95% CI: 0.418, 1.107) and log rank p-value of 0.1187 were observed. The results of these analyses suggest a diminished treatment effect for these populations.

Because of the limited number of study subjects with WHO performance status 2 (n=10), lymph node size \geq 5 cm (n=67), and treated in the United States (n=24), analyses of PFS in these subject populations was not meaningful.

In the analyses of time to alternative treatment, Campath was superior to chlorambucil with a log-rank p-value of 0.0001, prolonging time to alternative treatment by 261 days (8.6 months) when compared to chlorambucil with medians of 708 days (23.3 months) vs. 447 days (14.7 months). However, subgroup analyses by Rai stage for time to alternative treatment suggest no difference between Campath and chlorambucil for Rai stage III/IV subjects. It is noted that although time to alternative treatment was included as a secondary endpoint in the study, it was not among the endpoints identified in the multiple endpoints adjustment; that is, there was no pre-specified adjustment proposed for this secondary endpoint.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety profile for Campath was reviewed and described in detail in the original BLA application, STN 103948/0. The studies reviewed in the original BLA were three single arm clinical trials in subjects with B-CLL (n=149) who had been treated previously with alkylating agents and fludarabine. Synopses of these legacy data were included with this application.

In addition, clinical data from 294 subjects receiving either Campath (147) or chlorambucil

(147) during the conduct of CAM 307 were reviewed and analyzed to assess overall safety. A number of datasets provided by the applicant were utilized to accomplish this review and each is discussed separately under the heading to which it applies. These data were analyzed for safety signals specific to known toxicities of Campath and results were compared to the Campath legacy studies and current product labeling. In addition, analyses were performed on certain subsets of events including, but not limited to, deaths, SAEs, cytopenias, infections, infusion reactions, cardiac toxicity, and immunogenicity. These analyses were also compared to the results from the legacy studies cross-referenced in the application. In addition, the safety database was analyzed at all levels of the MedDRA hierarchy in order to identify new safety signals. Pertinent CRFs, case narratives, and data listings were reviewed in order to assess specific safety issues.

7.1.1 Deaths

Case report forms, narrative summaries, and subject profiles were reviewed for the four subjects dying within 30 days and nine subjects dying within 180 days of receiving their last study treatment dose on either treatment arm. Case report forms were also reviewed for all deaths occurring during the study follow up period up to the data cut-off. A complete review of all deaths on CAM 307 was performed and those occurring within 180 days of study treatment are summarized below. The deaths occurring on the Campath treatment arm were a particular focus for this analysis. Deaths from the single arm legacy studies were also reviewed.

Table 10 summarizes all subjects who died during the conduct of study CAM 307 listed by treatment arm and includes the interval between last study treatment and date of death. A total of 48 deaths (16%) occurred which were balanced between the two treatment arms.

Table 10 CAM 307 Death by Arm

Deaths and Treatment Interval	Campath n	Campath %	Chlorambucil n	Chlorambucil %
Deaths w/in 30 days of last dose	1	.3	3	1.0
Deaths 31 - 180 days of last dose	3	1.0	6	2.0
Deaths > 180 days of last dose	20	6.6	15	5.0
Total Deaths	24	8.0	24	8.0

In their analysis of the deaths on CAM 307, the applicant chose to highlight deaths occurring within 30 days of last treatment dose. Based upon the prolonged pharmacodynamic effects of Campath, deaths occurring within 180 days of treatment may reasonably be attributable to treatment. Therefore, FDA's analysis includes deaths occurring within 180 days of last treatment.

In a subject population with untreated, progressive B-CLL, age at diagnosis, co-morbidities attendant to age, and underlying immune dysfunction resulting from the disease process are often contributory factors in any clinical scenario leading to death. In addition, it is known that treatment with Campath leads to profound immune suppression. Therefore, the additive effects of treatment with Campath in a population already compromised must be taken into consideration in any assessment of the causes of death.

The deaths occurring on the Campath treatment arm of CAM 307 are consistent with the number and causes of death expected with Campath treatment in the setting of B-CLL

historically. Table 11 summarizes the causes of death in three legacy studies of previously treated B-CLL patients referenced in this application. The causes of death were those attributed by FDA in its review of the original Campath BLA application, STN 103948/0, dated May 4, 2001.

Table 11 CAM 005, 009, 211 Causes of Death

Total deaths w/in 180 days of last dose (All subjects n = 149)	30
Disease progression	8
Disease complication	1
Infection	14
Inanition	1
Thrombocytopenia w/ hemorrhage	3
PML	1
Suicide	1
Unknown	1

Table 12 summarizes attribution for the CAM 307 causes of death made by the applicant and FDA.

Table 12 CAM 307 FDA Attribution of Cause of Death

Cause of death	Campath		Chlorambucil	
	Applicant	Reviewer	Applicant	Reviewer
Total w/in 180 days of last dose	4	4	9	9
Disease progression	1	-	3	1
Disease complication	1	-	-	-
Infection	1	3	2	4
Cardiac	1	1	2	2
Secondary Malignancy	-	-	2	2

Of the thirteen deaths occurring within 180 days of the last treatment dose on either arm of CAM 307, only one death on the chlorambucil arm (Subject 2005-1029) was attributed to study drug by the applicant. The only death in the Campath treatment group within 30 days of last treatment (Subject 1301-1177) was not attributed to study drug. The cause of death in this case was reported as kidney, heart and lung insufficiency and was associated with blood cultures positive for *Candida albicans*. While the subject's CLL, pre-existing medical conditions and a recent prior hospitalization for infection may have contributed to the subject's demise, there is no evidence to rule out Campath as a major contributing factor.

For the three subjects whose deaths occurred between 31 and 180 days of last receiving Campath, only one (Subject 4001-1270) was reasonably attributable to the stated cause (sudden cardiac death) based on the history and data provided. The other deaths had an infectious component as the proximate cause of death. In the first case (Subject 4002-1013), the subject died as a result of septic shock. In the second case (Subject 4007-1240), the subject died of liver failure secondary to apparent re-activation of viral hepatitis. Campath's contribution to immune dysfunction leading to these deaths cannot be ruled out.

Following are case summaries for deaths occurring during CAM 307 within 180 days of last treatment dose grouped by treatment arm. Not summarized are two deaths (Subjects 1016-1254 and 1301-1256) attributed to secondary malignancies, neuroendocrine carcinoma and squamous cell carcinoma of the lung. Both were diagnosed within months after randomization and both subjects had been treated with chlorambucil.

Campath Treatment Group:

Subject 1301-1177 was a 73 yo female diagnosed in August, 2003. RAI III, PS 1 at baseline. Randomized January 3, 2004. Baseline diagnoses included angina pectoris, HTN, nephrotic syndrome, autoimmune hemolytic anemia and cholelithiasis. (b) (6) prior to randomization, subject was hospitalized and diagnosed with nephrotic syndrome. During hospitalization, an e. coli UTI was also diagnosed. Antibiotics and other appropriate therapies were administered. There is no record of the date of discharge. The first dose of Campath was administered on January 6, 2004. Three days later, diarrhea developed which responded to loperamide. Subject required re-hydration. On January 16, 2004, cultures were positive for candida species and antifungals were administered. The last dose of Campath (30mg IV) was also given on this date. On January 17 and 18, subject received intensive symptomatic and antifungal treatment. Anuria, hypotension and severe abdominal pain developed on (b) (6). Massive ascites and cholelithiasis were revealed by ultrasound. Hypovolemic shock, cardiorespiratory and renal insufficiency followed. Date of death was recorded as (b) (6). Causes of death reported were systemic candida albicans sepsis and e coli UTI.

Subject 4001-1270 was a 52 yo male diagnosed in March, 1997. RAI IV, PS 0 at baseline. Randomized May 10, 2004. Baseline diagnoses included ischemic heart disease, decreased LVF, and mitral insufficiency. Two MIs were reported from (b) (6) and (b) (6). Treatment began on May 19, 2004 and ended on August 13, 2004. Subject was found dead in his home on (b) (6). Cause was sudden cardiac death attributed by the investigator to a h/o ischemic heart disease.

Subject 4002-1013 was a 66 yo male diagnosed in August, 2002. RAI IV, PS 1 at baseline. Randomized August 29, 2002. Baseline diagnoses included mild HTN controlled with enalapril. Treatment began on September 9, 2002 and ended on November 9, 2002 with investigator determined partial response. The subject was hospitalized in (b) (6) with fever of 39.5° C and a creatinine of 2.86 mg/dL. He became anuric, hypotensive and died on (b) (6) due to culture negative septic shock. On the date of death laboratory evaluation also revealed BUN 257 mg/dL, creatinine 7.62 mg/dL, bilirubin 7.6 mg/dL, SGOT 969 U/L, SGPT 157 U/L, GGPT 135U/L, LDH 8656 U/L. The investigator attributed death to CLL. Per IRRP, subject was in CR at time of death.

Subject 4007-1240 was a 69 yo male diagnosed in July 2003. RAI I, PS 1 at baseline. Randomized March 29, 2004. Baseline diagnoses included paroxysmal atrial fibrillation, HTN, hepatitis B, and hyperthyroidism. Treatment began on (b) (6) and ended (b) (6). The subject was hospitalized during the entirety of his treatment, initially due to CMV viremia treated with ganciclovir and subsequently bronchopneumonia treated with tobramycin. He recovered and was discharged. At the end of his treatment a mild increase in liver enzymes was noted. Six weeks after the end of treatment, the subject's condition was deteriorating and severe hepatic dysfunction was apparent by laboratory evaluation (ALT 2058 U/L, AST 2044 U/L, T bilirubin 198 UMOL/L). Initially, the subject refused hospitalization, but was subsequently admitted. A hepatitis evaluation revealed HAV, HCV and CMV negative; HBsAg positive, HBeAg negative, anti-HBe positive, HBV DNA could not be done owing to severe hyperbilirubinemia. HDV and EBV could not be excluded. In spite of appropriate treatment, liver insufficiency progressed and death occurred on (b) (6). The investigator attributed the event to hepatic insufficiency of unknown origin probably due to virus. The IRRP suggested that baseline HBV was exacerbated by immunosuppression from CLL or Campath, or both.

Chlorambucil Treatment Group:

Subject 1301-1257 was a 69 yo male diagnosed in April, 2004. RAI IV, PS 2 at baseline. Randomized on April 22, 2004. First and only dose of chlorambucil was given on (b) (6). Sudden, unexplained death on (b) (6). No autopsy.

Subject 2005-1029 was a 71 yo male diagnosed October, 2002. RAI II, PS 0 at baseline. Randomization on November 11, 2002. Baseline diagnoses included HTN, BPH and moderate nocturia. Treatment began (b) (6) after which profound neutropenia (grade 4) and sepsis developed requiring prolonged hospitalization. Subject discharged on (b) (6) with diagnoses *pseudomonas aeruginosa*, enterococcus sepsis, and perianal mucositis from which he was recovered. Delayed second treatment was given on January 16, 2003 and a final treatment on February 12, 2003. Again admitted for neutropenia and sepsis on (b) (6) when he was found at home unconscious. CT cerebrum was within normal limits. ECG was suggestive of MI. Blood cultures were positive for *Listeria monocytogenes*. Death date recorded as (b) (6). Cause *Listeria* encephalitis attributed by investigator as possibly related to chlorambucil. Loss of consciousness was related to CLL. No autopsy.

Subject 9009-1121 was a 75 yo female diagnosed July, 21, 2003. RAI IIIA, PS 0 at baseline. Randomized September 2, 2003. Baseline diagnoses included exudative pleuritis, mitral valve insufficiency, cardiac insufficiency, atrial fib, and HTN. Treatment began September 8, 2003. Another dose was given on (b) (6) after subject hospitalized for back pain three days prior. Subject became somnolent after chlorambucil was given. CVA suspected; hydration, mannitol, 2 units packed cells, antibiotics and supportive care given. Lapsed into coma on (b) (6), date of death. Autopsy cause of death reported as cardiac insufficiency. This was attributed by the investigator to baseline mitral valve insufficiency.

Subject 1402-1274 was a 75 yo male diagnosed in March, 2004. RAI II, PS 0 at baseline. Randomized May 25, 2004. Baseline diagnoses included BPH, HTN, chronic bronchitis, balanitis and a number of other minor diagnoses. Treatment began on June 2, 2004 and

ended November 4, 2004 when he was discontinued from study treatment due to ITP. The subject was hospitalized with bronchopneumonia and suspected but unconfirmed PE on (b) (6). He died of (b) (6) and the cause of death attributed by the investigator was bronchopneumonia related to progression of disease.

Subject 4002-1057 was a 64 yo female diagnosed in March, 2003. RAI IV, PS 1 at baseline. Randomized March 18, 2003. Baseline diagnoses included HTN. Subject had been transfused 2 units of packed cells prior to enrollment owing to pancytopenia. Treatment began on March 19, 2003 and ended on May 13, 2003. Progressive disease was diagnosed on June 10, 2003 and alternative treatment began on (b) (6). In (b) (6), the patient was hospitalized and treated for pneumonia. Sepsis with shock developed during this hospital stay and the subject died on (b) (6). Death was attributed by the investigator to disease progression.

Subject 5004-1215 was a 55 yo female diagnosed in November, 2003. RAI II, PS 0 at baseline. Randomized February 20, 2004. There were baseline LFT elevations and a waiver was obtained. Other baseline diagnoses included HTN, nevus regio facialis, a remote history of HAV (1972), and thrombophlebitis in March, 2003. Treatment began on February 23, 2004 and ended on March 22, 2004. The subject was discontinued from study due to progressive disease on April 19, 2004. Campath was given on April 21, 2004 and CHOP was started on May 17, 2004. Cause of death, which occurred on (b) (6), was attributed by the investigator to progressive disease.

Subject 9010-1269 was a 56 yo male diagnosed in March, 2004. RAI I, PS 1 at baseline. Randomized May 6, 2004. Baseline diagnosis included chronic gastritis and h/o splenectomy due to trauma (1989). Treatment began on May 12, 2004 and ended on August 4, 2004 as a result of a determination by the investigator that the disease failed to respond to treatment. Additional chlorambucil was given in August, but changed to a fludarabine-based regimen in September, 2004. The subject died on (b) (6) and the investigator attribution was suspected pulmonary TB. The IRRP review questioned the original CLL diagnosis and stated there was no data to support a diagnosis of progressive disease.

7.1.2 Other Serious Adverse Events

The AE1 dataset was the primary source for analysis of serious adverse events (SAEs). This dataset included subject deaths within thirty days of receiving study drug. Serious adverse events occurring at any time during the conduct of the study were identified. Multiple occurrences of the same SAE were eliminated from the dataset prior to analysis. Accuracy of coding from verbatim term to MedDRA 9.0 Preferred Term (PT) was verified by a review of AE line listings. Events were then grouped and analyzed at individual levels of the MedDRA hierarchy, by treatment group and other relevant subgroups. Data listings, CRFs, and narratives were also reviewed for cases of particular interest. Finally, these data were compared to the legacy study data.

In CAM 307, a serious adverse event (SAE) was defined as any experience suggesting a significant hazard, contraindication, side effect, or precaution that resulted in death, a life threatening experience, hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, a congenital anomaly or birth defect, or medical or surgical intervention to prevent one of the foregoing outcomes. Serious adverse

events were presented and graded according to NCI CTC version 2.0. Serious adverse event reporting was to occur until the time of alternative treatment or for 6 months following the last administration of study drug, whichever occurred first. Follow up for all SAEs continued until stabilization (for persistent impairment), resolution, or subject death.

Table 13 represents the incidence of SAEs grouped by treatment arm and MedDRA System Organ Class (SOC). Although this reviewer was unable to confirm the exact number of subjects with SAEs indicated in the CSR (n=75), the overall analysis was similar. FDA analysis revealed 73 subjects, 51 (34.7%) treated with Campath and 22 (15%) treated with chlorambucil, who experienced 120 episodes of one or more SAEs. Of the total number of events, 83 (56.5%) occurred in subjects treated with Campath and 37 (25%) in those treated with chlorambucil.

The most common SAEs reported with Campath treatment during CAM 307 were infections, especially CMV, infusion reactions, and cytopenias. Toxicities of this nature are expected with Campath and strategies for prevention, early identification, and treatment for them are available. The SAEs reported during the conduct of CAM 307 are consistent with those noted previously with Campath and are included in current product labeling.

Because there was a three-fold disparity in cardiac events between treatment arms, this reviewer performed an in-depth evaluation of each subject with a cardiac-related SAE. Narratives, CRFs, and line listings served as a basis for this evaluation. This reviewer concluded that characteristics of the CLL patient population with regard to age, comorbidities, and cardiac risk factors may predispose them to cardiac events. However, their risk may be increased in the face of certain secondary stressors such as infections or infusion reactions. Current labeling contains adequate information on the occurrence of cardiac toxicities experienced during treatment with Campath. In addition, FDA monitoring of post marketing periodic safety updates continues. Therefore, at this time, no additional steps to ensure patient safety are needed or will be required.

Table 13 CAM 307 SAE Incidence by Arm

MedDRA SOC	Campath	Chlorambucil
Blood and Lymphatic System Disorders	6	3
Cardiac Disorders	6	2
Ear and Labyrinth Disorders	1	0
Gastrointestinal Disorders	0	1
General Disorders and Administration Site Conditions	8	3
Hepatobiliary Disorders	2	0
Immune System Disorders	1	0
Infections and Infestations	13	2
Injury, Poisoning and Procedural Complications	0	1
Investigations	0	1
Musculoskeletal and Connective Tissue Disorders	0	1
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	2	3
Nervous System Disorders	3	1
Psychiatric Disorders	0	1

MedDRA SOC	Campath	Chlorambucil
Renal and Urinary Disorders	1	0
Respiratory, Thoracic and Mediastinal Disorders	2	1
Skin and Subcutaneous Tissue Disorders	4	0
Vascular Disorders	2	2

Second Malignancies

Five subjects developed second malignancies during the conduct of CAM 307, two subjects treated with Campath and three subjects treated with chlorambucil. These included two adenocarcinomas of the lung (1301-1256 and 8001-1141), breast cancer (5004-1232), testicular cancer (9002-1231), and melanoma (4007-1245). Only the development of melanoma was deemed related to study treatment (chlorambucil).

7.1.3 Dropouts and Other Significant Adverse Events

The end of treatment (EOT0) listing dataset was the primary source used for the initial analysis and characterization of treatment discontinuations. This dataset contained the investigator assessment of subject status at the end of therapy (completed or discontinued early). A subset of subjects not completing protocol treatment were also reviewed and analyzed. A total of 135 treatment discontinuations for any reason were identified. These data were further analyzed and subsets of specific reasons for discontinuation were reviewed. Dataset AE1 was also reviewed and a subset of subjects coded as "discontinued" was analyzed and compared to the EOT0 data. Available CRFs, narrative summaries, and data listings were reviewed to evaluate and confirm causes of treatment discontinuations. In addition, a subset of the data was compiled to further evaluate the causes of treatment discontinuations. Accuracy of coding from verbatim term to MedDRA Preferred Term (PT) was verified by a review of approximately 5000 AE line listings from this data subset. Treatment discontinuations from the legacy studies referenced in this submission were also reviewed and compared to the data from CAM 307. Other significant adverse events were analyzed similarly and a complete discussion of the analyses is included below.

7.1.3.1 Overall profile of dropouts

The total number of subjects who discontinued treatment prior to completing study treatment per protocol was 135/297 (45%). This included 48 subjects (32.2%) who received Campath and 87 subjects (58.8%) who received chlorambucil. The reasons given for treatment discontinuation overall are summarized in **Table 14**. Thirty-nine subjects were discontinued from treatment due to investigator determined disease progression, two who received Campath and 37 who received chlorambucil.

Comment: This disparity may stem in part from the disease characteristics of the subject population in this study (i.e., subjects with evidence of disease progression at time of enrollment), the overall resistance of B-CLL to alkylating agents, variable response rates for chlorambucil (30% to 70%) in treatment naive patients historically, and the duration and intensity of the treatment regimens in this study (Campath: 3 x per week for up to 12 weeks vs. chlorambucil: once per month for up to 12 months).

Two subjects, one from each treatment arm, discontinued treatment due to protocol violations. Eighteen subjects had their treatment discontinued as the result of adverse

events. Treatment discontinuations in another 39 subjects were attributed to “investigator decision”. Review of the CRFs for these subjects indicated that four were actually discontinued due to AEs, including leukopenia (Subject 1013-1268/chlorambucil), CMV infection (Subject 2009-1038/Campath), anemia (Subject 4008-1149/chlorambucil), and thrombocytopenia (Subject 5001-1107/Campath).

Table 14 CAM 307 Discontinuations for Any Reason

REASONDC	Campath	Chlorambucil
Adverse Event	18 (12%)	2 (1.4%)
Deceased	1 (0.7%)	3 (2.0%)
Disease Progression	2 (1.3%)	37 (25%)
Infection	8 (5.4%)	5 (3.4%)
Investigator Decision	10 (7.0%)	29 (20%)
Autoimmune Anemia/Thrombocytopenia	1 (0.7%)	5 (3.4%)
Protocol Violation	1 (0.7%)	1 (0.7%)
Refused Further Treatment	7 (4.7%)	5 (3.4%)

7.1.3.2 Adverse events associated with dropouts

Table 15 summarizes the 38 subjects who discontinued treatment for adverse events. The verbatim reason for study discontinuation from the EOT0 dataset is utilized in this table. The number includes subjects who refused further treatment as a result of an adverse event and subjects who were discontinued due to “investigator decision” with an adverse event identified as the reason for discontinuation. Among these, there were 27 subjects (18.3%) who received Campath and 11 subjects (7.4%) who received chlorambucil. Deaths were not included in this analysis.

While the incidence of AEs in the Campath arm is greater than in the chlorambucil arm, the character and frequency of the adverse events leading to treatment discontinuation in this trial are not different from those that appear in current Campath labeling. Given the clinical experience with Campath to date, cytopenias, infusion reactions, and infections attributable to this agent were expected. All are discussed in greater detail herein.

Table 15 CAM 307 Discontinuations for Adverse Event (Safety Population)

Reason for Study Discontinuation	Campath® (n = 147)	Chlorambucil (n = 147)
HEMATOLOGIC		
ANAEMIA	0	3 (2%)
HAEMOLYTIC ANAEMIA	0	1 (0.7%)
LEUKOPENIA	0	1 (0.7%)
NEUTROPENIA	3 (2%)	1 (0.7%)
THROMBOCYTOPENIA	1 (0.7%)	2 (1.3%)
TOTAL	4 (2.7%)	8 (5.4%)
CARDIAC		
ASYSTOLE	1 (0.7%)	0
ATRIAL FIBRILLATION	1 (0.7%)	0

Reason for Study Discontinuation	Campath® (n = 147)	Chlorambucil (n = 147)
INSUFFICIENCY CARDIORESPIRATORY	1 (0.7%)	0
CHEST PAIN	1 (0.7%)	0
TOTAL	4 (2.8%)	0
GASTROINTESTINAL		
DIARRHEA	1 (0.7%)	0
TOTAL	1 (0.7%)	0
INFECTION		
CMV REACTIVATION	9	1 (0.7%)
TOTAL	9 (6.1%)	1 (0.7%)
INFUSIONAL		
FEVER	1 (0.7%)	0
HYPEREMIA OF SKIN	1 (0.7%)	0
HYPOTENSION	1 (0.7%)	0
SHIVERS	1 (0.7%)	0
URTICARIA	2 (1.3%)	0
URTICARIAL RASH	1 (0.7%)	0
TOTAL	7 (4.8%)	0
ENDOCRINE		
DIABETES MELLITUS	1 (0.7%)	0
TOTAL	1 (0.7%)	0
PULMONARY		
DYSPNEA	1 (0.7%)	2 (1.3%)
RHINORRHEA	1 (0.7%)	0
TOTAL	2 (1.3%)	2 (1.3%)

7.1.3.3 Other significant adverse events

The following adverse events associated with Campath were reported commonly during CAM 307, continue to be reported frequently in postmarketing reports, and are addressed in Campath labeling.

Infections

CAM 307 required both pneumocystis prophylaxis (with trimethoprim/sulfamethoxazole or its equivalent) and antiviral prophylaxis (with famciclovir or its equivalent) for subjects receiving Campath during therapy, and for a minimum of two months following the last dose or until CD4 + counts were ≥ 200 cells/ μ L.

The following data were derived from the INFECT1 analysis dataset and represent all

infection events by MedDRA PT. These include infections linked to the MedDRA System Organ Class (SOC) "Infections and Infestations" as the primary SOC as well as those linked to other primary SOCs. In their analysis, the applicant chose to focus on infections coded in the AE1 dataset and linked to "Infections and Infestations" as the primary SOC. As a result, there is discordance between incidence totals for non-CMV infections compiled by the applicant and by FDA.

Overall, infections were reported during the study in 132 subjects (89.8%) treated with Campath and 96 subjects (65.3%) treated with chlorambucil. Excluding CMV, there were 109 subjects (74.1%) treated with Campath and 96 subjects (65.3%) treated with chlorambucil in whom infections occurred. For subjects who experienced Grades 3 to 5 infections, there were 31 (21.1%) who received Campath and 14 (9.5%) who received chlorambucil.

Table 16 summarizes the incidence rates for infections during CAM 307.

It was noted during an analysis of the adverse event and infection datasets that although the CRFs required investigators to capture the causative organism when reporting infections, this information was actually reported in a minority of cases. The Dataset Tip Sheet provided by the applicant confirmed this observation in a "Note to Files" dated October 27, 2006 which states: "In the current data sets about 68 cases were (sic) causative organism are reported/available, and about 130 cases where the causative organism is unknown/not available." It was not possible to determine specific infection rates based on causative organism because this data was not collected adequately to perform such an analysis. Causative organisms (excluding CMV) reported for the Campath treatment arm in the INFECT1 dataset included: bacillus, mycobacterium tuberculosis, candida species, clostridium difficile, e. coli, enterococcus species, haemophilus influenza, helicobacter pylori, HZV/VZV, klebsiella species, MRSA, pseudomonas species, streptococcus, and staphylococcus.

Table 16 CAM 307 Infections

	Campath n=147	Chlorambucil n=147	Total n=294
Infections	132 (89.8%)	96 (65.3%)	228 (77.6%)
Infection SAEs	37 (25.2%)	2 (1.3%)	39 (13.3%)
Infections excluding CMV	109 (74.1%)	96 (65.3%)	205 (69.7%)

Cytomegalovirus

Data on cytomegalovirus events were reported in a number of different datasets including the analysis datasets AE1, INFECT1, INFECT2 and CMV1. These datasets were independently reviewed and analyzed to confirm the CMV incidence rates reported in the Clinical Study Report (CSR). The events are summarized in **Table 17**. Note that as a result of data collection, coding, and dataset design features of CAM 307, and the analysis datasets from which the data were derived, incidence rates for CMV viremia in this table differ from those in the common adverse event tables (see section 7.1.5.4).

Both CMV infections and CMV viremia were included in the adverse event datasets and

were coded with the MedDRA lower level term (LLT) "Cytomegalovirus viremia". As a result, it was not possible to distinguish CMV infection from CMV viremia in the AE datasets utilizing MedDRA. Only the infection and CMV datasets allowed for specific identification of CMV events.

Grading of CMV events was based entirely on investigator discretion.

As a result of prior experience with Campath, cytomegalovirus events were anticipated during CAM 307 and occurred commonly. For Campath treated subjects, CMV antibody testing by ELISA was performed at screening and CMV PCR assays were performed at screening, weekly through the end of treatment, and bi-weekly for two months following treatment. For chlorambucil treated subjects, CMV antibody testing by ELISA was performed at screening and CMV PCR assays were performed at screening and monthly through one month post treatment.

Because of protocol requirements for CMV testing and data capture, CMV infections and CMV viremia were reported separately using MedDRA coding conventions to define and distinguish between the two events. CMV infections were defined as a report of a positive CMV by PCR for subjects who had one or more symptoms consistent with CMV infection (e.g., fever). CMV viremia was defined as a report of a positive CMV by PCR for subjects who had no evidence of symptomatic CMV infection. FDA considers all subjects who were treated with antivirals as a result of a positive CMV by PCR to be CMV infections. This includes subjects who were CMV PCR positive and who were described in the CSR as "asymptomatic".

Campath therapy was interrupted or discontinued for a CMV event as follows: "Patients who develop a positive *qualitative* PCR assay for CMV will have therapy held and a PCR assay performed 1 week later. If the *follow-up PCR* assay is positive or if there are signs and symptoms consistent with *active* CMV disease (e.g., fever, pulmonary, or GI findings), then Campath therapy will be discontinued and IV ganciclovir therapy or equivalent initiated. If the repeat assay is *negative* and the patient remains *asymptomatic*, patients may continue on therapy with weekly PCR monitoring for CMV and continued antiviral prophylaxis." (CSR Appendices 16.1.1 CAM 307 protocol, Mar 16, 2001, section 5.2.1.5)

Although CMV antibody testing was performed for all subjects who enrolled in CAM 307, the applicant noted that no analysis based on CMV antibody testing was performed and reporting of CMV antibody results were abbreviated in the study database. Therefore, baseline CMV antibody status as associated with later development of CMV infection and viremia for CAM 307 subjects is not known.

CMV infection as defined by the applicant was reported in 23 subjects (15.6%) treated with Campath and 0 subjects treated with chlorambucil during CAM 307. Of these infections, 8 (5.4%) were serious adverse events. All subjects were treated with anti-viral therapy and all infections were reported to have resolved.

Eighty-two subjects (55.8%) treated with Campath were CMV positive by PCR at least once during the study as well as 12 subjects (8.2%) treated with chlorambucil. Sixteen cases (10.9%) of CMV viremia were serious adverse events; all subjects had been treated with Campath. For subjects treated with Campath who developed CMV viremia, 36 (44%) were treated with antivirals. The median time to onset of CMV viremia was 70 days.

Comment: A statement in the Clinical Study Report (CSR) noted that in many European countries, particularly in eastern Europe, CMV viremia was reported as an SAE because

patients were routinely admitted for ganciclovir treatment. These subjects were noted to be "asymptomatic". None of the subjects treated with chlorambucil who developed CMV viremia, where 11 of 12 were treated in European countries and 9 of 12 in Eastern Europe, were admitted for CMV treatment.

Table 17 CAM 307 CMV Incidence by Arm

	Campath N = 147	Chlorambucil N = 147	Total N = 294
CMV Infection	23 (15.6%)	0	23 (7.8%)
CMV Infection SAE	8 (5.4%)	0	8 (2.7%)
CMV Viremia	82 (55.8%)	12 (8.2%)	94 (32%)
CMV Viremia treated with antivirals	36 (24.5%)	0	36 (24.5%)
CMV Viremia SAE	16 (10.9%)	0	16 (5.4%)

Infusion Reactions

Subjects who received treatment with Campath were premedicated with diphenhydramine 50 mg IV and either acetaminophen or paracetamol (500 to 1000 mg PO). In addition, hydrocortisone (or its equivalent) and meperidine were permitted as clinically indicated.

The applicant's analysis of infusion reactions focused on chills, pyrexia, nausea, vomiting and hypotension by week on treatment. Reported were a decreasing number of subjects at risk as the study progressed as well as a decreasing incidence of these particular events. An analysis was performed to verify the applicant's findings. The analysis was complicated by design inconsistencies in the datasets that did not allow seamless consolidation of the data from different datasets. As a result, it was not possible to discern actual week of treatment in approximately 10% of the events captured in a dataset derived from the AE1 and CAMPATH1 datasets. Based on a summary of events by week, this reviewer was able to confirm the applicant's report that the frequency of infusion reactions decreased over time on treatment. However, the precise incidence of these adverse events as reported in the CSR could not be verified.

FDA review of the original BLA licensure application for Campath included analysis of the following adverse events considered infusion related: chills, rigors, tremors, pyrexia, nausea, vomiting, rash, pruritis, urticaria, dyspnea, bronchospasm, increased sweating, temperature changes, tachycardia and peripheral edema. A similar analysis of the CAM 307 data was performed during this review. One hundred and twenty seven subjects (86.4%) experienced one or more infusion reactions. There were 695 separate events reported. **Table 18** is a summary of infusion reactions reasonably attributable to Campath utilizing NCI CTCAE version 3 criteria for cytokine release syndrome/acute infusion reaction as a guide.

Table 18 CAM 307 Infusion Related Events by MedDRA PT

MedDRA PT	All Grades	All Grades%	Grade 3&4	Grade 3&4%
Pyrexia	102	69.4	15	10.2
Chills	78	53.1	23	15.6
Nausea	26	17.7	1	0.7
Hypotension	24	16.3	2	1.4
Urticaria	23	15.6	3	2.0
Headache	21	14.3	1	0.7
Dyspnoea	20	13.6	6	4.1
Rash	19	12.9	1	0.7
Vomiting	16	10.9	0	0
Tachycardia	14	9.5	0	0
Anxiety	11	7.5	0	0
Oedema peripheral	7	4.8	0	0
Pruritus	6	4.1	0	0
Back pain	5	3.4	1	0.7
Tremor	5	3.4	0	0
Bronchospasm	3	2.0	2	1.4
Retching	1	0.7	0	0

Tolerance to Campath infusion reactions in subjects premedicated with diphenhydramine and acetaminophen or paracetamol may develop over time. In an assessment of factors contributing to the development of tolerance, one must consider the contributions made by glucocorticoids, meperidine, antiemetics, and antipyretics prescribed as premedication or treatment for infusion related effects. For example, there were 52 Campath treated subjects (35.4%) who received one or more doses of a glucocorticoid during CAM 307. In addition, there were over 50 other WHODRUG (version 2003) medication classifications of drugs prescribed for Campath infusion reactions during the course of the study. There were no formal analyses undertaken by the applicant correlating the effects of premedication on infusion related events and none were undertaken by FDA during the review of this application.

Table 19 lists the glucocorticoids prescribed and the number of treatment events for Campath treated subjects. Table 20 is a summary of steroid use during CAM307 reproduced from the Clinical Study Report (CAM 307 CSR, Table 12-63).

Table 19 CAM 307 Glucocorticoids

Glucocorticoid	Tx events (n)
Amcinonide	1
Dexamethasone	5
Hydrocortisone	64
Hydrocortisone sodium succinate	2
Methylprednisolone	9
Methylprednisolone sodium succinate	3
Prednisolone	3
Prednisone	7

Table 20 CAM 307 Summary of Steroid Use

Category	Campath (N=147)	Chlorambucil (N=147)	Overall (N=294)
Patients who had at least one steroid in study	94 (63.1%)	14 (9.5%)	108 (36.1%)
Patients who had at least one steroid reported as pre-medication	64 (43.0%)	1 (0.7%)	65 (21.7%)
Patients who had at least one steroid reported as concomitant medication	51 (34.2%)	13 (8.8%)	64 (21.4%)
Patients who had at least one steroid reported as concomitant medication indicated for an AE	47 (31.5%)	6 (4.1%)	53 (17.7%)

The applicant correctly noted that the design of CAM 307 did not require reporting of dose or duration of medications. Therefore, an accurate measure of the impact of glucocorticoids on the development of tolerance for infusion related events cannot be ascertained. In addition, any contribution made by glucocorticoids to the efficacy results of this study is unable to be measured.

An analysis of infusion related events leading to discontinuation of Campath treatment is also relevant. This reviewer attributed seven (4.8%) separate infusion related toxicities as leading to study discontinuation (see **Table 15**).

Hematologic Effects

By protocol requirement, only laboratory abnormalities associated with symptoms were to be coded as adverse events. As a result, only these laboratory abnormalities are included as part of the adverse event datasets and discussed here. Although not included in the adverse event tables that follow, cytopenias are discussed fully later in this review and are considered adverse events by FDA.

Cytopenias associated with Campath are well documented in legacy studies and postmarketing reports. Because of the limited number of adverse events associated with cytopenias during CAM 307, differences in incidence rates for pancytopenia, autoimmune idiopathic thrombocytopenia, autoimmune hemolytic anemia, and other cytopenias were not clinically meaningful. In addition, cytopenias are adequately described in current product labeling.

Cardiac Effects

There were a number of cardiac events temporally related to Campath infusions. Twenty subjects (13.6%) experienced one or more cardiac events within two days of receiving Campath with the majority occurring on the date of infusion. The total number of events was 32. Of these, 27 were rhythm disturbances, specifically tachycardia, sinus tachycardia and supraventricular extrasystole. Dysrhythmias can be expected in association with infusion related events such as pyrexia and hypotension. In addition, there was one grade 4 cardiac arrest, one grade 4 sinus bradycardia, one grade 2 angina pectoris, and one grade 1 cyanosis reported on dates of Campath infusion. As noted previously, the population demographics of B-CLL with regard to age, co-morbidities, and cardiac risk factors may predispose these patients to cardiac events. However, the risk may be increased in the face of certain secondary stressors such as those experienced commonly during Campath infusions. Cardiac risks are adequately described in current Campath labeling. While no additional steps to ensure patient safety are needed at this time, careful review of

postmarketing safety data should continue.

7.1.4 Other Search Strategies

Search strategies are discussed in conjunction with the data to which they refer. No other search strategies were employed.

7.1.5 Common Adverse Events

For an analysis of common adverse events (AE), the analysis dataset AE1 was utilized as the primary dataset. This dataset contained all AEs experienced during CAM 307 reported as one record per subject per AE per visit. This reviewer was unable to confirm the overall number of subjects who experienced an AE reported by the applicant in the CSR (n = 268). The incidence rates discussed below were derived from a subset of the AE1 dataset containing one row per subject per AE and grouped by maximum toxicity. These data were then tabulated and analyzed. Note that all laboratory abnormalities appearing in the following tables and discussion are only those associated with a symptom. The protocol required that only abnormal labs associated with a symptom were to be considered an adverse event. A full analysis of the range of laboratory abnormalities during CAM 307 is discussed later in this review. FDA considers all laboratory abnormalities adverse events (as defined by NCI CTCAE version 3.0, utilized for CAM 307 laboratory grading).

In order to examine the data at a depth of granularity sufficient to detect safety signals that may have been obscured otherwise, adverse events were analyzed at each level of the MedDRA hierarchy. All AE tabulations were also compared to legacy study data, the product label, and postmarketing safety updates in an attempt to identify new safety signals.

7.1.5.1 Eliciting adverse events data in the development program

During CAM 307, subjects were assessed monthly for all adverse events. Adverse events were followed and reported through one month post treatment. Drug related and unresolved events were followed and reported until resolution through six months after last study treatment or alternative treatment, whichever was sooner. Serious adverse events, infections, and febrile neutropenia were followed and reported through six months or alternative treatment, whichever was sooner. For the purposes of data reporting, progressive disease was not considered an adverse event. However, the CSR noted that two such events were reported as adverse events.

Case report forms for CAM 307 required recording of new events or symptoms, worsening of baseline abnormalities, and grading of events using NCI CTC version 2 criteria where applicable. The forms did not contain check lists for eliciting adverse events. However, checklists were provided for physical examinations, specifically to record disease related symptoms.

It does not appear that the adverse event data collected was compromised by the approach used to collect it.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded utilizing MedDRA version 9 and were presented to include all five levels of the MedDRA hierarchy. Adverse event grading was performed utilizing NCI

CTC version 2. A side by side comparison of verbatim term to MedDRA Lower Level Term (LLT) was performed to verify the accuracy of the coding process. This included a review of approximately 5000 AE line listings. Coding was deemed appropriate in the majority of cases. The cases where this reviewer's judgment differed from the coder's were not clinically meaningful and would not have had a significant impact on the study's safety results had they been coded differently.

7.1.5.3 Incidence of common adverse events

The safety database for CAM 307 was comprised of 294 subjects who were randomized and received treatment. To determine the number of subjects who experienced an adverse event (AE) at any time during CAM 307, the AE1 dataset was first grouped by patient identifier, MedDRA terms, treatment arm, and maximum AE grade. This resulted in a dataset containing one row per subject per AE by maximum grade. The remaining dataset contained only those subjects who had experienced at least one AE. These data were then tabulated for the total number of subjects, AE events by grade, and incidence rates per arm. There were 252 subjects (86%) who experienced any AE and 114 subjects (46.2%) who experienced grade 3 to 5 AEs during the conduct of CAM 307. One hundred and forty-one subjects (95.9%) treated with Campath experienced one or more adverse events and 73 subjects (49.6%) experienced grades 3 to 5 adverse events. Of the subjects treated with chlorambucil, 111 (75.5%) experienced one or more adverse events and 41 subjects (27.9%) experienced grades 3 to 5 adverse events. The total number of adverse events experienced by all subjects during the study was 1,288 (812 for Campath and 476 for chlorambucil). **Table 21** summarizes the AE data and **Table 22** is a listing of adverse events by MedDRA PT with an incidence of > 2% on either arm.

The most common adverse events associated with Campath were infusion reactions, infections, and cytopenias. Common infusion reactions included pyrexia (69.4%), chills (53.1%), nausea (17.6%), headache (14.3%), hypotension (16.3%), urticaria (15.6%), dyspnea (13.6%), rash (12.9%), vomiting (10.9%), and tachycardia (9.5%). Note that subjects received premedication with diphenhydramine and acetaminophen (or its equivalent). Glucocorticoids and other antihistamines were also permitted and administered as premedication.

Also common during CAM 307 were CMV-related events. Although CMV infections were included in the AE1 datasets, both CMV infections and CMV viremia were coded with the MedDRA lower level term (LLT) "Cytomegalovirus viremia". As a result, it was not possible to distinguish CMV infection from CMV viremia in the AE datasets. Only the infection and CMV datasets allowed for specific identification of CMV events. For this reason, CMV infections do not appear in the common adverse event tables in this review except as subsumed under the MedDRA hierarchy terms to which they were linked. Other dataset design considerations discussed previously account for the discrepancies in incidence rates for CMV in the common adverse event tables when compared to other tables and discussions of CMV in this review. See section 7.1.3.3 for a full discussion of CMV events.

CMV infection, defined as a positive CMV by PCR with one or more symptoms consistent with CMV infection (e.g. fever), was reported in 15.6% of subjects treated with Campath. CMV viremia, defined as a positive CMV by PCR without evidence of symptoms, was reported in 44.2% of subjects treated with Campath, of whom 44% received antiviral

treatment.

As noted previously, a specific analysis of other infections by causative organism would not be informative as a result of inadequate reporting of causative organisms in CAM 307. Cytopenias associated with adverse events were reported in 10% or fewer subjects during the study. However, an analysis of all hematologic laboratory data revealed an increase in incidence rates for cytopenias in subjects treated with Campath. The incidence rates for specific cytopenias are discussed in detail in section 7.1.7.3 of this review.

7.1.5.4 Common adverse event tables

Table 21 CAM 307 Overall Adverse Event Incidence by Arm

	Campath (812 events)	Chlorambucil (476 events)
AEs All Grades n (%)	141 (95.9%)	111 (75.5%)
AEs Grade 3 – 5 n (%)	73 (49.6%)	41 (27.9%)
Any SAE n (%)	83 (56.4%)	35 (23.8%)
AE resulting in study withdrawal n (%)	39 (26.5%)	18 (12.2%)

Table 22 CAM 307 Adverse Event Incidence by MedDRA PT (> 2% Either Arm)

MedDRA PT	Campath All Grades		Chlorambucil All Grades		Campath Grades 3 - 5		Chlorambucil Grades 3 - 5	
	n	%	n	%	n	%	n	%
Pyrexia	102	69.4	16	10.9	15	10.2	1	0.7
Chills	78	53.1	1	0.7	5	3.4	0	0.0
Cytomegalovirus viraemia	65	44.2	12	8.2	6	4.1	0	0.0
Nausea	26	17.7	55	37.4	1	0.7	1	0.7
Urticaria	23	15.6	1	0.7	3	2.0	0	0.0
Hypotension	23	15.6	0	0.0	2	1.4	0	0.0
Headache	21	14.3	11	7.5	1	0.7	0	0.0
Dyspnoea	20	13.6	10	6.8	6	4.1	4	2.7
Hypertension	20	13.6	3	2.0	7	4.8	1	0.7
Rash	19	12.9	6	4.1	1	0.7	0	0.0
Fatigue	18	12.2	19	12.9	2	1.4	1	0.7
Vomiting	16	10.9	27	18.4	0	0.0	1	0.7
Neutropenia	15	10.2	5	3.4	12	8.2	5	3.4
Diarrhoea	15	10.2	6	4.1	1	0.7	0	0.0
Insomnia	15	10.2	5	3.4	0	0.0	0	0.0
Tachycardia	14	9.5	1	0.7	0	0.0	0	0.0
Anaemia	11	7.5	13	8.8	7	4.8	9	6.1
Anxiety	11	7.5	2	1.4	0	0.0	0	0.0
Cough	11	7.5	8	5.4	0	0.0	0	0.0

MedDRA PT	Campath All Grades		Chlorambucil All Grades		Campath Grades 3 - 5		Chlorambucil Grades 3 - 5	
	n	%	n	%	n	%	n	%
Thrombocytopenia	10	6.8	9	6.1	9	6.1	7	4.8
Abdominal pain	9	6.1	7	4.8	1	0.7	1	0.7
Oedema peripheral	7	4.8	6	4.1	0	0.0	1	0.7
Asthenia	6	4.1	3	2.0	0	0.0	0	0.0
Erythema	6	4.1	1	0.7	0	0.0	0	0.0
Pruritus	6	4.1	4	2.7	0	0.0	0	0.0
Abdominal pain upper	5	3.4	2	1.4	0	0.0	0	0.0
Back pain	5	3.4	8	5.4	1	0.7	2	1.4
Dizziness	5	3.4	8	5.4	1	0.7	0	0.0
Tremor	5	3.4	1	0.7	0	0.0	0	0.0
Hyperhidrosis	5	3.4	3	2.0	0	0.0	0	0.0
Sinus tachycardia	4	2.7	0	0.0	0	0.0	0	0.0
Constipation	4	2.7	2	1.4	1	0.7	0	0.0
Dyspepsia	4	2.7	5	3.4	0	0.0	0	0.0
Arthralgia	4	2.7	4	2.7	0	0.0	1	0.7
Syncope	4	2.7	0	0.0	4	2.7	0	0.0
Epistaxis	4	2.7	2	1.4	1	0.7	1	0.7
Bradycardia	3	2.0	0	0.0	1	0.7	0	0.0
Non-cardiac chest pain	3	2.0	3	2.0	0	0.0	0	0.0
Oedema	3	2.0	2	1.4	0	0.0	0	0.0
Weight decreased	3	2.0	3	2.0	0	0.0	0	0.0
Anorexia	3	2.0	9	6.1	0	0.0	0	0.0
Muscular weakness	3	2.0	0	0.0	0	0.0	0	0.0
Musculoskeletal pain	3	2.0	2	1.4	0	0.0	0	0.0
Myalgia	3	2.0	4	2.7	0	0.0	0	0.0
Hypoesthesia	3	2.0	1	0.7	0	0.0	0	0.0
Paraesthesia	3	2.0	1	0.7	0	0.0	0	0.0
Broncho-spasm	3	2.0	0	0.0	2	1.4	0	0.0
Dermatitis allergic	3	2.0	1	0.7	1	0.7	0	0.0
Vertigo	2	1.4	4	2.7	0	0.0	0	0.0
Flatulence	2	1.4	3	2.0	0	0.0	0	0.0
Night sweats	2	1.4	7	4.8	0	0.0	1	0.7
Atrial fibrillation	1	0.7	3	2.0	1	0.7	2	1.4
Pharyngitis	1	0.7	3	2.0	0	0.0	0	0.0
Rhinitis	1	0.7	6	4.1	0	0.0	0	0.0
Bone pain	1	0.7	4	2.7	0	0.0	0	0.0
Muscle spasms	1	0.7	4	2.7	0	0.0	0	0.0
Somnolence	1	0.7	3	2.0	0	0.0	0	0.0
Depression	1	0.7	3	2.0	0	0.0	0	0.0
Pharyngolaryngeal pain	1	0.7	5	3.4	0	0.0	0	0.0
Nasopharyngitis	0	0.0	3	2.0	0	0.0	0	0.0

Table 23, Table 24, and Table 25 list adverse events reported at the SOC, HLGT and HLT levels of the MedDRA hierarchy with an incidence of $\geq 5\%$ on either arm and $> 3\%$ difference between arms.

Table 23 CAM 307 Adverse Event Incidence by MedDRA SOC (greater than or equal to 5% for either arm and 3% difference between arms)

MedDRA SOC	Campath All Grades		Chlorambucil All Grades		Campath Gr 3-5		Chlorambucil Gr 3-5	
	n	%	n	%	n	%	n	%
General Disorders and Administration Site Conditions	122	83.0	39	26.5	22	15.0	4	2.7
Infections and Infestations	67	45.6	25	17.0	8	5.4	2	1.4
Gastrointestinal Disorders	53	36.1	73	49.7	5	3.4	2	1.4
Skin and Subcutaneous Tissue Disorders	52	35.4	24	16.3	4	2.7	4	2.7
Vascular Disorders	45	30.6	5	3.4	10	6.8	2	1.4
Respiratory, Thoracic and Mediastinal Disorders	38	25.9	20	13.6	11	7.5	5	3.4
Nervous System Disorders	36	24.5	27	18.4	6	4.1	4	2.7
Cardiac Disorders	33	22.4	10	6.8	10	6.8	4	2.7
Blood and Lymphatic System Disorders	31	21.1	26	17.7	26	17.7	19	12.9
Psychiatric Disorders	22	15.0	11	7.5	0	0.0	1	0.7
Musculoskeletal and Connective Tissue Disorders	17	11.6	26	17.7	1	0.7	3	2.0
Metabolism and Nutrition Disorders	12	8.2	14	9.5	3	2.0	1	0.7
Renal and Urinary Disorders	7	4.8	4	2.7	2	1.4	2	1.4
Immune System Disorders	5	3.4	1	0.7	3	2.0	0	0.0
Injury, Poisoning and Procedural Complications	1	0.7	8	5.4	0	0.0	1	0.7

Table 24 CAM 307 Adverse Event Incidence by MedDRA HLGT (greater than or equal to 5% either arm and 3% difference between arms)

MedDRA HLGT	Campath All Grades		Chlorambucil All Grades		Campath Gr 3-5		Chlorambucil Gr 3-5	
	n	%	n	%	n	%	n	%
Body temperature conditions	117	79.6	17	11.6	18	12.2	1	0.7
Viral infectious disorders	65	44.2	8	5.4	6	4.1	0	0.0
Gastrointestinal signs and symptoms	43	29.3	63	42.9	1	0.7	2	1.4
General system disorders NEC	34	23.1	29	19.7	3	2.0	2	1.4
Epidermal and dermal conditions	33	22.4	13	8.8	2	1.4	2	1.4
Respiratory disorders NEC	32	21.8	19	12.9	7	4.8	5	3.4
Cardiac arrhythmias	26	17.7	4	2.7	6	4.1	2	1.4
Decreased and nonspecific blood pressure disorders and shock	25	17.0	0	0.0	3	2.0	0	0.0
Angioedema and urticaria	23	15.6	1	0.7	3	2.0	0	0.0

MedDRA HLT	Campath All Grades		Chlorambucil All Grades		Campath Gr 3-5		Chlorambucil Gr 3-5	
	n	%	n	%	n	%	n	%
Headaches	21	14.3	11	7.5	1	0.7	0	0.0
Vascular hypertensive disorders	20	13.6	3	2.0	7	4.8	1	0.7
Gastrointestinal motility and defaecation conditions	19	12.9	7	4.8	2	1.4	0	0.0
White blood cell disorders	18	12.2	6	4.1	15	10.2	6	4.1
Sleep disorders and disturbances	15	10.2	5	3.4	0	0.0	0	0.0
Anxiety disorders and symptoms	12	8.2	2	1.4	0	0.0	0	0.0

Table 25 CAM 307 Adverse Event Incidence by MedDRA HLT (greater than or equal to 5% either arm and 3% difference between arms)

MedDRA HLT	Campath All Grades		Chlorambucil All Grades		Campath Gr 3-5		Chlorambucil Gr 3-5	
	n	%	n	%	n	%	n	%
Febrile disorders	102	69.4	16	10.9	15	10.2	1	0.7
Body temperature perception	78	53.1	1	0.7	5	3.4	0	0.0
Cytomegaloviral infections	65	44.2	6	4.1	6	4.1	0	0.0
Vascular hypotensive disorders	24	16.3	0	0.0	2	1.4	0	0.0
Urticarias	23	15.6	1	0.7	3	2.0	0	0.0
Headaches NEC	21	14.3	11	7.5	1	0.7	0	0.0
Breathing abnormalities	20	13.6	10	6.8	6	4.1	4	2.7
Rashes, eruptions and exanthems NEC	20	13.6	7	4.8	1	0.7	0	0.0
Vascular hypertensive disorders NEC	20	13.6	3	2.0	7	4.8	1	0.7
Rate and rhythm disorders NEC	18	12.2	1	0.7	1	0.7	0	0.0
Neutropenias	16	10.9	6	4.1	13	8.8	6	4.1
Diarrhoea (excl infective)	15	10.2	6	4.1	1	0.7	0	0.0
Disturbances in initiating and maintaining sleep	15	10.2	5	3.4	0	0.0	0	0.0
Anxiety symptoms	12	8.2	2	1.4	0	0.0	0	0.0
Supraventricular arrhythmias	10	6.8	3	2.0	4	2.7	2	1.4

Table 26 and Table 27 summarize adverse events by Standardized MedDRA Queries (SMQ). These are groupings of terms from one or more MedDRA SOC that relate to a defined medical condition or area of interest. The results of SMQ level analysis can highlight areas for further inquiry. Terms are grouped as either broad or narrow in scope which correlate to sensitivity and specificity. Note that p-values are intended for ranking purposes only and are not intended for a determination of statistical significance.

Table 26 CAM 307 Standardized MedDRA Queries by p-Value (Broad Scope)

p-Value	SMQ (Broad Scope)	Campath n=149	Chlorambucil n=148
	At least one SMQ	67.8	50.0
0.0000	Anaphylactic reaction	15.4	2.0
0.0001	Angioedema	22.8	6.8

0.0003	Cardiac arrhythmias	19.5	5.4
0.0007	Possible arrhythmia related investigations, signs and symptoms	14.8	3.4
0.0113	Leukopenia	12.1	4.1
0.0138	Shock	4.0	0
0.0179	Pseudomembranous colitis	11.4	4.1
0.0297	Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	7.4	2.0

p-Values were derived from a Mantel-Haenszel test for ranking purposes only

Table 27 CAM 307 Standardized MedDRA Queries by p-Value (Narrow Scope)

p-Value	SMQ (Narrow Scope)	Campath n=149	Chlorambucil n=148
	At least one SMQ	40.9	21.6
0.0000	Angioedema	15.4	1.4
0.0113	Leukopenia	12.1	4.1
0.0248	Shock	3.4	0
0.0833	Asthma/bronchospasm	2.0	0
0.0833	Shock-associated circulatory or cardiac conditions (excl Torsades de pointes)	2.0	0
0.0869	Haematopoietic cytopenias	16.1	9.5

p-Values were derived from a Mantel-Haenszel test for ranking purposes only

The foregoing tables were the product of analyses undertaken to identify common adverse events at all levels of the MedDRA hierarchy. These analyses confirmed that the adverse events identified during the PT level analysis were the source of the most common safety signals identified. MedDRA SMQ analyses were undertaken to provide another level of depth in the examination of safety issues. No new safety signals for Campath were identified.

7.1.7 Laboratory Findings

The basic laboratory results datasets (HEMA1, CHEM1) contained both baseline and maximum grade post baseline laboratory results during the treatment and post treatment periods for subject samples evaluable for that period. The entire safety population was not represented for each parameter listed in each dataset. Therefore, the analyses of incidence rates in this section were based on the number of subjects with available data for each laboratory parameter analyzed. In addition, it is noted that the HEMA1 analysis dataset was among those affected by the SAS programming error discussed previously. This dataset was corrected and re-submitted by the applicant and is the source of part of the analyses that follow.

7.1.7.1 Overview of laboratory testing in the development program

All subjects entered into study CAM 307 were required to have histologically confirmed, previously untreated B-CLL, RAI stage I through IV with evidence of progressive disease and in need of treatment at the time of study entry. Progressive disease was defined in the protocol as:

- Disease-related B symptoms > 2 weeks
- Evidence of progressive marrow failure
- Progressive splenomegaly or other organomegaly

- Progressive lymphadenopathy
- Progressive lymphocytosis with increase of > 50% over 2 months or anticipated doubling time < 6 months

In light of the disease process and these criteria, hematologic abnormalities at baseline were expected.

Per protocol, CBC with differential and platelets were repeated weekly for the first two months on study for both treatment arms. Thereafter, subjects treated with Campath had these labs evaluated weekly while chlorambucil treated subjects were evaluated monthly. Creatinine, glucose, AST, ALT and total bilirubin were repeated monthly as clinically required for subjects on both treatment arms. In addition, direct and indirect Coombs testing was performed at baseline and then monthly as clinically indicated for subjects on both treatment arms. Immunoglobulin and $\beta 2$ microglobulin assays were performed at baseline and then monthly for all subjects. Laboratory results were summarized and graded using NCI CTCAE version 3.0. As noted previously in this review, abnormal labs not associated with a symptom or clinical syndrome were not considered an adverse event by the protocol. However, they are considered adverse events by FDA for the purposes of this review. In addition, the applicant did not perform an assessment of the relationship between a laboratory abnormality and study treatment unless the abnormality was reported as an adverse event.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Drug-control comparisons of laboratory values were limited to analyses of the differences between the Campath and chlorambucil treatment arms of CAM 307. To the extent practicable, results were compared to available results in the legacy studies referenced in this application.

7.1.7.3 Standard analyses and explorations of laboratory data

Baseline hematologic values were analyzed and there were no significant differences noted between treatment arms. As could be expected in a population with B-CLL, there were only 3 grade 0 (i.e., within the limits of laboratory normal range) absolute lymphocyte counts (ALC) at baseline for both the Campath (n=147) and chlorambucil (n=147) treatment arms. All other baseline ALCs were above the upper limit of normal and were not given an NCI CTCAE grade in the HEMA1 analysis dataset.

Analyses of baseline creatinine, glucose, AST, ALT and total bilirubin were also conducted. There were no significant differences noted between treatment arms for these results.

Analyses of hematologic and chemistry results for the treatment period through thirty days post treatment were also conducted. In addition to the analyses of comparative incidence rates for abnormal laboratory results, minimum, maximum, median, and mean laboratory results for subjects treated with Campath were analyzed. These analyses were performed utilizing the paired t-test. This test compares results for the chosen variable at different time points, usually before and after an event. For the following analyses, laboratory results before and after treatment with Campath were compared.

Absolute lymphocyte count

The CSR states that the shifts in this cell population "are not interpretable...due to the underlying disease process and the known target antigen of Campath". However, it is important to note the effect of Campath on the absolute lymphocyte count (ALC) because of the clinical implications associated with immunosuppression.

During Campath treatment and including a period up to 30 days post treatment, 143/145 evaluable subjects (98.6%) reported a maximum decrease in ALC to CTCAE version 3.0 grade 3 or 4. For subjects treated with chlorambucil, only 4/144 evaluable subjects (2.8%) reported a maximum ALC decrease to grade 3 or 4.

Utilizing the paired t-test, analyses of minimum, maximum, mean and median results for ALC in subjects treated with Campath were performed. Clinically meaningful and statistically significant decreases in the minimum ALC were observed. The minimum result on treatment was 0 and at baseline $1.2 \times 10^9/L$. The p-value was < 0.0001 .

These findings are, as the applicant suggests, reflections of the disease process in B-CLL as well as the Campath target antigen. These data also suggest that the contribution of Campath to the decreases in ALC seen during this study are both interpretable and clinically meaningful.

CD3+/CD4+ and CD3+/CD8+ lymphocytes

Lymphocyte subsets were assessed monthly during CAM 307 utilizing flow cytometry. As expected based on Campath's target antigen and previous clinical experience with this agent, CD3+/CD4+ and CD3+/CD8+ counts during treatment were below $200 \times 10^6/L$ (the CSR reports CD3+/CD4+ medians of $0 \times 10^6/L$ during month one, $1 \times 10^6/L$ during month two, and CD3+/CD8+ medians of $1.5 \times 10^6/L$ during month one, $4 \times 10^6/L$ during month two). Recovery of lymphocytes after discontinuation of Campath was prolonged with a median time to CD4+ cell recovery > 200 of six months post treatment. Of 122 subjects tested, 70 (57%) had CD4+ cell counts > 200 within five months after completion of Campath treatment and 52 (43%) had CD4+ cell counts < 200 at five months or greater after completion of Campath treatment. These results were confirmed by analysis of the CD3P1 dataset. Results reported in the CSR for lymphocyte subsets were confirmed and the overall conclusions and recovery times were identical to those reported.

Absolute neutrophil count

During treatment and including a period up to 30 days post treatment, 65/146 subjects (44.5%) treated with Campath reported a maximum grade 3 or 4 decrease in absolute neutrophil count (ANC) while 39/144 subjects (27.1%) treated with chlorambucil reported decreases to the same grades.

The magnitude of difference in incidence rates for neutropenia between treatment arms in this study is clinically meaningful because it represents an increase in infection risk for subjects treated with Campath. The median time to onset of grade 3 or 4 neutropenia with Campath treatment was 4.4 weeks and 3.7 weeks with chlorambucil treatment.

Utilizing the paired t-test, analyses of ANC minimum, maximum, mean, and median results for Campath treated subjects during the on treatment and baseline periods were performed. Although statistically significant decreases in the minimum and median results for ANC

were observed ($p = < 0.0001$), the results were not clinically meaningful.

WBC

The CSR states that the shifts in this cell population "are not interpretable...due to the underlying disease process and the known target antigen of Campath". The magnitude of difference in incidence rates between treatment arms and the statistical significance of the difference in a subject population that was balanced for disease characteristics contradict this conclusion. During treatment and including a period up to 30 days post treatment, 92/147 subjects treated with Campath (62.6%) reported decreased WBC to grades 3 or 4, while only 2/146 subjects treated with chlorambucil (1.4%) reported the same grade decreases.

Hemoglobin

During treatment and including a period up to 30 days post treatment, there were no clinically meaningful differences in hemoglobin results between treatment arms. There were 20/146 subjects (13.7%) treated with Campath and 28/145 subjects (19.3%) treated with chlorambucil with grade 3 or 4 decreases in hemoglobin reported.

Utilizing the paired t-test, an analysis of Campath minimum, maximum, median and mean results for hemoglobin during the on treatment period as compared to baseline revealed clinically meaningful and statistically significant changes in minimum results only. The minimum result was 9.5 g/L on treatment and 12.0 g/L baseline. The p-value was < 0.0001 .

Platelets

During treatment and including a period up to 30 days post treatment, there were no clinically meaningful differences in platelet results between treatment arms.

There were 20/147 subjects (13.6%) treated with Campath and 21/147 subjects (14.3%) treated with chlorambucil reporting grade 3 or 4 results.

Utilizing the paired t-test, an analysis of Campath minimum, maximum, median and mean results for platelets during the on treatment period as compared to baseline was performed. Although a statistically significant decrease in the minimum platelet result as compared to baseline was observed ($p = < 0.0001$), the result was not clinically meaningful.

Chemistries

The majority of CAM 307 chemistry results during the treatment period and including a period up to 30 days post treatment were reported as grade 0, 1 or 2. The incidence rates were not significantly different between treatment arms. There were a total of 11 subjects with grade 3 or 4 chemistry results reported during Campath treatment and 10 subjects reported during chlorambucil treatment. For subjects treated with Campath, 10 subjects reported grade 3 and one subject reported grade 4 glucose results. There were no other grade 3 or 4 chemistry results reported for Campath. For subjects treated with chlorambucil, there were four subjects with grade 3 and two subjects with grade 4 glucose results reported. There were also two grade 4 creatinine results and one grade 4 SGPT (ALT) result reported with chlorambucil. In addition, an analysis of Campath minimum, maximum and median chemistry values utilizing the paired t-test revealed no statistically significant or clinically meaningful differences in values during the on treatment period compared to baseline.

β -2 Microglobulin

At baseline and overall during the conduct of CAM 307, there were no clinically meaningful or statistically significant differences in β -2 microglobulin results between the treatment arms.

Immunoglobulin

At baseline and overall during the conduct of CAM 307, there were no clinically meaningful or statistically significant differences in the results for IgG, IgA, and IgM between the treatment arms.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Three subjects discontinued treatment because of laboratory abnormality adverse events. These were discontinuations based on investigator decisions for leukopenia (Subject 1013-1268/chlorambucil), anemia (Subject 4008-1149/ chlorambucil), and thrombocytopenia (Subject 5001-1107/Campath).

7.1.7.4 Additional analyses and explorations

None were undertaken.

7.1.8 Vital Signs

Analyses of vital signs from the AE1 and PHYEXAM1 analysis datasets as well as the data listing datasets DOSEVIT0 and ABNVIT0 were performed. Where feasible, the data were evaluated for treatment arm differences. Comparisons between treatment arms were limited by protocol requirements for data collection which were based on the different schedules of administration for each study agent.

7.1.8.1 Overview of vital signs testing in the development program

Vital signs, including weight, were reported during and after treatment with Campath and during the dose escalation period. In addition, vital signs were recorded monthly during the on treatment and follow up periods for both treatment arms.

7.1.8.2 Selection of studies and analyses for overall drug-control comparison

CAM 307 is the only study for which analyses of vital signs were performed.

7.1.8.3 Standard analyses and explorations of vital signs data

Baseline diastolic and systolic blood pressure, temperature, respiration, and pulse data were analyzed. There were no clinically meaningful differences between treatment arms.

Vital sign adverse events associated with Campath infusions were previously discussed (see section 7.1.3.3). The incidence rates for vital sign adverse events were: pyrexia 69.4%, hypotension 15.6% and tachycardia 9.5%. Grade 3/4 pyrexia was reported in 10.2% of subjects and there was one subject who dropped out of the study due to pyrexia. The incidence rate for grades 3 and 4 hypotension was 1.4% and for tachycardia 0.

7.1.10 Immunogenicity

An analysis to detect the presence of anti-Campath antibodies was performed on serum samples obtained during study CAM 307. Antibodies were tested at baseline, monthly during treatment, and at 1, 2, and 6 months following the end of treatment. A total of 1047 samples were received by the analyzing laboratory, (b) (4). Using an ELISA assay, anti-human antibodies (HAHA) were detected in 11 of 133 subjects (8.3%). Two subjects

with detectable anti-Campath antibody titers were also weakly positive when analyzed for neutralizing antibodies. One subject discontinued therapy early due to an adverse event and ten subjects responded to therapy, 3 were complete responses and 7 were partial responses. Although the data are limited, there is no evidence to suggest the presence of anti-Campath antibodies had an impact on response to therapy.

For a complete analysis and discussion of the immunogenicity data please see the Office of Clinical Pharmacology review.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted in support of this application.

7.1.12 Special Safety Studies

No special safety studies were conducted in support of this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal phenomena are known. Campath has no expected potential for abuse.

7.1.14 Human Reproduction and Pregnancy Data

There are no studies of Campath in pregnant or lactating women.

7.1.15 Assessment of Effect on Growth

Information from the published medical literature is available on the treatment of Campath in children. However, the indication supported in this application occurs almost exclusively in adults. Recent reports of studies measuring growth in children who have been treated with Campath are summarized here.

In a study published in *Transplantation Proceedings* (Ueno, 2006, *Transplant Proc.*), five pediatric subjects were treated with alemtuzumab as induction for multivisceral transplantation. Routine steroids were not administered to this group. Growth curves before and after transplant were plotted and analyzed. It was expected that reduction of steroid use would improve post transplant "catch-up" growth. This was not the case with only one subject responding as expected.

In another study (Ellis D, 2007, *Transplantation*), 34 children undergoing renal transplantation were administered either antithymocyte globulin (n=8) or alemtuzumab (n=26) followed by tacrolimus monotherapy. Fifteen pre-adolescents had a greater increase in height Z-score at one year when compared to case-matched historical controls who were weaned off steroids by 6 months after transplantation and received twice daily tacrolimus.

7.1.16 Overdose Experience

There were reports of two overdoses in the Periodic Safety Update Report (PSUR) submitted in support of this application. No new safety signals were identified as a result of these reports. There were no overdoses identified in CAM 307 or the legacy studies submitted in support of this application.

Current product labeling states the following: "Initial doses of (b) (4) Campath greater than 3 mg are not well tolerated. One patient who received 80 mg as an initial dose by IV infusion experienced acute bronchospasm, cough, shortness of breath, followed by anuria and death... Single doses of Campath greater than 30 mg or a cumulative weekly dose

greater than 90 mg should not be administered as higher doses have been associated with a higher incidence of pancytopenia.”

Pursuant to labeling negotiations, the applicant was asked to provide a complete report of the overdose experience with Campath to date. It was reported that patients receiving overdoses (b) (4) recommended daily dose experienced bone marrow aplasia, infections and severe infusions reactions. The reported maximum dose received was 90 mg.

There is no known antidote for Campath overdosage. Treatment consists of supportive care.

7.1.17 Postmarketing Experience

Two Periodic Safety Update Reports (PSUR) were submitted with this application. The reports included surveillance from worldwide sources for the periods November 8, 2005 through May 7, 2006 and May 8, 2006 through May 7, 2007. The reports, summaries of all individual case histories, and summary tabulations of coded terms provided with the reports were reviewed. Adult and pediatric patients with a number of different types of malignancies (CLL, lymphoma, MDS, acute leukemia, CTCL/Sezary syndrome) and other conditions (solid organ transplant, MS, ANCA-associated vasculitis) were represented. There were also two follow-up reports on pregnancy outcomes after treatment with Campath. Infections, hematologic abnormalities, and infusion related reactions predominated in safety reporting. In addition, cardiac and autoimmune disorders were represented. There were also four reports of fatal progressive multifocal leukoencephalopathy (PML). Overall, safety concerns attributable to treatment with Campath identified in PSUR are described in current labeling.

7.2 Adequacy of Patient Exposure and Safety Assessments

Exclusive of clinical trials, over (b) (4) patients have received Campath worldwide to date. This number, combined with patients treated with Campath during study CAM 307 and other legacy studies, as well as the extent of exposure and safety assessments undertaken, are adequate to evaluate the safety of Campath.

7.2.1.3 Extent of exposure (dose/duration)

CAM 307 provided for treatment with Campath up to three times weekly for a maximum of 12 weeks including the dose escalation period. The intended treatment period was interpreted by investigators differently. This is reflected by the fact that some subjects received treatment for a total of 12 weeks in spite of dose delays or interruptions while others received treatment for 12 calendar weeks from initiation of therapy regardless of whether or not drug was administered.

Subjects receiving Campath during CAM 307 (n = 147) were to have started dose escalation at 3 mg on day one of treatment. This occurred in 145/147 subjects. Two subjects were treated with an incorrect Campath dose on day one. Subject 1013-1033 received 30 mg on day one and developed grade 3 back pain and dyspnea as well as hypotension, fever, chills, anxiety, retching and tachycardia on the date of infusion. A myocardial infarction (from which the subject recovered) was reported on day two. This subject did not complete therapy per protocol. Subject 4002-1056 received 10 mg on day one and developed dyspnea, anxiety, fever, chills and muscle pain on the date of infusion,

then grade 4 thrombocytopenia on day four. After a dose delay, this subject went on to complete therapy per protocol.

In addition, four subjects were discontinued from Campath treatment prior to achieving the 30 mg target dose as a result of infusion related adverse events. Subject 1401-1195 received one dose of Campath and developed hypotension, sinus bradycardia, fever and vomiting. Treatment was discontinued. Subject 4008-1135 experienced asystole requiring resuscitative measures after one dose of Campath and refused further treatment thereafter. Subject 8001-1207 developed hypotension, hypoxia, fever, rigors and dyspnea after one dose of Campath and the reason given for discontinuation of treatment was "Investigator Decision: history of tuberculosis". Subject 9006-1189 developed atrial fibrillation, chills, fever, vomiting and fatigue after one dose of Campath and discontinued therapy thereafter. The remaining subjects received at least one dose of the 30 mg target dose.

For all subjects who received at least one dose of Campath (n = 147), the median cumulative dose was 956 mg (range: 2 to 1645 mg). The median duration of exposure was 11.7 weeks with a median weekly dose of 82 mg (interquartile range: 69 mg to 90 mg).

For subjects who achieved the 30 mg target dose and who received at least one dose at this level (n=143), the median cumulative dose was 956 mg (range: 103 to 1645 mg). The median duration of exposure was 12 weeks with a median weekly dose of 80 mg (interquartile range: 65 mg to 86 mg).

Dose delays occurred for 80 subjects (54.4%) receiving Campath on one or more occasions. Adverse event (66 cases) and infection (29 cases) were the major reasons given for dose delay. In addition, neutropenia was cited as the reason for dose delay in three cases, thrombocytopenia in three cases, scheduling conflicts in three cases and "other" in 12 cases. Seventeen subjects (11.6%) had their Campath doses reduced.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical data sources were used.

7.2.2.1 Other studies

All studies relevant to this application have been discussed herein.

7.2.2.2 Postmarketing experience

Periodic Safety Update Reports (PSUR) for the period August 11, 2005 – July, 05, 2006 and May 8, 2006 through May 7, 2007 were submitted with the current application and reviewed. Campath is marketed in 17 countries and there are market authorizations for up to 43 countries. There have been over (b) (4) patients treated with Campath worldwide. During the reporting period, study CAMMS223 was put on partial clinical hold. As a result, the applicant developed and implemented a risk minimization plan for immune thrombocytopenia in multiple sclerosis which is ongoing. (see also section 7.1.17 Postmarketing Experience)

7.2.2.3 Literature

Safety reports from the medical literature were reviewed with the PSURs described in sections 7.1.17 and 7.2.2.2.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with Campath since the original FDA accelerated approval

on May 7, 2001 in combination with post-marketing studies is adequate for consideration of conversion to full approval.

7.2.4 Adequacy of Special and/or In Vitro Testing

Not applicable to this trial.

7.2.5 Adequacy Animal of Routine Clinical Testing

Routine testing conducted during CAM 307 was adequate to evaluate safety.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal drug-drug interaction studies were performed during the development of Campath and none were performed during the conduct of CAM 307. This is a therapeutic biologic protein which is neither metabolized nor excreted in the same ways as small molecule drugs. No data are available concerning the incompatibility of Campath with other drug substances. However, data are emerging from the published literature on the drug-drug interaction potentials of therapeutic monoclonal antibodies which may provide useful clinical information and suggest a direction for further studies should Campath become part of combination chemotherapy regimens.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the completeness of data based on protocol requirements for CAM 307 is adequate for an assessment of safety. There were a number of data errors, inconsistencies and omissions identified by FDA during the review cycle. The errors neither substantially affected FDA's analyses nor changed the study results.

7.2.9 Additional Submissions, Including Safety Update

All safety data related to Campath were contained in this application and the cross-referenced legacy studies. Post-marketing safety data were also submitted with this application, continue to be filed by the applicant, and are evaluated routinely by FDA. All available data were included in the safety analysis.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Infections

Overall during CAM 307, infections occurred in 132 subjects (89.8%) treated with Campath and 96 subjects (65.3%) treated with chlorambucil. CMV infection was reported in 23 subjects (15.6%) treated with Campath and 0 subjects treated with chlorambucil. Of these infections, 8 (5.4%) were serious adverse events. All subjects were treated with anti-viral therapy and all infections were reported to have resolved.

CMV viremia occurred in 82 subjects (55.8%) treated with Campath and 12 subjects (8.2%) treated with chlorambucil. In subjects treated with Campath who developed CMV viremia, 44% were treated with antivirals. Sixteen cases (10.9%) of CMV viremia were serious adverse events and all occurred in subjects treated with Campath.

Infusion reactions

One hundred and twenty seven subjects receiving Campath (86.4%) experienced one or more infusion reactions. There were 695 separate events reported. The most common

infusion reactions reported were pyrexia (69.4%), chills (53.1%), nausea (17.7%), hypotension (15.6%), urticaria (15.6%), headache (14.3%), dyspnea (13.6%) and vomiting (10.9%). Seen less frequently, with incidence rates of < 10%, were tachycardia, anxiety, pruritis, tremor and bronchospasm.

Cytopenias

During Campath treatment, 143/145 evaluable subjects (98.6%) reported a maximum decrease to grade 3 or 4 absolute lymphocyte count. Treatment with Campath resulted in decreased CD3+/CD4+ and CD3+/CD8+ counts below $200 \times 10^6/L$. Recovery after discontinuation of Campath was prolonged with a median time to > 200 CD4+ cells of six months. There were 65/146 subjects (44.5%) with a maximum decrease to grade 3 or 4 absolute neutrophil count. A grade 3 or 4 decrease in white blood cell count was reported in 92/147 subjects (62.6 %) during treatment with Campath

Immunogenicity

In eleven of 133 subjects (8.3%) evaluated during and after treatment with Campath, anti-human antibodies (HAHA) were detected utilizing an ELISA assay. Two subjects with detectable anti-Campath antibody titers were also weakly positive when analyzed for neutralizing antibodies.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Data from CAM307 were reviewed to assess the overall frequency of adverse events for subjects treated with Campath as contrasted with those in the comparator arm, chlorambucil. In addition, these results were compared to summaries of data from the single arm legacy studies, the current product label, and postmarketing safety updates. There was no pooling of data from these sources.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

After the dose escalation period, subjects treated with Campath were to receive a maximum daily dose of 30 mg and a maximum weekly dose of 90 mg. An analysis of all \geq grade 3 adverse events grouped by maximum grade, MedDRA SOC and cumulative minimum, maximum, mean, and median doses of Campath revealed no obvious trend suggestive of a dose dependent relationship between Campath single dose or cumulative dose and adverse events. Otherwise notable were two grade 5 cardiac events, sudden cardiac death and cardiac failure, which occurred at cumulative doses of 1046 mg and 1063 mg respectively (median cumulative dose was 956 mg with a range of 2 mg to 1645 mg). These events were discussed previously in this review (see sections 7.1.1 and 7.1.3.3).

7.4.2.2 Explorations for time dependency for adverse findings

As discussed in section 7.1.3.3, infusion reactions associated with Campath occur with frequency early during the course of treatment and decrease over time. **Table 28**, reproduced from the CSR (Table 12-43), indicates an incidence of chills for Campath treated subjects of 43.5% with 89 events, pyrexia of 60.5% with 144 events, nausea of 12.9% with 22 events, vomiting of 6.8% with 11 events and hypotension of 15% with 26 events during week one. By week 12, the incidence of each event was under 5% with

pyrexia noted in 4.1%, chills in 0%, nausea in 1%, vomiting in 2.1% and hypotension in 0.

Table 28 Campath Infusion Related Events Over Time

Week	Patients at Risk	Chills		Pyrexia		Nausea		Vomiting		Hypotension	
		n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
1	147	64 (43.5)	89	89 (60.5)	144	19 (12.9)	22	10 (6.8)	11	22 (15.0)	26
2	141	9 (6.4)	11	20 (14.2)	25	4 (2.8)	5	1 (0.7)	1	2 (1.4)	2
3	136	6 (4.4)	10	18 (13.2)	25
4	130	11 (8.5)	18	15 (11.5)	19	3 (2.3)	3	1 (0.8)	2	.	.
5	109	7 (6.4)	11	23 (21.1)	25	3 (2.8)	5	1 (0.9)	2	.	.
6	98	7 (7.1)	9	12 (12.2)	17	1 (1.0)	1
7	93	3 (3.2)	4	8 (8.6)	8	1 (1.1)	2
8	95	1 (1.1)	1	13 (13.7)	15	1 (1.1)	1	1 (1.1)	1	.	.
9	96	4 (4.2)	4	7 (7.3)	10	1 (1.0)	4	1 (1.0)	4	.	.
10	98	3 (3.1)	4	6 (6.1)	10	2 (2.0)	2	2 (2.0)	2	1 (1.0)	2
11	101	3 (3.0)	3	7 (6.9)	11	.	.	1 (1.0)	1	1 (1.0)	1
12	97	.	.	4 (4.1)	9	1 (1.0)	1	2 (2.1)	2	.	.
>12	42	1 (2.4)	3	4 (9.5)	11	1 (2.4)	1	1 (2.4)	1	1 (2.4)	1

In addition, as discussed previously in section 7.1.7.3, decrease in lymphocytes and lymphocyte subpopulations with Campath treatment were profound and persistent. The median CD4+ cell count was zero during the first month of Campath treatment. The median time to recovery of CD4+ counts to > 200 cells was 6 months post treatment.

7.4.2.3 Explorations for drug-demographic interactions

A review of the relationship between Campath and gender revealed that males experienced higher rates of common drug related adverse events compared to females for pyrexia (65.4% versus 60.5%), CMV viremia (58.7% versus 41.9%), neutropenia (10.6% versus 4.7%), and chills (51.9% versus 46.5%). Females experienced higher rates of CMV infection (18.6% versus 10.6%), hypotension (18.6% versus 12.5%), and urticaria (20.9% versus 12.5%). (See CSR Table 12-31)

A similar review of age-drug interactions focused on the age groups of interest identified in the CAM 307 protocol (i.e., < 65 and ≥ 65). Subjects ≥ 65 experienced higher rates of nausea (19.2% versus 9.5%) and vomiting (11.5% versus 4.2%) when compared to subjects < 65. Subjects < 65 experienced higher rates of CMV viremia (58.9% versus 44.2%), rash (14.7% versus 7.7%), and urticaria (17.9% versus 9.6%) when compared to subjects ≥ 65. (See CSR Table 12-30)

The majority of subjects who participated in this trial and were treated with Campath were caucasian (n = 146/147). Therefore, no explorations for drug-race effects were undertaken.

7.4.2.4 Explorations for drug-disease interactions

During CAM 307 peripheral blood and bone marrow samples (where available) were collected from the safety evaluable population (n=294) monthly during treatment and at one, two, six and twenty-four months after treatment. Flow cytometry was utilized to assess tumor markers, including CD52 expression and the emergence of CD52 negative clones at relapse. There were data analyzed to assess CD52 expression at least once for 283 subjects, 139 who received Campath and 144 who received chlorambucil. In subjects who received Campath, complete loss of CD52 expression was observed in two subjects, but both

recovered CD52 expression prior to their relapse. There was transient loss of CD52 expression during or immediately following Campath in some subjects, but CD52 expression was maintained for all subjects for whom data were available at or near the time of progression.

7.4.2.5 Explorations for drug-drug interactions

None were undertaken.

7.4.3 Causality Determination

Infusion reactions, cytopenias, especially prolonged lymphopenia, immunosuppression, and infections, especially CMV, are deemed causally related to Campath and are the result of antibody and target mediated mechanisms. These reactions are adequately described in current labeling.

8. ADDITIONAL CLINICAL ISSUES

Clinical Benefit

Analyzed during this review is whether there is a demonstrable clinical benefit to patients with B-CLL treated with an agent that prolongs PFS, but has no impact on overall survival. In the original Campath BLA application, FDA's review focused on resolution of B symptoms, bulky adenopathy, and organomegaly as measures of clinical benefit. Also considered were resolution of cytopenias and transfusion independence. Similar explorations of the CAM 307 data were undertaken. Baseline disease characteristics were well-balanced between treatment arms. Changes in disease characteristics favoring Campath during the study were small but measurable. In addition, progression free survival was prolonged and the overall response rate and complete response rate were increased for subjects treated with Campath. These results were statistically significant and clinically meaningful. The benefits of treatment with Campath for patients with B-CLL may mitigate the related toxicities. Summaries of treatment effects for specific disease characteristics follow.

At the baseline screening visit for CAM 307, B symptoms (fever, nightsweats, weight loss) were reported commonly. Nightsweats were most common, reported in 64 subjects (43%) treated with Campath, with 36 subjects (24.2%) reporting moderate to severe symptoms. For subjects treated with chlorambucil, 69 (46.6%) reported nightsweats and 47 (31.8%) reported moderate to severe symptoms. Overall, at the end of 3 months of treatment, nightsweats were reported in 5 subjects (3.4%) treated with Campath and 20 subjects (13.5%) treated with chlorambucil. In subjects who responded to treatment, at the end of 3 months of treatment, nightsweats were reported in 5 subjects who had received Campath (3.4%) and 9 subjects who had received chlorambucil (11.0%). At the end of treatment visit overall, nightsweats were reported by 6 subjects (4.0%) treated with Campath and 21 subjects (14.2%) treated with chlorambucil.

Fever, weight loss greater than 10% from baseline, \geq grade 2 fatigue, and pain were reported infrequently at baseline. As a result, no analyses of these symptoms as measures of clinical benefit were performed.

Lymphadenopathy was reported at baseline in a majority of subjects, however, only 33 subjects (22%) randomized to Campath and 34 subjects (23%) randomized to chlorambucil

were reported as having enlarged lymph nodes ≥ 5 cm. As previously noted, subgroup efficacy analyses do not support the clinical benefit of Campath in subjects with enlarged lymph nodes ≥ 5 cm (see section 6.1.2). However, at the end of treatment visit overall, lymphadenopathy had completely resolved in 13 subjects (8.7%) treated with Campath and 12 subjects (8.1%) treated with chlorambucil, while 38 subjects (25.5%) treated with Campath and 37 subjects (25%) treated with chlorambucil had summary lymph node measurements < 1 cm.

Palpable hepatomegaly at baseline (measured below the right costal margin at the mid-clavicular line) was reported in 43 subjects (28.9%) randomized to Campath and 15 subjects (10.1%) randomized to chlorambucil. Overall, at the end of 3 months of treatment, hepatomegaly was reported in 11 subjects (7.4%) treated with Campath and 18 subjects (12.2%) treated with chlorambucil. In subjects who responded to treatment, at the end of 3 months of treatment hepatomegaly was reported in 9 subjects who had received Campath (7.3%) and 8 subjects who had received chlorambucil (9.8%). At the end of treatment visit overall, 8 subjects (5.4%) treated with Campath and 4 subjects (2.7%) treated with chlorambucil had palpable hepatomegaly reported.

Palpable splenomegaly at baseline (≥ 2 cm below the costal margin) was reported in 53 subjects (35.6%) randomized to Campath and 56 subjects (37.8%) randomized to chlorambucil. Overall at the end of 3 months of treatment, hepatomegaly was reported in 17 subjects (11.4%) treated with Campath and 45 subjects (30.4%) treated with chlorambucil. In subjects who responded to treatment, at the end of 3 months of treatment splenomegaly was reported in 15 subjects who had received Campath (12.1%) and 22 subjects who had received chlorambucil (26.8%). At the end of treatment visit overall, 7 subjects (4.7%) treated with Campath and 12 subjects (8.1%) treated with chlorambucil had palpable splenomegaly reported.

Baseline decreased hemoglobin (< 11 g/dL) was reported in 32 subjects (21.5%) randomized to Campath and 41 subjects (27.7%) randomized to chlorambucil. At the end of treatment visit overall, hemoglobin < 11 g/dL was reported in 10 subjects (6.7%) treated with Campath and 19 subjects (12.8%) treated with chlorambucil.

Decreased platelet count ($< 100 \times 10^9/L$) at baseline was reported in 26 subjects (17.4%) randomized to Campath and 28 subjects (18.9%) randomized to chlorambucil. At the end of treatment visit overall, 6 subjects (4.0%) treated with Campath and 17 subjects (11.5%) treated with chlorambucil were reported to have platelet counts $< 100 \times 10^9/L$.

Blood Products and Growth Factors

Data were tabulated utilizing the safety population from the BLDPROD0 dataset (n=294). Including a period of one month prior to the screening visit, 7 subjects (4.8%) randomized to the Campath treatment arm received blood products (6 subjects packed red cells, 1 subject platelets). During the same period, 5 subjects (3.4%) randomized to the chlorambucil treatment arm received packed red cells. Reasons given for the transfusions during the baseline period included physician discretion, decreased hemoglobin, fatigue, bleeding prophylaxis before bone marrow biopsy, dental extraction, hysterectomy and cardiac surgery. During the entire conduct of the study, 3 subjects treated with Campath and 5 subjects with chlorambucil received red cell transfusions. In addition, platelet transfusions were received by 1 subject treated with Campath.

Data from the GROWFCT0 dataset were also tabulated. The incidence rates for erythropoietin products were balanced between treatment arms with 5 subjects (3.4%) on each arm reporting their use. In addition, use of colony stimulating factors were reported by 15 subjects (10.2%) on the Campath arm and 6 subjects (4.1%) on the chlorambucil arm.

CMV and Interruption of Campath Treatment

A journal article (O'Brien, 2006, *Clin Lymphoma Myeloma*) was submitted with this application to support the applicant's assertion of the following position: "Asymptomatic laboratory positive CMV (i.e., CMV viremia) should not necessarily be considered a serious infection requiring interruption of alemtuzumab therapy, as was specified in CAM307. The CMV management guidelines recommended by experts in the field have matured since the design of CAM307" (see CSR section 2.5.5.2 Clinical Overview, Adverse Events).

Reviewed in the O'Brien article were results from seven clinical trials of single-agent Campath conducted in 456 patients with B-CLL from 2002 to 2006. Only two of the studies enrolled previously untreated patients, and Campath was administered intravenously in one study and subcutaneously in the other. The review included data from CAM 307, the study submitted in support of this application. In six of the studies, routine viral prophylaxis was administered. Symptomatic CMV infections ranged from 4% to 29% while the incidence rates for CMV viremia were not reported. The author speculated that "(t)he wide range of reported incidences might be a result of several important differences between (sic) the studies in design, patient population, and viral detection methods". In addition, whether Campath treatment was interrupted when a patient was determined to be CMV positive in these studies was not reported. There appear to be questions and inconsistencies across these studies making them inadequate to support a proposed change in Campath labeling relative to interruption of Campath therapy for CMV viremia.

FDA would like to evaluate data from studies designed to determine the safety implications of continuing Campath treatment in cases of symptomatic and asymptomatic CMV viremia. FDA has requested that the applicant provide these data. No data have been submitted to date.

8.1 Dosing Regimen and Administration

FDA Recommendation: Administer as an IV infusion over 2 hours. Do not administer as intravenous push or bolus.

Required Escalation to Recommended Dose (At initiation of dosing or if held for >7 days):

- 3 mg daily until infusion reactions ^{(b)(4)}
- then 10 mg daily until infusion reactions (b) (4)

Recommended Dose:

- 30 mg/day three times per week on alternate days (e.g., Mon-Wed-Fri) for 12 weeks

Single doses of greater than 30 mg or cumulative doses greater than 90 mg per week increase the incidence of pancytopenia.

Current Labeling: "Campath therapy should be initiated at a dose of 3mg administered as a 2 hour IV infusion daily. When Campath 3mg daily dose is tolerated (e.g., infusion-related toxicities are ≤ Grade 2), the daily dose should be escalated to 10mg and continued

until tolerated. When the 10mg dose is tolerated, the maintenance dose of Campath 30mg may be initiated. The maintenance dose of Campath is 30mg/day administered three times per week on alternate days (i.e., Monday, Wednesday, and Friday) for up to 12 weeks. In most patients, escalation to 30 mg can be accomplished in 3 - 7 days. Dose escalation to the recommended maintenance dose of 30 mg administered three times per week is required. Single doses of Campath greater than 30 mg or cumulative weekly doses of greater than 90 mg should not be administered since higher doses are associated with an increased incidence of pancytopenia. Campath should be administered intravenously only. The infusion should be administered over a 2 hour period. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**"

8.2 Drug-Drug Interactions

No data are available concerning the incompatibility of Campath with other drug substances. No formal drug interaction studies were performed.

8.3 Special Populations

There were no specific studies submitted with this application to evaluate dosing of Campath based on race, gender, age or major organ impairment. However, subgroup analyses of the CAM 307 data related to efficacy and safety were conducted and the results are discussed in sections 6.1.4.3 and 7.4.2.3 of this review.

8.4 Pediatrics

Information from the published medical literature is available on the treatment of children with Campath. However, the indication supported in this application occurs almost exclusively in adults.

Studies from recent published medical literature related to growth are discussed in section 7.1.15.

8.5 Advisory Committee Meeting

No Advisory Committee meeting relating to this application was held or is planned.

8.6 Literature Review

The applicant submitted an extensive list of references as a part of this application. The references were reviewed by FDA. In addition, selective searches of the medical literature relevant to specific issues and topics of concern pertaining to this application were performed. Relevant references follow the review.

8.7 Postmarketing Risk Management Plan

During the 2005-2006 reporting period, study CAMMS223 was put on partial clinical hold and the applicant developed and implemented a risk minimization plan for immune thrombocytopenia in multiple sclerosis which is ongoing.

No postmarketing risk management plan is required based on this review's safety findings.

9. OVERALL ASSESSMENT

9.1 Conclusions

Campath demonstrated a statistically significant improvement in progression free survival

(PFS) when compared to chlorambucil as single agent treatment for patients with B-CLL who had been previously untreated, had evidence of disease progression and were in need of treatment. Campath prolonged the median progression free interval by 88 days (2.9 months) when compared to chlorambucil (medians: 445 days/14.6 months vs. 357 days/11.7 months). The log-rank p-value after adjustments for Rai stage group was 0.0001 and the estimated hazard ratio was 0.58 (95% CI 0.43, 0.77).

Campath demonstrated an increased overall response rate of 83% vs. 55% with a p-value < 0.0001 and an estimated odds ratio of 3.99 (95% CI: 2.33, 6.84). These results indicate that the odds of an improved treatment response is four times more likely to occur with Campath than with chlorambucil. Campath also demonstrated an increased complete response rate of 24% vs. 2% when compared to chlorambucil (p < 0.0001).

No survival benefit was demonstrated.

The most common and serious adverse reactions with Campath were cytopenias, infusion reactions, and infections (cytomegalovirus). Some of these reactions resulted in fatalities. No new safety signals were identified during the review of CAM 307. The results obtained from this study are consistent with current product labeling.

Clinical benefit in this subject population was determined based on response to treatment, a prolonged treatment free interval and symptom control. The risks associated with Campath treatment can be severe. However, in a risk/benefit analysis of this agent for treatment of B-CLL, the potential benefits may mitigate the frequency and severity of the risks.

9.2 Recommendation on Regulatory Action

Conversion to regular approval is recommended for Campath as a single agent for treatment of B-cell Chronic Lymphocytic Leukemia.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The applicant has developed and implemented a risk minimization plan for immune thrombocytopenia in multiple sclerosis (MS) which is ongoing. In addition, a research program dedicated to identifying patients with MS at risk for developing ITP has been developed. Campath is not approved for the treatment of MS.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

There were extensive format and content changes to the label to conform with the Physician's Labeling Rule (21 CFR 201.57). A copy of the original proposed label is attached.

9.5 Comments to Applicant

The data from CAM 307 submitted in support of this application fulfills PMC # 1 made during the original Campath BLA accelerated approval on May 7, 2001 (STN 103948/0).

In addition, the final study reports submitted (b) (4)

(b) (4) PMC #4 (requiring a quantitative analysis of the incidence and magnitude of HAHA and anti-idiotypic antibodies at study entry and following exposure to Campath) are under review.

10. APPENDICES

10.1 Review of Individual Study Reports

CAM 307 was the only new study reviewed for this application. This review discusses the data from this study at length. Synopses of the legacy data study reports as well as the FDA reviews of those data were also reviewed.

10.2 Line-by-Line Labeling Review

Implementation of the Physician's Labeling Rule (21 CFR 201.57) required extensive format and content changes to the label. The original submitted version of the label is appended to this review. The format and text to be included in the final version of the label continue to be discussed with the applicant.

FDA has recommended the following major changes in the content of the originally proposed label:

(b) (4)

38 Page(s) Withheld

Trade Secret / Confidential (b4)

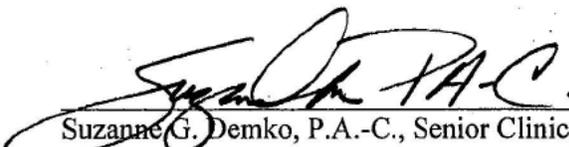
Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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09-12-2007

Date


Jeff Summers, M.D., Team Leader, DBOP, OODP

09-12-2007

Date

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 103948/5070

ENVIRONMENTAL ASSESSMENT



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration

Center for Drug Evaluation and Research Bethesda, MD 20892

Date: August 13, 2007

To: STN103948 File

From: Sean Fitzsimmons, Ph.D. Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies *Sean Fitz 8/13/07*

Through: Marjorie Shapiro, Ph.D., Chief, LMDI *Marjorie Shapiro 8/13/07*

Subject: Review of STN 103948-5070 Efficacy Supplement claim for categorical exclusion for environmental assessment

Submitted: March 28, 2007

Sponsor:

Genzyme Corporation
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San Antonio, TX 78229-2263

Contact:

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Associate Director, Regulatory Affairs
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Background

Supplement 103948.5070 contains data from study CAM 307, a phase III study that evaluated Campath for use as front-line therapy in patients with progressive B-cell CLL to support a change in the labeled indication.

The sponsor states that this supplement meets the criteria for categorical exclusion under 21 CFR section 25.31(b). The original BLA for Campath was granted under such an exemption in May 2001. Section 25.31(b) provides for a categorical exclusion regarding an action on an NDA, abbreviated application, or a supplement to such applications, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per

billion. In the case of the Campath drug product, the concentration or distribution of the substance itself and therefore, its metabolites and degradation products, would be significantly less than one part per billion at the point of entry into the aquatic environment. The action, therefore, would not alter significantly the concentration in the environment. There is no information indicating that additional environmental information is warranted.

The claim of categorical exemption is accepted.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 103948/5070

PHARMACOLOGY REVIEW

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA; STN	103948/5070
Submission Date(s)	3/19/2007, 3/28/2007
PDUFA Due Date	9/19/07
Brand Name	Campath®
Generic Name	Alemtuzumab
Reviewer	Angela Yuxin Men, M.D., Ph.D.
Team Leader	Hong Zhao, Ph.D.
OCP Division	DCP 5
OND Division	OODP/DBOP
Indication	B Cell Chronic Lymphocytic Leukemia (B-CLL)
Sponsor	Genzyme
Submission Type	sBLA (converting to a full approval)

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1. EXECUTIVE SUMMARY

Alemtuzumab (Campath[®], MabCampath[®]) is a recombinant, humanized monoclonal antibody that is directed against CD52, a cell surface glycoprotein, which is expressed on surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and tissues of the male reproductive system. Campath received accelerated approval by FDA on May 7, 2001 for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. At the time of initial accelerated approval of Campath, the Sponsor agreed nine post marketing commitments (PMCs). In this submission, the Sponsor is seeking for a full approval for Campath by submitting the clinical efficacy and safety results from a phase 3 confirmatory study (CAM307). In addition, incidence of loss of CD52 expression and immunogenicity were examined as part of the CAM307 study. These analyses were performed to satisfy the following (b) (4):

(b) (4)

PMC#4: A quantitative analysis of the incidence and magnitude of HAHA (human anti-human antibody) and anti-idiotypic antibodies at study entry and following exposure to Campath

No additional pharmacokinetic data were collected in CAM307, and the previous conclusions regarding the clinical pharmacology aspects of Campath remain unchanged.

1.1. Recommendation

From a clinical pharmacology perspective, the analysis of the incidence and magnitude of HAHA at study entry and following exposure to Campath is acceptable. The sponsor proposed labeling statement regarding immunogenicity is supported by the data.

(b) (4)

See Section 3 for Sponsor proposed labeling changes and the reviewer recommended labeling modifications.

1.2. Phase 4 Study Commitment

There is no phase 4 commitment.

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Immunogenicity:

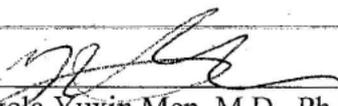
Using an enzyme-linked immunosorbent assay (ELISA), anti-human antibodies (HAHA) were detected in 11 of 133 (8.3%) first line patients. In addition, two patients were weakly positive for

neutralizing activity. Of the 11 patients, one discontinued therapy early due to an adverse event, 3 experienced complete responses (CR), and 7 experienced partial responses (PR). In previous clinical studies, four of 211 (1.9%) previously-treated patients were found to have antibodies to Campath following treatment. The incidence of HAHA is 6% higher for the first line patients than previously treated ones. First line patients may be less immuno-compromised than previously treated patients, therefore, these patients could have a greater risk of developing anti-Campath antibodies.

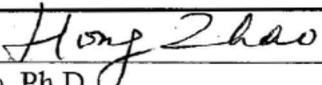
CD52 Expression:

There is no conclusion drawn on the incidence of CD52-expression at the time of relapse or disease progression during or following Campath therapy due to insufficient data collected and limitation in data collection. Apparent loss of CD52 expression at or near the time of progression has not been observed in any patient.

There is no additional pharmacokinetic data collected in CAM307 and there is no change regarding the clinical pharmacology section of Campath.


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2. QUESTION-BASED REVIEW

(Reviewer's Note: this section includes only updates on Intrinsic Section. Please refer to the original review for other information.)

2.1. General Attributes

No updates.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support claims?

The sponsor conducted a Phase 3, open-label, international, multicenter, randomized, comparative study (CAM307) of alemtuzumab vs chlorambucil as first-line therapy in patients with progressive B-cell chronic lymphocytic leukemia (B-CLL). The primary objective of this study is to demonstrate that Campath is superior to chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival (PFS). A total of 297 enrolled patients were randomized on a 1:1 basis to 1 of 2 treatment arms, Arm A (Campath, n=149) and Arm B (chlorambucil, n=148). Campath was administered intravenously (IV) daily at a starting dose of 3 mg. The dose was increased to 10 mg when the dose was well tolerated; the same procedure was followed when the dose was increased from 10 mg to 30 mg. All subsequent doses of Campath were 30 mg administered three times per week for up to 12 weeks, inclusive of dose escalation period(s). Chlorambucil was administered orally at a dose of 40 mg/m² monthly for a maximum of 12 cycles.

Anti-Campath antibodies (HAHA) were tested at baseline and at 1, 2, and 6 months following the end of therapy. Samples from patients on CAM307 arm were analyzed HAHA using an ELISA. Samples that tested positive by ELISA were further analyzed using an anti-Campath neutralizing antibody assay.

CD52 expression was assessed in peripheral blood samples (and in bone marrow aspirates where available) in CAM307. CD52 expression was measured using a flow cytometry technique. Assessment of CD52 expression was performed at screening, monthly during treatment, at the end of treatment, and at 1, 2, 6, and 24 months after treatment. There was no protocol-mandated assessment of CD52 expression specifically at the time of relapse or progression.

2.3. Intrinsic Factors

2.3.1. Other factors that are important to understand the drug's efficacy and safety.

2.3.1.1. Immunogenicity:

As with all therapeutic proteins, there is a potential for immunogenicity. In trials supporting the original accelerated approvals, anti-Campath antibodies were measured in previously treated B-CLL patients. Four of 211 (1.9%) previously-treated patients were found to have antibodies to

Campath. The levels of antibody measured in three of the four patients were low (164 to 262U/mL; the limit of detection reported for the assay at that time was 160 U/mL). One patient was antibody negative up to one month post-treatment then developed a high concentration of anti-Campath antibodies 5 months post-treatment, measured at a single time point.

In CAM307, a total of 539 samples from 154 Campath-treated patients were analyzed for anti-Campath antibodies. Table 1 shows a summary of anti-Campath antibody results for the patients in the Campath arm of the safety population. Overall, 13 samples from 11 patients in CAM307 tested positive (> 444 U/mL) for anti-Campath antibodies. At baseline, one of 125 patients (0.8%) tested positive. Overall, a total of 11 out of 133 patients (8.3%) had a positive anti-Campath antibody result during the follow up period, with a total of 12 positive samples post-treatment in these 11 patients. The patient who was positive at screening had multiple positive samples during the follow up period.

Table 1. Summary of Anti-Campath Antibody Results (CAM307)

Visit	Patients With Assessments	Positive
Screening	125	1 (0.8%)
On Treatment Month 1	9	.
On Treatment Month 2	10	.
On Treatment Month 3	3	.
End of Treatment	21	.
Post-Treatment Month 1	117	3 (2.6%)
Post-Treatment Month 2	112	3 (2.7%)
Post-Treatment Month 3	5	.
Post-Treatment Month 5	2	.
Post-Treatment Month 6	102	6 (5.9%)
Post-Treatment Month 7	6	.
Overall Post-Treatment	133	11 (8.3%)

All of the 13 positive samples were tested using the neutralizing assay. Two of the post-dose samples tested were weakly positive for neutralizing antibodies. One occurred at 6 months follow-up and the other was at 2 months follow-up.

The incidence of HAHA in CAM307 appears to be higher than previous-treated patients (8.3% versus 1.9%). This might be due to that first line patients are less likely to be as immunocompromised as previous-treated patients.

In order to assess whether development of anti-Campath antibodies had any effect on efficacy, 11 patients who were anti-Campath antibody positive were evaluated for response outcomes. One patient was on treatment for 11 days and refused further treatment due to adverse reaction. For the remaining ten patients, 7 showed partial response (PR) and 3 showed complete response (CR). Ten of the eleven patients who had positive HAHA did have adverse events that were potentially infusion-related (e.g. fever, chills) and most of these events were Grade 1 or 2. There

appears to be no evidence of impact of the presence of HAHA on response to therapy or any unexpected unique safety issues associated with the development of those antibodies.

2.3.1.2. CD52 expression:

Analyses have been performed to evaluate whether there is any relationship between CD52 expression measured at the protocol specified time points and patients' date of relapse or progression. These analyses also included date of death as well as progression, but this applied to only one patient in each arm who died in the absence of documented progression and for whom CD52 data were available within the specified time frames.

Table 2 shows a summary of patients for whom CD52 data were available at or around the time of progression. Overall, 283 patients who received treatments had at least one CD52 assessment, with 139 in the Campath arm. In order to assess the expression of CD52 at or near the time of relapse or disease progression, analyses were performed for CD52 expression where data were available within ± 30 days of relapse or progression or -30 days of death, as well as from 30 days prior to progression or death to any time post-progression.

Table 2. Summary of CD52 Data (CAM307)

Category	Campath (N=147)	Chlorambucil (N=147)
Number of Patients Who Had At Least One CD52 Assessment	139 (94.6%)	144 (98.0%)
Number of Rai I-IV Patients that Progressed (IRRP) or Died	82 (55.8%)	109 (74.1%)
Patients who had CD52 measurement within +/- 30 days of Progression or Death	31 (21.1%)	75 (51.0%)
Patients who had CD52 measurement within +/- 60 days of Progression or Death	43 (29.3%)	83 (56.5%)
Patients who had CD52 measurement on -30 days to any time after date of progression or death	44 (29.9%)	81 (55.1%)
Patients who had CD52 measurement on or within 30 days of progression or death	20 (13.6%)	53 (36.1%)
Patients who had CD52 measurement only after 30 days of progression or death	24 (16.3%)	28 (19.0%)

Table 3 shows a summary of the percent of CD52 expression on tumor cells measured around the time of progression or death.

Table 3. Summary of CD52 Tumor Cells Measured Around Time of Progression or Death

Statistics	Campath (N=147)	Chlorambucil (N=147)
Number of progressions (IRRP) or death due to any cause ²	82 (100.0%)	109 (100.0%)
%CD52 tumor cells (10⁶/L) measured within ±30 days of progression or -30 days of death		
N	31	75
Mean (SD)	98.3 (6.36)	99.9 (0.23)
Median	100.0	100.0
Range	70, 100	99, 100
Q1, Q3	100.0, 100.0	100.0, 100.0
%CD52 tumor cells (10⁶/L) measured within 30 days prior to progression or death or any time after progression		
N	44	81
Mean (SD)	98.8 (5.37)	99.8 (1.12)
Median	100.0	100.0
Range	70, 100	92, 100
Q1, Q3	100.0, 100.0	100.0, 100.0

In patients treated with Campath for whom data were available within +/- 30 days of progression (n=31), the median CD52 expression was 100%. For patients for whom CD52 expression data were available from 30 days prior to any time after progression yielded similar results; the median remained at 100%. Of these 44 patients, only 2 had CD52 expression ≤90% (80% and 70%, respectively). No loss of CD52 expression was observed in patients who appeared to be refractory to Campath (n=5).

In the Campath arm, of the CD52 data available at any time point, four patients had loss of CD52 expression and two of which had progressed disease. However, prior to progression, CD52 expression returned to essentially 100%. Apparent loss of CD52 expression near the time of progression was not observed in any patient.

Data collected within +/- 30 days of progression or death from 31 patients did not show complete loss of CD52 expression near the time of progression or death. However, because there was no CD52 data collected within +/- 30 days of progression or death for majority (>70%) of patients in Campath arm in study CAM307, no conclusion could be drawn on the incidence of loss of CD52 expression at the time of relapse or disease progression during or following Campath therapy.

2.4. Extrinsic Factors

No updates.

2.5. General Biopharmaceutics

No updates.

2.6. Analytical

The assays used to measure HAHA and CD52 expression are reviewed by the CMC review team.

3 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 103948/5070

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

sBLA/Serial Number: 103948/5070
Drug Name: Genzyme Alemtuzumab (Campath®)
Indication(s): Relapsed or refractory B-Cell chronic lymphocytic leukemia (B-CLL)
Applicant: Genzyme
Submitted date: March 19, 2007
PDuFA date: September 19, 2007
Review Priority: Priority review

Biometrics Division: Division of Biometrics V
Statistical Reviewer: Dr. Kallappa M. Koti
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Dr. Aloka Chakravarty, Director
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Medical Division: Division of Biologics Oncology Products
Clinical Team: Dr. Suzanne Demko, Dr. Jeff Summers (Team Leader)
Project Manager: Ms. Amy Gomez

Keywords: First-line therapy, NCIWG criteria, IRRP panel, Rai stage, Lymph node size, Progression free survival, Log-rank test, Kaplan-Meier curves, Overall Response Rate, p-value.

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1. EXECUTIVE SUMMARY

B-cell chronic lymphocytic leukemia (B-CLL) is the most common type of leukemia in adults in Europe and North America. It is a disease for which there is no cure, and mainly affects persons older than 50 years of age. Alemtuzumab is a sterile, clear, colorless, isotonic solution for injection. In the United States, is a recombinant, fully humanized monoclonal antibody against the CD52 antigen. Alemtuzumab received accelerated approval in 2001 for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. The accelerated approval was based on overall response rates.

Genzyme is providing a supplemental Biologics License Application (sBLA) for Campath that contains the data from the CAM307 study titled "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Campath (alemtuzumab) versus Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia" to support a change in the labeled indication and to satisfy the first post-marketing commitment. This submission also refers to four (all completed) clinical studies of Alemtuzumab: CAM211, 125-005-C92, 125-009-C92, and (b) (4). Details about these four studies are provided in the Appendix at the end of this review. This review focuses on study CAM307. The efficacy report is mainly based on study CAM307 where eligible patients were to have previously untreated, Rai stage I-IV disease, and be experiencing progression of their B-CLL requiring treatment. The primary objective of CAM307 was to demonstrate that Campath is superior to chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival (PFS).

The Sponsor has claimed that alemtuzumab is significantly superior to chlorambucil relative to the primary endpoint PFS, response rate, and time to alternative treatment in the overall study population of previously untreated patients with B-CLL. The Sponsor believes that CAM307 is an adequate and well-controlled study that verifies and describes the clinical benefit attributable to Campath and that the data from this study satisfy the post-marketing commitment identified in the approval letter dated May 7, 2001. This submission is a 6-month priority efficacy supplement.

1.1 Conclusions and Recommendations

- Protocol specified primary analysis of the primary efficacy endpoint progression-free survival (IRRP) indicates that alemtuzumab is superior to chlorambucil (log-rank test p-value = 0.0001). Alemtuzumab prolongs median disease progression by 88 day (2.9 months) compared to chlorambucil (PFS medians: 445 days [14.6 months] vs. 357 days [11.7 months]). However, a statistically significant difference in PFS was not demonstrated for the high risk subgroup of subjects.
- In terms of overall response rate, alemtuzumab (83%) is superior to chlorambucil (55%): p-value < 0.0001. The odds of a favorable response are 4 times higher for alemtuzumab compared to chlorambucil.

- A statistically significant difference in PFS was not demonstrated for the 24 US subjects.
- No survival benefit is demonstrated. Survival data are immature and patients in CAM307 are no longer being followed for overall survival.

The efficacy data from sBLA 103948/5070 indicate that alemtuzumab is efficacious and provide evidence in support of a change in the labeled indication.

1.2 Brief Overview of Clinical Studies

Genzyme has provided a supplemental Biologics License Application (sBLA) for alemtuzumab that contains the data from the CAM307 study titled "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Campath (Alemtuzumab) versus Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia". Here is an overview of study CAM307.

A total of 297 patients who met eligibility criteria and signed the informed consent document were randomized on a 1:1 basis to one of the two arms, Arm A (149) and Arm B (148). Randomization was accomplished by utilizing the Pocock's minimization method to ensure a balance between the two treatment arms with respect to the following factors: study center, Rai stage (Rai I-II vs. Rai III-IV), performance status (WHO = 0 vs. 1 or WHO = 2), age (< 65 vs. ≥ 65), sex (male, female), and maximum lymph node size (non palpable or < 5cm vs. ≥ 5 cm). This study was conducted at 44 centers located in North America and Europe.

Patients were required to begin treatment within 7 days after randomization. Patients enrolled in Arm A were treated to a maximum of 12 weeks with Alemtuzumab, inclusive of dose escalation period(s). Patients in this arm were treated with 30 mg IV 3x/week for 12 weeks. Patients enrolled in Arm B were treated to a maximum of 12 months with chlorambucil. Chlorambucil was selected as the active control therapy since it is an established therapeutic option for first line B-CLL. Patients in this arm were treated with 40 mg/m² PO 1x/28 days for ≤ 12 cycles.

CAM307 was an international study. There were 24 subjects from the United States of America. The rest of the subjects were recruited from Europe. Demographic characteristics are similar across the two treatment arms for the intent-to-treat (ITT) population, i.e., all patients who were randomized to a treatment arm. Overall, there were more male than female patients, 213/297 male (72%) and 84/297 (28%), enrolled in the study. The study population was predominantly Caucasian, 295/297 patients were Caucasian. The majority of the study population was < 65 years old, 64.6% (192/297) were < 65 years old. The median age overall was 60 years. The majority of the study population was Rai stage I-II (193/297: 65%) as assessed by both investigator and the IRRP.

The efficacy of study treatment was determined by assessment of PFS, disease response using the NCIWG response criteria, overall survival, duration of response, time to treatment failure, and time to alternative therapy. The primary efficacy endpoint in this study was progression-free

survival (PFS). It was defined as the time from randomization date to the first objective documentation of disease progression or death due to any cause, and was based on an IRRP determination of eligibility (Rai stage and B-CLL diagnosis) and date of progression. Patients not progressed and alive as of the date of last evaluation will be considered censored at that time point. All randomized patients were evaluated for efficacy on an intent-to-treat basis (n = 297).

An interim analysis, required by the protocol after the study had followed 50 patients per arm through four months following the date of randomization, was reported at the DSMB meeting of April 21, 2004. An interim efficacy and safety analysis was performed after a total of 95 patients have progressed. The final analysis of PFS between Alemtuzumab and Chlorambucil was to be tested at the pre-specified significance level of 0.048. Comparison of PFS between alemtuzumab and Chlorambucil were performed using the log-rank test, stratified by Rai stage (I-II or III-IV). Two events occurred in patients who had an unconfirmed B-CLL diagnosis by the IRRP. The primary analysis was based on 191 PFS events. The difference in PFS was highly statistically significant (p = 0.0001) with an estimated hazard ratio of 0.58 (95% confidence interval [CI]: 0.43, 0.77) after adjustment by Rai stage group, meaning that the risk of progression or death in treatment naïve B-CLL patients treated with alemtuzumab is 42% less than for those treated with chlorambucil. The overall Kaplan-Meier median PFS was 445 days (14.6 months) for patients in the alemtuzumab arm and 357 days (11.7 months) for patients in the chlorambucil arm based on the IRRP determination of disease progression. The overall response rate, i.e., the rate of patients having either complete response or partial response, was significantly higher for the Campath treated patients compared to the chlorambucil treated patients; specifically there were 83.2% patients in the alemtuzumab arm had overall response compared to 55.4% patients in the chlorambucil arm. A secondary objective of the trial was to compare overall survival between the two treatment arms. However, there were not enough or long enough follow-up data to detect a difference in the overall survival.

1.3 Statistical Issues and Findings

- Study CAM307 recruited only 24 (8%) subjects from the United States (North America). Therefore, a meaningful analysis of U.S. subjects can not be done. When trying to extrapolate the results outside the U.S. patients to U.S. patients, the difference in medical practice should be considered. Table 4.2.2 summarizes the PFS results for those United States B-CLL patients. A statistically significant difference in PFS was not demonstrated for the 24 US subjects.
- According to the Protocol, a secondary objective was to compare overall survival. This was reasserted in the face-to-face meeting of October 12, 2006. Comparison of overall survival between alemtuzumab and chlorambucil was supposed to be done using log-rank test, stratified by Rai stage groups. But now the Sponsor's study report states: "CAM307 was not designed or powered to detect differences in overall survival. There was no overall difference in survival with a total of 24 deaths in the alemtuzumab arm, and 24 deaths in the chlorambucil arm. There were not enough events or enough follow-up data to detect a difference in the overall survival." Survival data are immature and patients in CAM307 are no longer being followed for overall survival.

- Results of the subgroup analyses are of concern. WHO performance status was one of the stratification factors at the time of randomization. As seen from Table 4.2.5, the trial included only 10 (3.5%) subjects who were partially or fully bedridden. This subgroup analysis was too small to perform a reliable evaluation of whether a treatment difference exists. As seen in Section 4, statistical significance was not reached on a difference in PFS between alemtuzumab and chlorambucil (p-value > 0.05) in high-risk subjects, in subjects with lymph node size ≥ 5 cm, and in older subjects (age ≥ 65).
- The Sponsor has calculated the PFS (IRRP) hazard ratio using the Cox proportional hazards model, which requires the ratios of hazards rates under the two treatment arms be constant over time. The appropriateness of the proportional hazards regression method and the validity of the results depend on the correctness of the proportional hazards assumption. The proportional hazards assumption is checked using the SAS log-log survival (LLS) curves. The LLS plot in Figure 3.1.2 does not exhibit parallel pattern. This suggests that the ratio of hazard rates varied greatly over time. That is, the hazards were far from proportional. A test of the validity of the proportional hazards assumption was also used by introducing the time-dependent explanatory variable $X = \text{treatment} * (\log \text{PFS2} - 5.39)$, where 5.39 is the mean of log PFS2. This test gives a non-significant result (p-value = 0.94). An increasing or decreasing hazard ratio over time has not been demonstrated. There is a 25% increase in median progression-free survival (11.7 versus 14.6 months).

2. INTRODUCTION

2.1 Overview

Chronic Lymphocytic Leukemia (CLL) is a neoplastic disorder characterized by increased numbers of clonal leukemia cells that appear as mature lymphocytes. In most cases, these cells express B-cell markers, have prolonged cell survival, and accumulate in the blood, bone marrow, and lymphatic organs. Patients with CLL are generally immunosuppressed due to both the underlying disease and toxicity of prior chemotherapies. As a result of this immunosuppression, infection is a major cause of morbidity and mortality. The survival of CLL patients greatly varies with the stage of their disease.

Alemtuzumab (Campath®, MabCampath®) is a recombinant, humanized monoclonal antibody that is directed against CD52, a cell surface glycoprotein, which is expressed on B-CLL cells as

well as many normal hematopoietic cells. Alemtuzumab is produced in mammalian cell (Chinese hamster ovary) suspension culture in a medium containing neomycin. Alemtuzumab received accelerated approval in 2001 for the treatment of patients with B-cell chronic lymphocytic (B-CLL) who have been treated with a prior alkylating agent and who have failed prior treatment with fludarabine. In Europe alemtuzumab is indicated for the treatment of patients with CLL who have been treated with alkylating agents and who have failed to achieve a complete or partial response or achieved only a short remission (6 months) following fludarabine phosphate therapy.

Alemtuzumab was initially studied as a single agent in previously treated B-CLL patients who had been exposed to prior therapies that included alkylating agents and fludarabine. The original evidence of the efficacy and safety of Alemtuzumab in previously treated B-CLL patients was derived from three, single-arm, clinical studies: CAM211 and two supportive Phase 2 studies, 125-005-C92 and 125-009-C92. The primary efficacy endpoint for all three studies was the proportion of patients with objective responses consisting of either a complete response (CR) or partial response (PR) according to the 1996 NCIWG.

The clinical trial data presented in this submission are derived from study CAM307, which was a Phase III, open-label, international, multi-center, randomized, comparative study of alemtuzumab vs. chlorambucil as first-line therapy in patients with progressive B-CLL. The first patient in this study was randomized on December 5, 2001, and the last patient was randomized on July 15, 2004. The last patient completed the study drug on May 4, 2005. The date of data cut off for CAM307 was June 1, 2006. A total of 297 patients were randomized on a 1:1 basis to one of the two arms, alemtuzumab (149) and chlorambucil (148). Patients were required to begin treatment within 7 days after randomization. Patients enrolled in Arm A were treated to a maximum of 12 weeks with Alemtuzumab, inclusive of dose escalation period(s). Patients in this arm were treated with 30 mg IV 3x/week for 12 weeks. Patients enrolled in Arm B were treated to a maximum of 12 months with chlorambucil. Chlorambucil was selected as the active control therapy since it is an established therapeutic option for first line B-CLL. Patients in this arm were treated with 40 mg/m² PO 1x/28 days for ≤ 12 cycles.

As part of a comprehensive clinical development plan, CAM307 was designed to extend existing data that demonstrated efficacy and safety in patients with B-CLL who were previously treated with other agents. In addition, CAM307 was designed to demonstrate the clinical benefit of alemtuzumab therapy in the first-line setting by assessing progressive-free survival, response rates, and other clinically meaningful time-to-event endpoints in a randomized setting. CAM307 demonstrates that therapy-naïve B-CLL patients treated with alemtuzumab have statistically significantly longer progression-free survival (PFS), and a higher overall response rate (ORR) and complete response (CR) rate than those treated with chlorambucil, with manageable and expected toxicities. The median progression free survival of patients treated with alemtuzumab is 445 days (14.6 months) whereas the median PFS of subjects treated with chlorambucil is 357 days (11.7 months). In addition, the overall response rate is significantly higher for the alemtuzumab treated patients (83%) compared to the chlorambucil treated patients (55%). The Sponsor claims that the data presented from CAM307 confirm the results of earlier studies submitted in support of the initial marketing application, in which the safety and efficacy of alemtuzumab in previously treated patients with B-CLL was demonstrated, and provide

substantial evidence in support of alemtuzumab as a novel, important first-line therapeutic alternative for these patients.

2.2 Data Sources

Data Location: \\Cbsap58\M\CTD_Submissions\STN103948\

Data sets used in this review: CAM307, EFF1

3. STATISTICAL EVALUATION

Original evidence of efficacy and safety in previously treated B-CLL patients was derived from three single-arm clinical studies: CAM211, an international, multi-center, pivotal Phase 2 study, and two supportive Phase 2 studies, 125-005-C92 and 125-009-C92. The primary efficacy endpoint for all three studies was the proportion of patients with objective responses consisting of either a complete response (CR) or partial response (PR) according to the 1996 NCIWG criteria as determined by an IRRP. The overall response rates in studies CAM211, 125-005-C92 and 125-009-C92 were 33%, 21%, and 29%, respectively. The Sponsor states that the clinical benefit of alemtuzumab in the treatment of B-CLL has now been confirmed through the results from CAM307.

3.1 Evaluation of Efficacy

The primary endpoint, progression free survival, has been recognized as a measure of clinical benefit in this disease (Rai, 2000, *N Engl J Med*) due to the long natural history of B-CLL and thus the benefit to patients in delaying disease progression. Consequently, progression-free survival (PFS) was chosen as the primary efficacy endpoint for study CAM307. It was defined as the time from randomization date to the first objective documentation of disease progression or death due to any cause, and was based on an IRRP determination of eligibility (Rai stage and B-CLL diagnosis) and date of progression.

Study Design and Endpoints

CAM307 was a Phase 3, open-label, multi-center, randomized, comparative study of alemtuzumab versus Chlorambucil as front line therapy in patients with progressive B-CLL. Eligible patients were to have previously untreated, Rai stage I-IV disease, and be experiencing progression of their B-CLL requiring treatment. After signing a written informed consent, patients who met the following criteria were eligible to be included in the trial.

- Diagnosis of B-CLL with CD5, CD19, or CD23 positive clone
- Rai stage I to IV disease with
- Disease-related B symptoms
- Evidence of progressive marrow failure
- Progressive splenomegaly to >2 cm

- Progressive lymphadenopathy
- Progressive lymphocytosis with an increase of > 50%
- Received no previous chemotherapy for B-CLL
- 18 years of age or older
- Life expectancy of at least 12 years
- Serum creatinine $\leq 2.0 \times \text{ULN}$ value
- Adequate liver function

Patients were randomized on a 1:1 basis to 1 of 2 treatment arms, Arm A for alemtuzumab and Arm B for chlorambucil. The investigator, the patient, and the sponsor knew the identity of the treatment. Randomization was accomplished by utilizing the minimization (adaptive randomization) method described by Pocock and Simon, using a randomization probability parameter of 0.8. The randomization ensured a balance between assessment arms with respect to the following prognostic factors: (1) study center, (2) Rai stage (I/II vs. III/IV), performance status (WHO 0 or 1 vs. WHO 2), (4) age (< 65 vs. ≥ 65), (5) gender, and (6) maximum lymph node size (< 5cm vs. ≥ 5 cm). Patients enrolled in Arm A were treated to a maximum of 12 weeks with alemtuzumab. Alemtuzumab was administered intravenously (IV) at a daily starting dose of 3 mg. The dose was increased to 10-30 mg when the dose was well tolerated. Patients enrolled in Arm B were treated to maximum of 12 months with chlorambucil. Chlorambucil was administered at a dose of 40 mg/m² orally (PO) once every 28 days. Treatment was repeated monthly (every 28 days) for a maximum of 12 cycles. Table 3.1.1 presents a summary of schedule of events.

Table 3.1.1: Schedule of Events

Activity	Screening	After Random. & Prior to treatment	During treatment		End of therapy	Post treatment follow-up	
			Weekly	Monthly		Monthly < 18 months	Every 3 Months > 18 m.
Informed consent	X						
Disease Assessment	X			X	X	X	X
WHO performance	X			X	X	X	
Cytogenetic analysis		X					
$\beta 2$ microglobulin	X			X	X		
Chest x-ray (PA)	X			X	X		
Imaging studies	X				X		
Campath dosing				X			
Chlorambucil dosing				X			
Disease progression				X	X	X	X
Infections				X	X	X	
Adverse Events				X	X	X	
Survival				X	X	X	X

Response evaluation was performed every month for all patients while on study therapy and at the completion of therapy or at the time of early discontinuation. The investigators were to use

the 1996 NCIWG response criteria to assess response to study treatment. The 1996 NCIWG response criteria are explained in Appendix II.

All randomized patients were evaluated for efficacy on an intent-to-treat (ITT) basis. A difference in PFS in the alemtuzumab versus chlorambucil arm is tested using the log-rank test, stratified by Rai stage. The primary efficacy analysis is based on an independent response review panel's determination of eligibility (Rai stage and B-CLL diagnosis), response, and date of disease progression after response for all patients. All confidence intervals for parameters to be estimated are constructed with a significance level of $\alpha = 0.05$. Kaplan-Meier analyses of time-to-event variables, including duration of response, time to disease progression, and survival are done using PROC LIFETEST in Statistical Application Software® (SAS).

According to Protocol CAM307-A3 dated February 9, 2004, the planned sample size of the study is 284 (142 per treatment arm). This sample size will allow the detection of a 50% increase (i.e., a seven month improvement) in median PFS in either arm, with 80% power and $\alpha = 0.05$ (two-sided). To ensure 80% power, the primary analysis will be conducted when at least 70% of the patients have progressed or dead, i.e., after a total of 190 failures, regardless of treatment arm. Assuming a 30-month accrual period, an estimated 18 month of follow-up after the last patient is enrolled will be needed to observe 190 failures. These estimates are based on a 14-month median PFS in the control arm and a 21-month PFS in the alemtuzumab arm. It is assumed that 5% of the patients who are randomized will not have a confirmed diagnosis of B-CLL or will not receive therapy and, therefore, will be in-evaluable for PFS analysis.

Patient Disposition, Demographic and Baseline Characteristics

Patients who met the following criteria were included in study CAM307.

- Histopathologically confirmed diagnosis of B-CLL with CD5, CD19, or CD23 positive clone
- Rai stage I through IV disease with evidence of progression as evidenced by the presence of one or more of the following: (i) Disease related B symptoms, (ii) Evidence of progressive marrow failure, (iii) Progressive splenomegaly to >2 cm below the left costal margin or other organomegaly with progressive increase over 2 consecutive clinic visits ≥ 2 weeks apart, (iv) Progressive lymphadenopathy with at least 5 sites of involvement with either two nodes at least 2 cm in longer diameter or one node ≥ 5 cm in longest diameter with progressive increase over 2 consecutive clinic visits ≥ 2 weeks apart, and (v) Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of <6 months
- Received no previous chemotherapy for B-CLL
- Life expectancy of at least 12 weeks; World Health Organization performance status of 0, 1, or 2; and 18 years of age or older
- Serum creatinine $\leq 2.0 \times$ the institutional upper limit of normal (ULN) value
- Adequate liver function as indicated by a total bilirubin, aspartate transferase (AST), and alanine transferase (ALT) $\leq \times$ the institutional ULN value, unless directly attributable to the disease

- Female patients with childbearing potential had to have a negative serum pregnancy test within 2 weeks prior to randomization. Male and female patients had to agree to use an effective contraceptive method while on study treatment, if appropriate, and for a minimum of 6 months following study therapy.

The intent to treat (ITT) set is defined as all patients who were randomized to a treatment arm. A total of 297 patients were randomized (149 to alemtuzumab, 148 to chlorambucil). Two patients were assigned a screening number but were screening failures and therefore were not randomized. The per protocol (PP) set is defined as all patients who were treated with study drug, met eligibility criteria, and had no major protocol violation that could affect efficacy. Table 3.1.2 presents a summary of patient disposition upon completing study therapy.

Table 3.1.2: Summary of patient disposition at the end of treatment

Disposition	alemtuzumab	Chlorambucil	Total
Complete study per protocol			
Yes	101 (67.8%)	61 (41.2%)	162 (54.5%)
No	48 (32.2%)	87 (58.8%)	135 (45.5%)
Investigator decision	10 (6.7%)	29 (19.6%)	39 (13.1%)
Refused further treatment	7 (4.7%)	5 (3.4%)	12 (4.0%)
Adverse event	18 (12.1%)	2 (1.4%)	20 (6.7%)
Infection	8 (5.4%)	5 (3.4%)	13 (4.4%)
Disease progression	2 (1.3%)	37 (25.0%)	39 (13.1%)
Protocol violation	1 (.7%)	1 (0.7%)	2 (0.7%)
Deceased	1 (0.7%)	3 (2%)	4 (1.3%)
Autoimmune anemia or Thrombocytopenia	1 (0.7%)	5 (3.4%)	6 (2.0%)

Statistical Methodologies

The primary efficacy endpoint PFS was defined as the time from the randomization date to the first objective documentation of disease progression or death due to any cause, and was based on an IRRP determination of eligibility (Rai stage and B-CLL diagnosis) and date of progression. Progression-free survival is based on the independent response review panel (IRRP) assessment using the 1996 National Cancer Institute Working Group (NCIWG) criteria for CLL. Progression free survival was calculated as: date of progression or death due to any cause, whichever is earlier – date of randomization + 1. Patients not progressed and alive as of the date of last evaluation will be considered censored at that time point. Patients who are evaluated but response assessment are missing will be treated as if the disease progressed on the date that the response was assessed as inevaluable plus one day. The primary efficacy endpoint PFS (IRRP) is labeled as PFS2. Types of events included in the PFS2 primary analysis are shown in Table 3.1.3.

Table 3.1.3: Type of events included in the PFS2 analysis

Category	Alemtuzumab	Chlorambucil	Total
Events of Disease Progression by the IRRP	74	99	173
Death without documented progression	8	10	18
Total	82	109	191

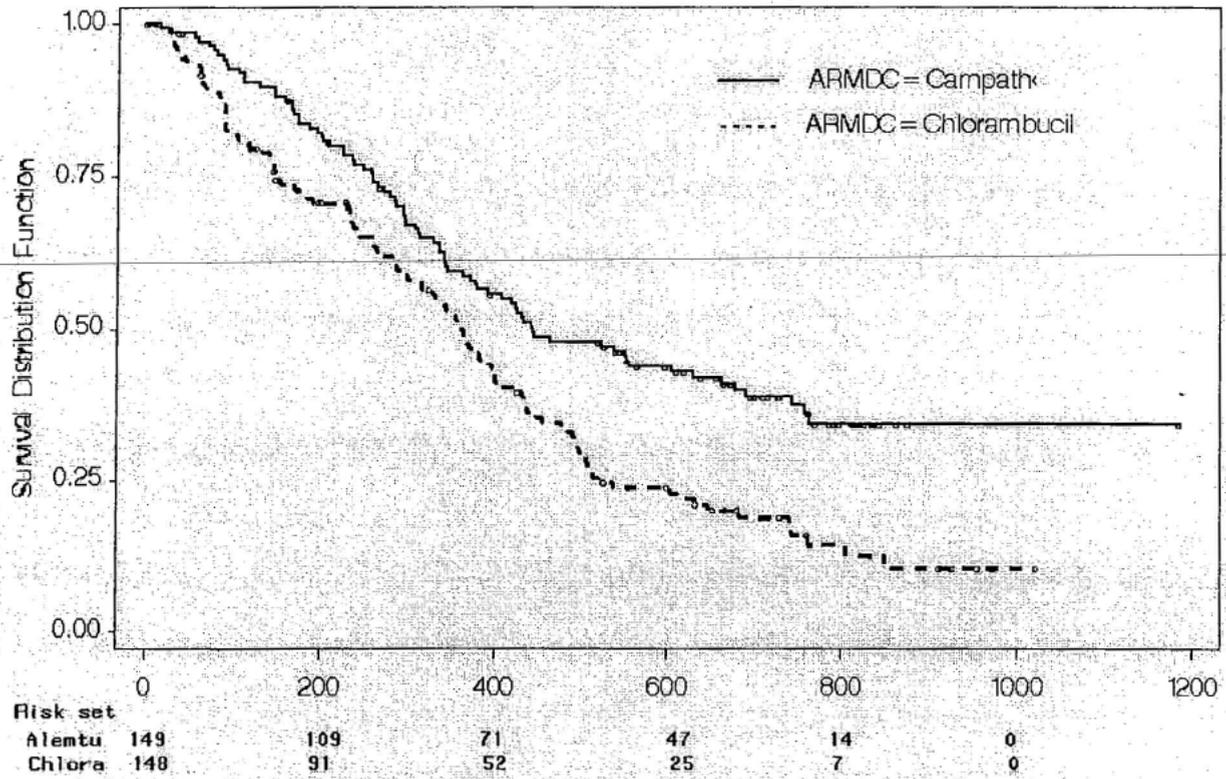
The results of unadjusted and adjusted analyses of PFS (IRRP) data using all patients are summarized in Table 3.1.4. According to this dataset, there are 11 subjects (7 in alemtuzumab arm, 4 in chlorambucil arm) who are censored at day 1 as they are unconfirmed as Rai I-IV per IRRP. The Rai stage HR (III/IV ÷ I/II) is 1.64 with a 95% confidence interval (1.225, 2.197). The stratified analysis is based on 288 subjects. The Kaplan-Meier curves for PFS2 are shown in Figure 3.1.1 below on the next page.

Table 3.1.4: Summary of analysis of PFS2 (in days)

	Statistic	Alemtuzumab	Chlorambucil
PFS2 (days)	N	149	148
Progressed	N (%)	82 (55%)	109 (73.6%)
Censored	N (%)	67 (45%)	39 (26.4%)
PFS2 (days)	Median [95% CI]	445 (374, 661)	357 (300, 401)
Hazard Ratio [95% CI]- adjusted for Rai		0.576 (0.431, 0.768)	
Log-rank p-value (unadjusted)		0.0002	
Log-rank p-value (adj. for Rai stage group)		0.0001	

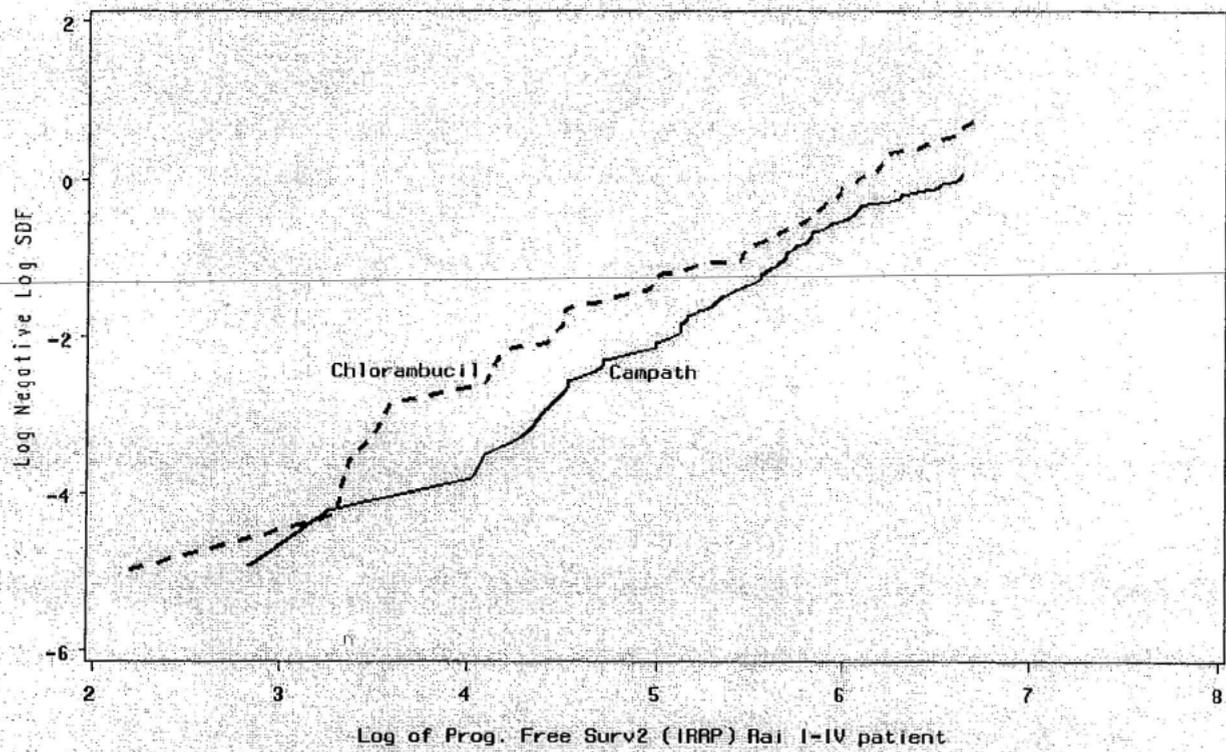
However, the LLS plot in Figure 3.1.2 does not exhibit parallel pattern. That is, the hazards were far from proportional. A test of the validity of the proportional hazards assumption is also used by introducing the time-dependent explanatory variable $X = \text{treatment} * (\log \text{PFS2} - 5.39)$, where 5.39 is the mean of log PFS2. This test also indicates that the hazards were not proportional.

Figure 3.1. 1: Kaplan-Meier curves for PFS2, the primary endpoint



Prog. Free Surv2 (IRRP) Rai I-IV patient

Figure 3.1. 2: The SAS LLS plot for PFS2



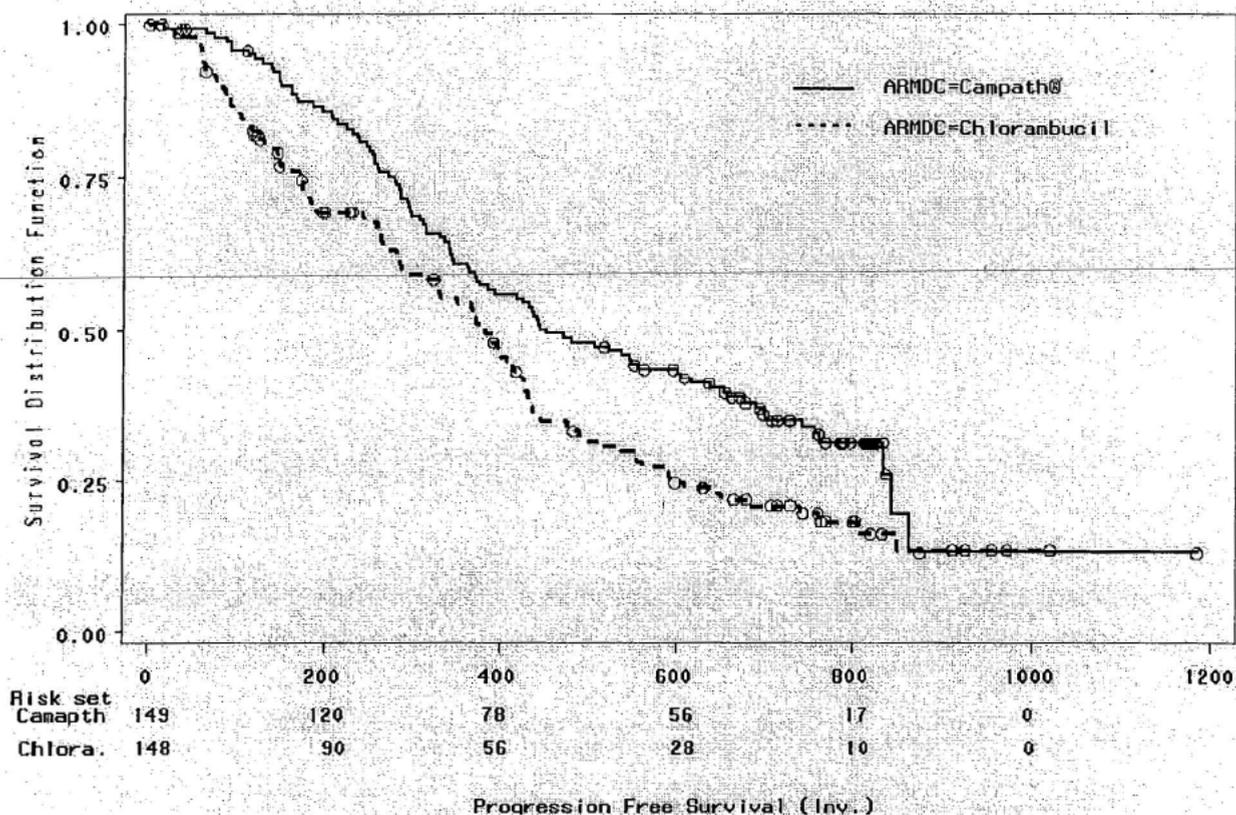
Sensitivity analyses of the primary efficacy endpoint

Progression free survival in days based on the investigator's assessment is calculated as date of progression or death due to any cause whichever is earlier – date of randomization + 1. The results of these data are summarized in Table 3.1.5 below. These results are consistent with those obtained from PFS2 analysis shown in Table 3.1.4. The Kaplan-Meier curves are shown in Figure 3.1.3.

Table 3.1.5: Summary of analysis of PFS (Investigator assessment)

	Statistic	Alemtuzumab	Chlorambucil
PFS (Investigator)	N	149	148
Progressed	N (%)	95 (63.8%)	106 (71.6%)
Censored	N (%)	54 (36.2%)	42 (28.4%)
PFS (Investigator)	Median [95% CI]	453 (374, 618)	383 (316, 427)
Hazard Ratio [95% CI]		0.672 (0.507, 0.89)	
Log-rank test p-value		0.0041	
Log-rank p-value (adjusted for Rai group)		0.0053 (n = 288)	

Figure 3.1. 3: Kaplan-Meier curves for PFS (Investigator assessment)



In addition to PFS (INV), the Sponsor has provided the following datasets for the purpose of sensitivity analyses. The definitions of endpoints corresponding to sensitivity analyses are explained below.

PFS1 Progression-free survival in days based on the IRRP assessment with patients who are assessed as unconfirmed as Rai I-IV per IRRP included at the date of last follow-up as an additional analysis of the primary variable PFS2. PFS in days = date of progression or death due to any cause whichever is earlier-date of randomization +1. Results of PFS1 analysis are consistent with the results of PFS2 analysis. The medians of PFS1 are 447 days [95% CI: (378, 678)] and 357 days [95% CI: (300, 401)] for alemtuzumab and chlorambucil, respectively. The unadjusted log-rank test p-value is < 0.0001. The hazard ratio when adjusted for Rai stage groups is 0.576 with a 95% confidence interval (0.431, 0.768). The log-rank test p-value when adjusted for Rai stage groups is 0.0001.

PFS3 Progression-free survival in days based on the IRRP assessment of response and progression, and the investigator assessed Rai stage. Hence 2 patients assessed by the investigator as Rai 0 were censored at day 1, otherwise, PFS3 = PFS1. Results of PFS3 analysis are consistent with the results of PFS2 analysis.

This reviewer examined the endpoint defined as the smaller of PFS3 and INV PFS, where censoring variable is defined as the smaller of PFS3C and INV PFS C. The medians of this new endpoint are 426 days [95% CI: (344, 550)] and 345 days [95% CI: (282, 398)] for alemtuzumab and chlorambucil, respectively. The unadjusted log-rank test p-value is 0.0003. The hazard ratio when adjusted for Rai stage groups is 0.611 with a 95% confidence interval (0.464, 0.806). The log-rank test p-value when adjusted for Rai stage groups is 0.0004.

PFS4 Same as PFS2, except that unconfirmed progression were censored at the date of progression as assessed by the IRRP. A summary of analysis is provided in Table 3.1.6 below. The PFS2 primary analysis set has 106 censored subjects whereas the number of censored subjects is 149. In particular the number of censored subjects in the alemtuzumab arm has increased from 67 in the PFS2 analysis set to 96 in the PFS4 analysis set. In the following table NA stands for *not available*.

Table 3.1.6: Sensitivity analysis - PFS4 in days

	Statistic	Alemtuzumab	Chlorambucil
PFS4	N	149	148
Progressed	N (%)	53 (35.6%)	80 (54%)
Censored	N (%)	96 (64.4%)	68 (46%)
PFS4	Median [95% CI]	NA (524, NA)	422 (365, 506)
Hazard Ratio [95% CI]		0.52 (0.367, 0.737)	
Log-rank test p-value (unadjusted)		0.0002	
Log-rank test p-value (adjusted for Rai group)		0.0002	

PFS5 Same as PFS2, except using date of first drug administration as the day of 1 rather than date of randomization, i.e., PFS = date of progression or death whichever is earlier - date of first drug administration + 1. Results of PFS5 analysis are consistent with the results of PFS2 analysis.

The medians of PFS5 are 441 days [95% CI: (372, 649)] and 351 days [95% CI: (297, 395)] for alemtuzumab and chlorambucil, respectively. The unadjusted log-rank test p-value is 0.0002. The hazard ratio when adjusted for Rai stage groups is 0.576 with a 95% confidence interval (0.431, 0.768). The log-rank test p-value when adjusted for Rai stage groups is 0.0001.

PFS6 Same as PFS2 with the inclusion of patients who had no documented progression by the IRRP but received alternative treatment included as event. Results of PFS1 analysis are consistent with the results of PFS2 analysis.

PFS7 Same as PFS2 except that patients who had the only reason for progression checked as based on lymph node only censored rather than included as event. A summary of analysis

is provided in Table 3.1.7 below. The PFS2 primary analysis set has 106 censored subjects whereas the number of censored subjects is 154. In particular the number of censored subjects in the alemtuzumab arm has increased from 67 in the PFS2 analysis set to 86 in the PFS4 analysis set.

Table 3.1.7: Sensitivity analysis - PFS7 in days

	Statistic	Alemtuzumab	Chlorambucil
PFS7	N	149	148
Progressed	N (%)	63 (42.3%)	80 (54%)
Censored	N (%)	86 (57.7%)	68 (46%)
PFS7	Median [95% CI]	671 (543, NA)	455 (400, 514)
Hazard Ratio [95% CI]		0.605 (0.434, 0.844)	
Log-rank test p-value (unadjusted)		0.0035	
Log-rank test p-value (adjusted for Rai group)		0.0034	

Secondary endpoints

The secondary objectives of CAM307 are to evaluate:

- Complete response (CR) and overall response rate (ORR) using the 1996 NCIWG criteria
- Duration of response
- Time to alternative treatment
- Survival, and
- Time to treatment failure

Analyses of these endpoints are summarized and presented below.

Overall survival

Overall survival is defined as the time from randomization to date of death due to any cause. CAM307 was not designed or powered to detect differences in overall survival. As seen from Table 3.1.8 below, there was no overall difference in survival with a total of 24 deaths in the alemtuzumab arm (84% censored), and 24 deaths in the chlorambucil arm (84% censored). There were not enough events or long enough follow-up data to expect to detect a difference in the overall survival.

Table 3.1.8: Overall Survival in days

	Statistic	Alemtuzumab	Chlorambucil
Overall survival	N	149	148
Dead	N (%)	24 (16%)	24 (16%)
Censored	N (%)	125 (84%)	124 (84%)
Overall survival	Median [95% CI]	NA (NA, NA)	NA (1135, NA)
Hazard Ratio [95% CI] - unadjusted		1.037 (0.588, 1.828)	
Log-rank test p-value (unadjusted)		0.88	

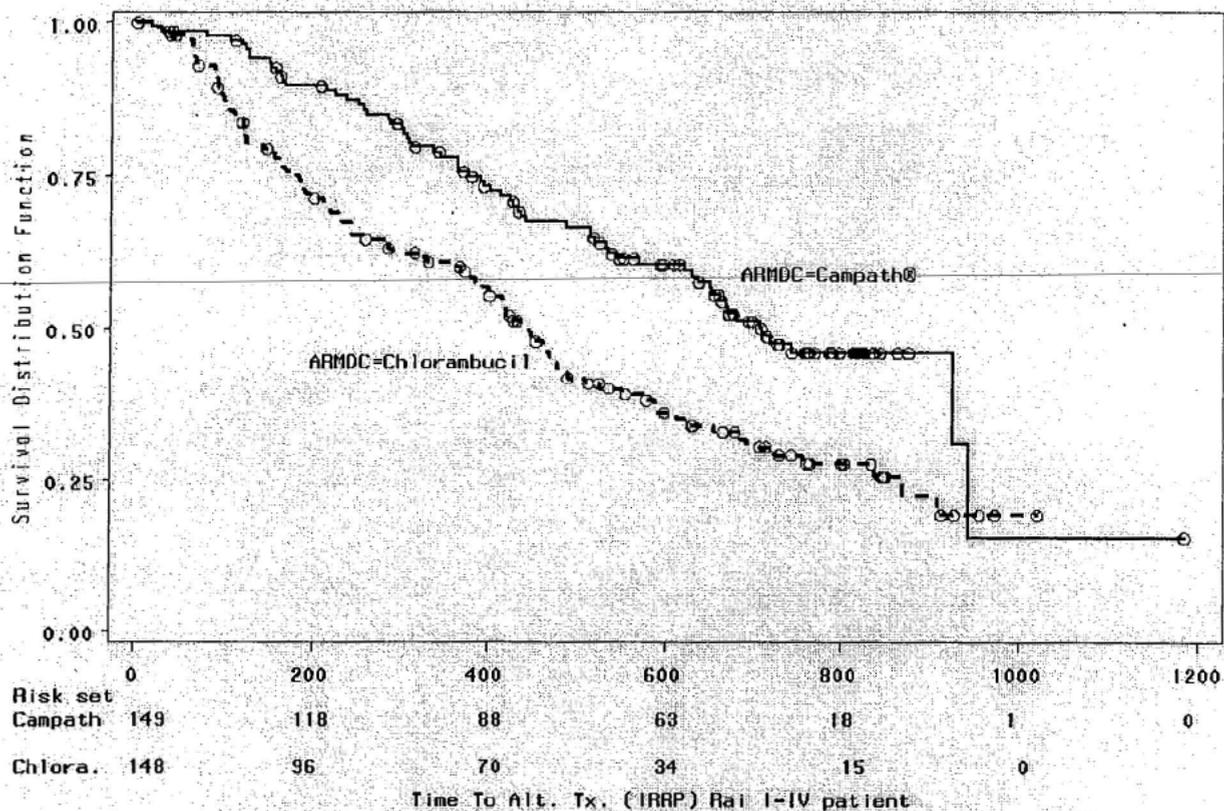
Time to alternative treatment

Time to alternative treatment (IRRP) is determined from the date of randomization to the date of alternative treatment or death due to any cause. It is abbreviated as TAT2. Table 3.1.9 below summarizes the results. The Kaplan-Meier curves are shown in Figure 3.1.4 below. Subgroup analyses by Rai stage groups are provided in Section 4.2. Inconsistency of results in low and high risk groups does not confirm the robustness of the primary TAT2 analysis.

Table 3.1.9: Time to Alternative Treatment (IRRP) in days

	Statistic	Alemtuzumab	Chlorambucil
TAT2	N	149	148
Event: alternative trt.	N (%)	65 (44%)	93 (63%)
Censored	N (%)	84 (56%)	55 (37%)
Time to Alternative Treatment	Median [95% CI]	708 (630, 943)	447 (384, 511)
Hazard Ratio [95% CI]- adjusted for Rai group		0.54 (0.39, 0.74)	
Log-rank test p-value- stratified by Rai group		0.0001	

Figure 3.1.4: Kaplan-Meier curves for Time to Alternative Treatment (IRRP)



Time to treatment failure

It is defined as the time from date of randomization to the earliest date of disease progression, death due to any cause, or discontinued from study treatment due to an AE. Treatment interruption due to an adverse event resulted in treatment delay over 4 weeks (i.e., 9 weeks [8 weeks + 1 week window] since the last dose for chlorambucil, or 4 weeks since the last scheduled dose for Alemtuzumab) are considered discontinuation of treatment for the purpose of comparing time to treatment failure between arms. The date of treatment failure is taken as the earliest date of the documented disease progression, death, or the start of the AE that resulted in treatment discontinuation.

Table 3.1.10: Time to Treatment Failure (TTF) in days- IRRP

	Statistic	Alemtuzumab	Chlorambucil
TTF	N	149	148
Treatment failed	N (%)	96 (64.4%)	115 (77.7%)
Censored	N (%)	53 (35.6%)	33 (22.3%)
Time to treatment failure	Median [95% CI]	299 (238, 409)	344 (282, 392)
Hazard Ratio [95% CI]		0.824 (0.627, 1.082)	
Log-rank test p-value		0.1551	

Overall Response Rate (IRRP)

The overall response rate (ORR) is the proportion of subjects who had either complete response (CR) or partial response (PR). See the Appendix for detailed definitions of CR and PR as determined by the 1996 NCIWG criteria. The endpoint which is labeled as IRRPRESP represents the best response to treatment as assessed by the IRRP, who were blinded to the treatment assignment. A summary of IRRPRESP is given in Table 3.1.11 below. The overall response rate was significantly higher for the alemtuzumab treated patients compared to the chlorambucil treated patients; specifically there were 124/149 patients (83.2%) in the Alemtuzumab arm compared to 82/148 patients (55.4%) in the chlorambucil arm; $p < 0.0001$. The estimated odds ratio is 3.99 [95% CI: 2.33, 6.84], which means that the odds of a favorable response are four times higher for alemtuzumab treated patients than those treated with chlorambucil. The stable disease (SD) rate was significantly lower for the Alemtuzumab treated patients compared to the chlorambucil treated patients. There were 9/149 patients (6%) with SD in the Alemtuzumab arm compared to 42/148 patients (28.4%) with SD in the chlorambucil arm; $p < 0.0001$.

Table 3.1.11: Best Response* (IRRP) - frequency (percentage)

	Chlorambucil	Campath	Total
Complete Response (CR)	3 (2.0%)	36 (20.0%)	39
Partial Response (PR)	79 (53.4%)	88 (59.0%)	167
Progressive Disease (PD)	18 (12.2%)	5 (3.4%)	23
Stable Disease (SD)	42 (28.4%)	9 (6.0%)	51
Not Evaluable	6 (4.0%)	11 (7.4%)	17
Total	148	149	297

* IRRPRESP

Analysis of overall response rates stratified by Rai stage (I/II, III/IV) are presented in Table 3.1.12 below.

Table 3.1.12: ORR (IRRP) summary by Rai stage

	Rai stage I/II			Rai stage III/IV		
	Yes	No	Total	Yes	No	Total
Campath	81 (88%)	11 (12%)	92	38 (76%)	12 (24%)	50
Chlorambucil	61 (63.5%)	35 (36.5%)	96	19 (39.6%)	29 (60.4%)	48
p-value (odds ratio)	<0.0001 (4.22)		188	0.0003 (4.83)		98
Overall result	p < 0.0001, odds ratio = 4.46 (2.25, 7.9) Breslow-Day test p-value = 0.0525					

Best response (Investigator)

This is the best response to treatment as assessed by the investigator (INVRESP). Best response was not evaluable for 4 subjects. In addition, it was missing for 36 subjects. A summary of the results is given in Table 3.1.13 below.

Table 3.1.13: Best Response (INV) - frequency (percentage)

	Chlorambucil	Alemtuzumab	Total
Complete Response (CR)	6 (4%)	46 (30.9%)	52
Partial Response (PR)	54 (36.5%)	69 (46.3%)	123
Progressive Disease (PD)	38 (25.7%)	7 (4.5%)	45
Stable Disease (SD)	31 (20.9%)	8 (5.4%)	39
Not Evaluable	1 (<1%)	3 (2%)	4
Missing	18 (12.6%)	16 (10.7%)	36
Total	148	149	297

Duration of response

The duration of response was defined in the protocol as the time from best response to disease progression or death due to any cause. The primary analysis censors patients who are unconfirmed as Rai I-IV per IRRP at day 1. A total of 124 subjects in the alemtuzumab arm, and 82 in the chlorambucil arm achieved CR or PR. The median duration of response for the alemtuzumab arm is 492 days whereas it is 386 days for the chlorambucil arm.

Results and Conclusions

Sponsor's Efficacy Conclusions

The efficacy data from CAM307 demonstrate superiority of Alemtuzumab compared to chlorambucil as assessed by PFS, response rate, and time to alternative therapy in the intent to

treat study population of previously untreated patients with progressive B-CLL requiring first-line therapy. Duration of best response was also longer in the alemtuzumab treated patients. The hazard ratio for PFS is 0.58 ($p = 0.0001$, stratified log rank test) after adjustment by Rai stage group, meaning that the risk of progression or death in treatment-naïve B-CLL patients treated with alemtuzumab is 42% less than for those treated with chlorambucil. Additionally, 83.2% of patients in the alemtuzumab arm had a response of either CR or PR compared to 55.4% of patients in the chlorambucil arm; $p < 0.0001$. There was a significantly higher percentage of CR patients in the alemtuzumab arm compared to the chlorambucil arm; 24.2% vs. 2.0%, respectively; $p < 0.0001$. Of note, response rates in the alemtuzumab arm of CAM307 also exceed or are comparable to single arm combination data in similar patient populations. The overall K-M median time to alternative treatment was 708 days (23.3 months) for patients in the alemtuzumab arm and 447 days (14.7 months) for patients in the chlorambucil arm, also highly statistically significant ($p = 0.0001$, stratified log-rank test).

3.2 Evaluation of Safety

Please see the medical officer's review for an evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The study population was predominantly Caucasian, 295/297 patients (99%) were Caucasian and 2/297 patients (0.7%) were Black (1 in each arm). Sub-group analyses for race are not provided.

Majority of the subjects in the trial were males. Of the 297, 213 were males and 84 females. Gender-wise distribution of males and females to the two treatment arms is shown in Table 4.1.1 below. Table 4.1.2 summarizes the PFS results by gender. In case of females, the proportion of PFS censored subjects in the alemtuzumab arm was higher compared to the chlorambucil arm (58 % vs. 24%). The log-rank test, for testing equality of censoring distributions between the two treatment arms shows a p-value of 0.0235. This means that the log-rank test p-value of 0.0129 shown in Table 4.1.2 for female subjects may not be reliable.

Table 4.1.1: Number of subjects by treatment and gender

Treatment	Male	Female	Total
Chlorambucil	107	41	148
Alemtuzumab	106	43	149
Total	213	84	297

Frequency missing = 2

Table 4.1.2: PFS2 subgroup analysis by gender

	Male		Female	
	Alemtuzumab	Chlorambucil	Alemtuzumab	Chlorambucil
Median PFS time	428	364	758*	357
Total # of subjects	213		84	
p-value (log-rank test)	0.0046		0.0129*	
Hazard Ratio (95% CI)	0.621 (0.445, 0.866)		0.482 (0.268, 0.868)	

* Censoring distributions are not equal

The average age of patients in the alemtuzumab arm was 59.8 years with a range from 35 to 86 years. The average age of patients in the chlorambucil arm was 59.2 years with a range from 36 to 83 years. Age group (<65 vs. ≥ 65) is a stratification factor for randomization. Details on allocation of subjects within these groups to treatment groups are shown in Table 4.1.3. Results of subgroup analyses of PFS are presented in Table 4.1.4. It appears that alemtuzumab may not have the desired effect among the geriatric (≥ 65 years) subgroup of patients.

Table 4.1 3: Number of subjects by treatment and age-group

Treatment	< 65 years	≥ 65 years	Total
Chlorambucil	96	52	148
Alemtuzumab	96	53	149
Total	192	105	297

Frequency missing = 2

Table 4.1.4: PFS2 subgroup analysis by age-group

	< 65 years		≥ 65 years	
	Alemtuzumab	Chlorambucil	Alemtuzumab	Chlorambucil
Median PFS time	539	355	381	380
Total # of subjects	192		105	
p-value (log-rank test)	0.0004		0.1187	
Hazard Ratio (95% CI)	0.526 (0.367, 0.753)		0.68 (0.418, 1.107)	

4.2 Other Special/Subgroup Populations

This study was conducted in 44 study clinics (sites) in 13 countries. Size of a study site varies from 1 to 28. Although study site was a stratification variable at randomization, site-wise subgroup analysis of PFS data is not possible and is not done here. Numbers of subjects recruited by country and treatment are provided in Table 4.2.1 below. As seen from Table 4.2.1, United States representation in terms of the number of subjects is very small. Analyses of PFS by region are presented in Table 4.2.2. A statistically significant difference in PFS was not demonstrated for the US subjects.

Table 4.2. 1: Number of subjects by Country and Treatment

Country	Alemtuzumab	Chlorambucil	Total
Czech Republic	20	19	39
Croatia	24	23	47
Estonia	1	1	2
France	2	2	4
Ireland	1	0	1
Italy	0	3	3
Lithuania	3	5	8
Netherlands	2	7	9
Poland	62	55	119
Serbia	15	13	28
Slovakia	5	7	12
United Kingdom	1	2	3
United States	13	11	24
Total	149	148	297

Table 4.2 .2: PFS (IRRP) comparison by region- United States vs. Europe

	United States		Europe	
	Alemtuzumab	Chlorambucil	Alemtuzumab	Chlorambucil
Median PFS in days	524	282	435	365
Total # of subjects	24		273	
p-value (log-rank test)	0.1965		0.0003	
Hazard Ratio (95% CI)	0.526 (0.195, 1.417)		0.578 (0.428, 0.782)	

The numbers of subjects by Rai stage × treatment are shown in Table 4.2.3 below. By definition, for randomization sake, subjects in stages I-II constitute a stratum and others in III-IV form another stratum. As seen from Table 4.2.3, Rai stage group III-IV representation in terms of the number of subjects is small compared to the Rai stage group I-II. As seen from Table 4.2.4, a statistically significant difference in PFS was not demonstrated for the high risk subgroup.

Table 4.2. 3: Number of subjects by Rai stage and treatment

Rai stage and Description	Alemtuzumab	Chlorambucil	Total
0: Lymphocyte count $15 \times 10^9/L$ or more, with 40% or more lymphocytes in marrow different count	0	2	2
I: Stage 0 plus enlarge lymph nodes	37	32	69
II: Stage 0 plus enlarge spleen, or liver, or both; Lymph nodes may or may not be enlarged	60	63	123
III: Stage 0 plus anemia; nodes may or may not be enlarged	23	22	45
IV: Stage 0 plus thrombocytopenia; organomegaly and anemia may or may not be present	27	28	55
Total	147	147	294

Table 4.2. 4: PFS2 subgroup analysis by Rai stage group

	Rai stage I/II		Rai stage III/IV	
	Alemtuzumab	Chlorambucil	Alemtuzumab	Chlorambucil
Median PFS time	661	380	309	260
Total # of subjects	188		98	
p-value (log-rank test)	0.0007		0.0663	
Hazard Ratio (95% CI)	0.532 (0.367, 0.771)		0.651 (0.411, 1.033)	

The numbers of subjects by WHO performance status × treatment are shown in Table 4.2.5 below. Of the 297 randomized, only 10 subjects were bedridden. No subgroup analysis is performed.

Table 4.2. 5: Number of subjects by treatment and WHO performance status

WHO performance status	Alemtuzumab	Chlorambucil	Total
No symptoms and able to walk: 0-1	142	142	284
Partly or fully bedridden: 2	5	5	10
Total	147	147	294

Frequency missing = 5

The numbers of subjects by lymph node size × treatment are shown in Table 4.2.6 below. Seventy-seven per cent of the subjects had lymph node size < 5 cm. Results of subgroup analyses are provided in Table 4.2.7 below.

Table 4.2. 6: Number of subjects by treatment and maximum lymph node size

Treatment	< 5 cm	≥ 5 cm	Total
Chlorambucil	114	34	148
Campath	115	33	148
Total	229	67	296

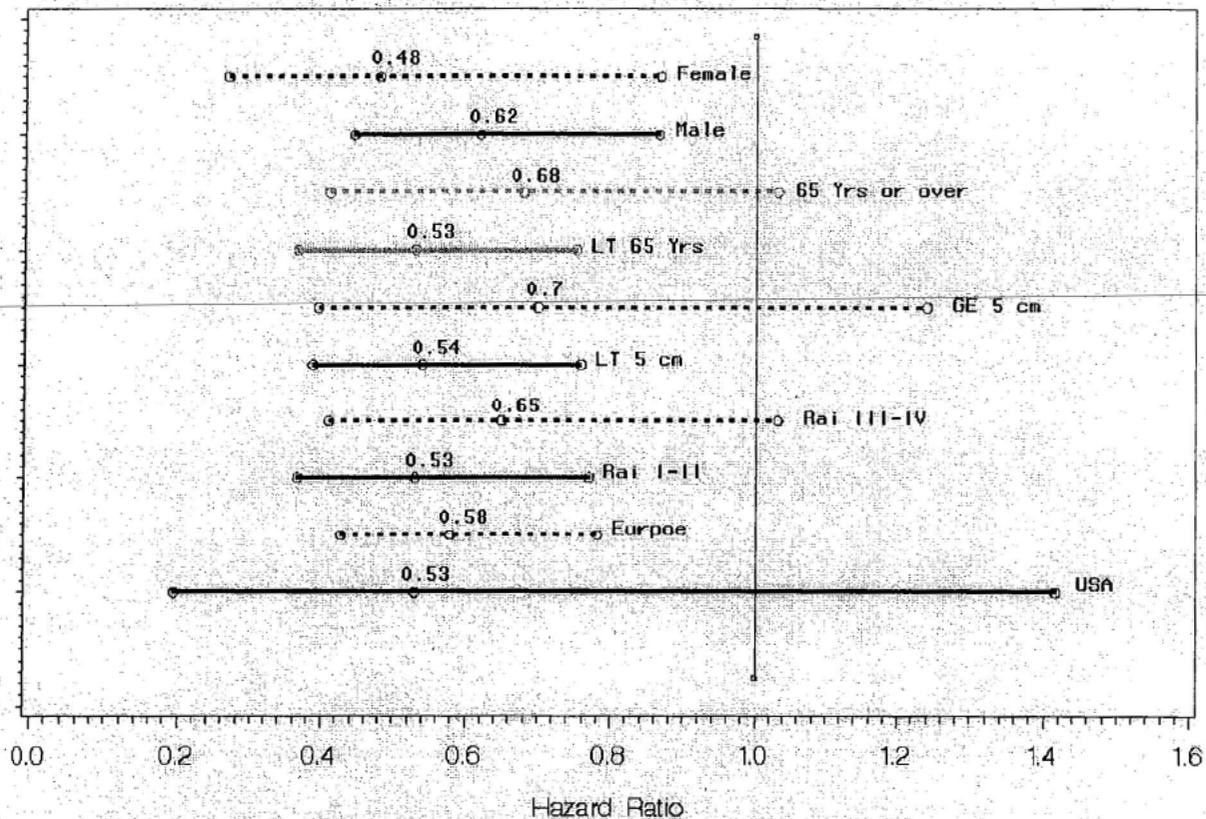
Frequency missing = 3

Table 4.2. 7: PFS2 subgroup analysis by maximum lymph node size

	Lymph Node < 5 cm		Lymph Node ≥ 5 cm	
	Alemtuzumab	Chlorambucil	Alemtuzumab	Chlorambucil
Median PFS time	539	380	343	267
Total # of subjects	229		67	
p-value (log-rank test)	0.0003		0.2208	
Hazard Ratio (95% CI)	0.543 (0.388, 0.759)		0.702 (0.396, 1.242)	

The results of these subgroup analyses of PFS are summarized below in Figure 4.2.1.

Figure 4.2.1: Subgroups analyses of PFS summarized



Statistical significance was not reached on a difference in PFS between alemtuzumab and chlorambucil (p -value > 0.05) in high-risk subjects, in subjects with lymph node size ≥ 5 cm, and in older subjects (age ≥ 65).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- Study CAM307 recruited only 24 (8%) subjects from the United States (North America). Therefore, a meaningful analysis of U.S. subjects can not be done. When trying to extrapolate the results outside the U.S. patients to U.S. patients, the difference in medical practice should be considered. Table 4.2.2 summarizes the PFS results for those United States B-CLL patients. A statistically significant difference in PFS was not demonstrated for the 24 US subjects.
- According to the Protocol, a secondary objective was to compare overall survival. This was reasserted in the face-to-face meeting of October 12, 2006. Comparison of overall survival between alemtuzumab and chlorambucil was supposed to be done using log-rank test, stratified by Rai stage groups. But now the Sponsor's study report states: "CAM307 was not designed or powered to detect differences in overall survival. There was no overall difference in survival with a total of 24 deaths in the alemtuzumab arm, and 24 deaths in the chlorambucil arm. There were not enough events or enough follow-up data to detect a difference in the overall survival." Survival data are immature and patients in CAM307 are no longer being followed for overall survival.

(b) (4)

- Results of the subgroup analyses are of concern. WHO performance status was one of the stratification factors at the time of randomization. As seen from Table 4.2.5, the trial included only 10 (3.5%) subjects who were partially or fully bedridden. This subgroup analysis was too small to perform a reliable evaluation of whether a treatment difference exists. As seen in Section 4, statistical significance was not reached on a difference in PFS between alemtuzumab and chlorambucil (p -value > 0.05) in high-risk subjects, in subjects with lymph node size ≥ 5 cm, and in older subjects (age ≥ 65).
- The Sponsor has calculated the PFS (IRRP) hazard ratio using the Cox proportional hazards model, which requires the ratios of hazards rates under the two treatment arms be constant over time. The appropriateness of the proportional hazards regression method and the validity of the results depend on the correctness of the proportional hazards assumption. The proportional hazards assumption is checked using the SAS log-log survival (LLS) curves. The LLS plot in Figure 3.1.2 does not exhibit parallel pattern. This suggests that the ratio of hazard rates varied greatly over time. That is, the hazards were far from proportional. A test of the validity of the proportional hazards assumption was

also used by introducing the time-dependent explanatory variable $X = \text{treatment} * (\log \text{PFS2} - 5.39)$, where 5.39 is the mean of $\log \text{PFS2}$. This test gives a non-significant result ($p\text{-value} = 0.94$). An increasing or decreasing hazard ratio over time has not been demonstrated. There is a 25% increase in median progression-free survival (11.7 versus 14.6 months).

5.2 Conclusions and Recommendations

- Protocol specified primary analysis of the primary efficacy endpoint progression-free survival (IRRP) indicates that alemtuzumab is superior to chlorambucil (log-rank test $p\text{-value} = 0.0001$). Alemtuzumab prolongs disease progression by 88 days (2.9 months) compared to chlorambucil (PFS medians: 445 days [14.6 months] vs. 357 days [11.7 months]). However, a statistically significant difference in PFS was not demonstrated for the high risk subgroup of subjects.
- In terms of overall response rate, alemtuzumab (83%) is superior to chlorambucil (55%): $p\text{-value} < 0.0001$. The odds of a favorable response are 4 times higher for alemtuzumab compared to chlorambucil.
- Study CAM307 recruited only 24 (8%) subjects from the United States (North America). Therefore, a meaningful analysis of U.S. subjects can not be done. A statistically significant difference in PFS was not demonstrated for the 24 US subjects.
- No survival benefit is demonstrated. Survival data are immature and patients in CAM307 are no longer being followed for overall survival.

The efficacy data from sBLA 103948/5070 indicate that alemtuzumab is efficacious and provide evidence in support of a change in the labeled indication.

APPENDICES

Appendix I: Listing of Clinical Studies of Alemtuzumab

Study #	Objectives	Design & Control	Test products(s): Regimen etc.	# of subjects	Diagnosis of patients	Treatment duration
CAM211	Safety and efficacy	Phase 2, open-label, Multicenter, Non-comparative	Alemtuzumab; 3mg-10mg-30 mg dose escalation; 30mg/day maintenance dose, 3 times per week on alternative days; IV	94 enrolled, 93 treated	Adults, 18 years of age or older with B-CLL who received an alkylating agent and for whom there was documentation of failure to fludarabine therapy	4-12 weeks
125-005-C92	Safety and efficacy	Phase 2, open-label, Multicenter (EU), Non-comparative	Alemtuzumab; 3mg or 10mg IV, or 10 mg SC dose escalation, 30 mg/day or 80 mg/day, 3 days per week; IV or SC	125 total: 60/NHL 53/CLL 12 Other	Adults, 18 years of age or older; NHL or CLL patients who failed to respond to or relapsed following conventional first-line or subsequent therapy	6-12 weeks
125-009-C92	Safety and efficacy	Phase 2, open-label, multicenter (US), non-comparative	Alemtuzumab; initiated daily dose of 10 mg/day until well tolerated; 30mg/day 3 times per week, or 80mg/day, 3 days per week; IV	24 total	Adults, 18 years of age or older; CLL patients who failed to respond to or relapsed following first-line treatment with fludarabine or other chemotherapy regimens followed by second- or third line fludarabine	8-16 weeks

(b) (4)

Appendix II: 1996 NCIWG Response Criteria

Complete Response (Duration \geq 2 months)

- Normal physical examination (including nodes, liver, spleen) and by X-ray
- No constitutional symptoms
- Lymphocytes \leq 4,000/ μ L
- Neutrophils \geq 1,500/ μ L
- Platelets $>$ 100,000/ μ L
- Hemoglobin $>$ 11.0 g/dL (un-transfused)
- Marrow normocellular for age, lymphs $<$ 30%, no nodules; if hypocellular marrow, repeat in 4 weeks

Partial Response (Duration \geq 2 months)

- Lymphocytes \geq 50% decrease from baseline, and
- Lymphadenopathy \geq 50% decrease from baseline, and/or
- Liver and/or spleen \geq 50% decrease from baseline
- Plus \geq 1 of:
 - Neutrophils \geq 1,500/ μ L or 50% increase over baseline
 - Platelets $>$ 100,000/ μ L or 50% increase over baseline
 - Hemoglobin $>$ 11.0 g/dL or 50% increase over baseline (un-transfused)
 - Otherwise CR with persistent nodules classified as nodular PR
 - Otherwise CR with persistent anemia or thrombocytopenia due to drug toxicity classified as PR and monitored prospectively.

Progressive Disease

- \geq 50% increase in sum of products of at least two nodes on two consecutive exams 2 weeks apart (at least one node must be \geq 2 cm); new nodes
- Liver/spleen \geq 50% increase or new palpable organomegaly
- Lymphocytes \geq 50% increase to \geq 5,000/ μ L
- Transformation to more aggressive histology (e.g., Richter's syndrome or PLL with $>$ 55% prolymphocytes)

Stable Disease

- All others

SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer:

Kallappa Koti
Kallappa M. Koti
Mathematical Statistician

Date: 9-6-07

Mark Rothmann 9-6-07
Statistical Team Leader: Dr. Mark Rothmann

Aloka Chakravarty 9/6/07
Biometrics Division V Director: Dr. Aloka Chakravarty

cc:
DBOP/Ms. Amy Gomez
DBOP/Dr. Suzanne Demko
DBOP/Dr. Jeff Summers
DBOP/Dr. Joseph Gootenberg
DBOP/Dr. Patricia Keegan
DB V/Dr. Mark Rothmann
DB V/Dr. Aloka Chakravarty
OB /Ms. Lillian Patrician
OB /Dr. Edward S. Nevius

c:\CAMPATHBL.doc

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 103948/5070

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Biologic Oncology Products

Application Number: BL STN 103948/5070

Name of Drug: Alemtuzumab (Campath)

Applicant: Genzyme Corporation

Material Reviewed:

Submission Date(s): March 19, 2007

Receipt Date(s): March 19, 2007

Submission Date of Structure Product Labeling (SPL): March 19, 2007

Type of Labeling Reviewed: WORD

Background and Summary

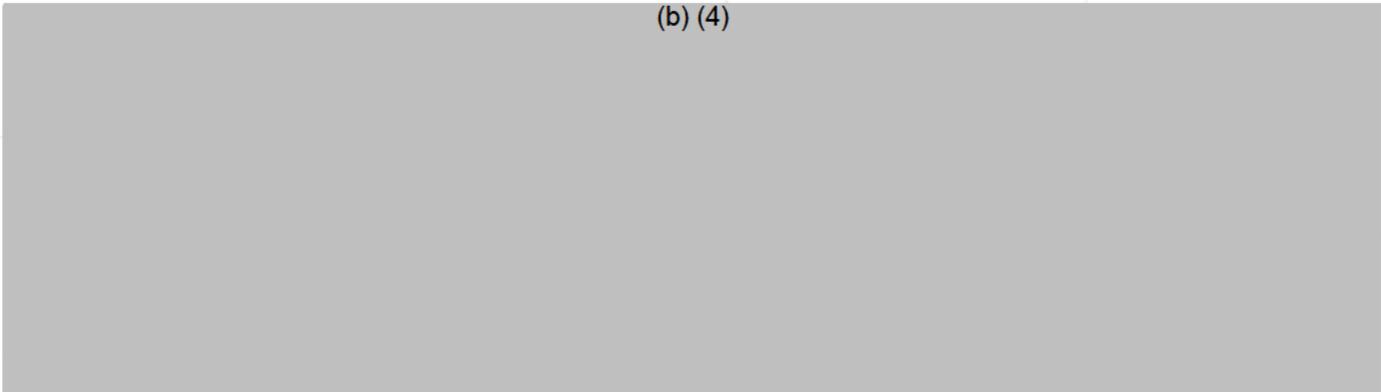
A draft revised Package Insert (PI) was provided with STN 103948/5070. This is an efficacy supplement to convert from accelerated to full approval and add indication of first line therapy for B-CLL. This represents the first label submitted for Alemtuzumab in Physician's Labeling Rule (PLR) format. The scope of the CSO label review is PLR format issues.

Review

The following issues/deficiencies have been identified in the proposed labeling.

Highlights:

(b) (4)



3 Page(s) Withheld

 Trade Secret / Confidential (b4)

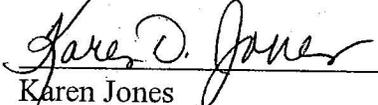
✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)


Amy Gomez, R.N., M.S.
Regulatory Project Manager

Supervisory Comment/Concurrence:


Karen Jones
Chief, Project Management Staff

Drafted: A Gomez 5.14.07

Revised/Initialed: 5.21.07

Finalized: 5.21.07

Filename: N\\DBOP\GomezA\BLA\Campath 103948\103948.5070\label and label reviews\CSO
Labeling Review PLR.doc

CSO LABELING REVIEW OF PLR FORMAT

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 103948/5070

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

9/5/2007

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 103948 Supplement Type (e.g. SE5): efficacy Supplement Number: 5070

Stamp Date: 3/20/07 PDUFA Goal Date: 9/19/07

HFD 107 Trade and generic names/dosage form: Alemtuzumab (Campath)

Applicant: Genzyme Corporation Therapeutic Class: CD52 directed cytolytic antibody

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.
Determination of the effectiveness of Campath is based on overall response rates. Comparative, randomized trials demonstrating increased survival or clinical benefits such as improvement in disease-related symptoms have not yet been conducted.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see

BL STN 103948/5070

Page 2

Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

BL STN 103948/5070

Page 4

This page was completed by:

A handwritten signature in black ink, consisting of several loops and a long horizontal stroke, positioned above a horizontal line.

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)



alemtuzumab (Campath®, MabCampath®)
Module 1: Administrative and Prescribing Information
Debarment Certification

1.3.3 Debarment Certification

Certification pursuant to 21 USC Section 306(k)(1) is provided on the following page.



alemtuzumab (Campath®, MabCampath®)
Module 1: Administrative and Prescribing Information
Debarment Certification

DEBARMENT CERTIFICATION

Certification pursuant to 21 USC Section 306(k)(1) Genzyme Corporation 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.

A handwritten signature in cursive script, appearing to read "Mark Hayes".

Mark Hayes, Vice President Regulatory Affairs

02 March 07

Date

LICENSING ACTION RECOMMENDATION

Applicant: Genzyme Corporation BLA #: 103948/5070

Product (established and proprietary names):

Alemtuzumab (Campath)

Indication / Requested change:

as a single agent for the treatment of B-cell chronic lymphocytic leukemia / conversion from accelerated approval to full approval and expansion of indication to include first line therapy

RECOMMENDED ACTION

- Approval, Refusal to File, Denial of application / supplement

RECOMMENDATION BASIS

(Select all that apply)

- Refusal to File Memo, Denial of Application/Supplement Memo, Approval Action - Discipline Reviews, Approval Action - 2° Review, Approval Action - 3° Review, Review of labeling, Package Insert - Content, Package Insert - SPL Data Elements, Package Insert - PLR Format, Patient Package Insert, Medication Guide, Container / Carton (OBP review), DMPQ Establishment inspections completed, DSI BiMo inspections completed, OBP Review of Protocols for lot no.(s), OBP Review of Test Results for lot no.(s), Review of Environmental Assessment, FONSI included, Categorical Exclusion

CLEARANCE - FDA PRODUCT RELEASE Required for Non-Specified Products Only

Lot no.(s) in support - not for release

Lot no.(s) for release

Director, Product Release Branch

CLEARANCE - REGULATORY REVIEW

- Compliance status checked - Acceptable, Compliance status checked - Hold (Requires justification for approval action), Compliance status check not required (CBE Labeling supplements ONLY)

Regulatory Project Manager (RPM) [Signature] AMY GOMEZ Date: 9/17/07

Chief, Project Management (CPMS) [Signature] FOR M.HUGHES (on email) Date: 9/19/07

FINAL CLEARANCE

Cross-Discipline Team Leader (if assigned) Date:

Responsible Division Director [Signature] Patricia Keegan Date: 9-19-2007

Gomez, Amy

From: O'Keefe, Katherine [Katherine.OKeefe@genzyme.com]
Sent: Wednesday, September 19, 2007 10:49 AM
To: Gomez, Amy
Subject: RE: request for PMC STN 103948/5070
Attachments: cover-letter-pmc.pdf; emfinfo.txt

Hi Amy,

Genzyme has no further changes to the proposed PMC language provided by FDA in your e-mail below. Attached please find the PMC cover letter which will be officially submitted to STN 103948/5070 today.

Kind regards,
Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Wednesday, September 19, 2007 8:15 AM
To: O'Keefe, Katherine
Subject: RE: request for PMC STN 103948/5070
Importance: High

Hi Katie,

We made a couple of edits to the proposed PMC language. I converted the bullets to sentences and the quarters to the last day of each quarter; Dr. Keegan added approx number of subjects and route as discussed during the teleconference yesterday. The PMC now reads:

1. To conduct a QT study according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in approximately 50 subjects receiving Alemtuzumab by the subcutaneous route of administration. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by December 31, 2008, and will be completed by September 30, 2010. A final study report will be submitted by June 30, 2011. A supplement with revised labeling, if applicable, will be submitted by September 30, 2011.

If there is no objection to our edits, please email me your PMC letter and submit it to STN 103948/5070. I will assume the letter date will be today since the language of the PMC has been modified. Please confirm.

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Tuesday, September 18, 2007 3:35 PM
To: Gomez, Amy
Subject: RE: request for PMC STN 103948/5070

Hi Amy,

I will work on the letter now. Please let me know when you have heard back from Dr. Keegan and I will finalize the letter. I can send a copy of it to you via e-mail tonight but we probably won't be able to send it through the ESG until tomorrow morning.

Katie

-----Original Message-----

From: Gomez, Amy [mailto: Amy.Gomez@fda.hhs.gov]

Sent: Tuesday, September 18, 2007 3:21 PM

To: O'Keefe, Katherine

Subject: RE: request for PMC STN 103948/5070

Dr. Keegan is in a meeting so I haven't received final comments on the language yet. Just in case, please be prepared to submit this language in a letter (dated today) to the BLA. I will check back with her this evening and I'll let you know if we have any concerns.

Thanks,

Amy

From: O'Keefe, Katherine [mailto: Katherine.OKeefe@genzyme.com]

Sent: Tuesday, September 18, 2007 2:40 PM

To: Gomez, Amy

Subject: RE: request for PMC STN 103948/5070

Hi Amy,

Genzyme has revised the timelines for the QT study according to this afternoon's teleconference. As discussed during the teleconference, the study design will require additional consultation and agreement between FDA and Genzyme and the outcome of these interactions may further impact the study design and consequently the timeline. Please note that the timelines provided below assume a SC QT study in 50 CLL patients and that the timelines for an IV QT study would be significantly longer due to anticipated enrollment challenges.

The revised proposed language for the approval letter for the CAM307 efficacy supplement is:

Genzyme has committed to conducting a QT study according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID). The milestones for this study are as follows:

- Protocol Submission: (b) (4)
- Study Initiation: Q4 2008
- Study Completion (LPO): Q3 2010
- Final Study Report: Q2 2011
- Supplement with Revised Labeling (if applicable): (b) (4)

Please confirm that you have received the revised timeline and let me know if you have any questions.

Kind regards,
Katie

-----Original Message-----

From: Gomez, Amy [mailto: Amy.Gomez@fda.hhs.gov]

Sent: Tuesday, September 18, 2007 8:43 AM

To: O'Keefe, Katherine

Cc: Hayes, Mark
Subject: request for PMC STN 103948/5070
Importance: High

Hi Katie,

In reviewing the supplement, Dr. Keegan noted that Genzyme had not previously committed to conducting a study on the impact of Alemtuzumab on QT. Please propose a post-marketing commitment to conduct a QT study adhering to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Please propose a timeline for conduct of the study, including:

Date protocol submitted
Date study initiation
Date study completion
Date final study report, and revised labeling if applicable, submitted

To facilitate discussion of the PMC, I have scheduled a teleconference for today 1-2pm. Please submit proposed language by 12 noon so we can review it in advance of the teleconference. Should we use the same call-in number for the teleconference?

Please confirm receipt of this request.

Thanks,

Amy

Amy Gomez, RN, MS
Regulatory Project Manager
Division of Biologic Oncology Products

Gomez, Amy

From: O'Keefe, Katherine [Katherine.OKeefe@genzyme.com]
Sent: Wednesday, September 19, 2007 4:25 PM
To: Gomez, Amy
Subject: RE: sBLA STN 103948/5070
Attachments: emfinfo.txt

Hi Amy,

Thank you for providing the courtesy copy of the approval letter for the efficacy and for all of your support during the last couple of weeks!

Kind regards,
Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Wednesday, September 19, 2007 3:56 PM
To: O'Keefe, Katherine
Cc: Hayes, Mark
Subject: sBLA STN 103948/5070
Importance: High

Hi Katie,

I have attached a courtesy copy of the approval letter for your efficacy supplement STN 103948/5070. Please confirm receipt.

The original will be sent in the mail.

Regards,

Amy

Amy Gomez, RN, MS
Regulatory Project Manager
Division of Biologic Oncology Products

Gomez, Amy

From: Gomez, Amy
Sent: Wednesday, September 19, 2007 8:15 AM
To: 'O'Keefe, Katherine'
Subject: RE: request for PMC STN 103948/5070
Importance: High

Hi Katie,

We made a couple of edits to the proposed PMC language. I converted the bullets to sentences and the quarters to the last day of each quarter; Dr. Keegan added approx number of subjects and route as discussed during the teleconference yesterday. The PMC now reads:

1. To conduct a QT study according to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Section IID) in approximately 50 subjects receiving Alemtuzumab by the subcutaneous route of administration. A detailed protocol for this study will be submitted by September 30, 2008. The study will be initiated by December 31, 2008, and will be completed by September 30, 2010. A final study report will be submitted by June 30, 2011. A supplement with revised labeling, if applicable, will be submitted by September 30, 2011.

If there is no objection to our edits, please email me your PMC letter and submit it to STN 103948/5070. I will assume the letter date will be today since the language of the PMC has been modified. Please confirm.

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Tuesday, September 18, 2007 3:35 PM
To: Gomez, Amy
Subject: RE: request for PMC STN 103948/5070

Hi Amy,

I will work on the letter now. Please let me know when you have heard back from Dr. Keegan and I will finalize the letter. I can send a copy of it to you via e-mail tonight but we probably won't be able to send it through the ESG until tomorrow morning.

Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Tuesday, September 18, 2007 3:21 PM
To: O'Keefe, Katherine
Subject: RE: request for PMC STN 103948/5070

Dr. Keegan is in a meeting so I haven't received final comments on the language yet. Just in case, please be prepared to submit this language in a letter (dated today) to the BLA. I will check back with her this evening and I'll let you know if we have any concerns.

Thanks,

9/19/2007

Gomez, Amy

From: Gomez, Amy
Sent: Tuesday, September 18, 2007 8:43 AM
To: 'O'Keefe, Katherine'
Cc: 'Hayes, Mark'
Subject: request for PMC STN 103948/5070
Importance: High

Hi Katie,

In reviewing the supplement, Dr. Keegan noted that Genzyme had not previously committed to conducting a study on the impact of Alemtuzumab on QT. Please propose a post-marketing commitment to conduct a QT study adhering to the principles of ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Please propose a timeline for conduct of the study, including:

- Date protocol submitted
- Date study initiation
- Date study completion
- Date final study report, and revised labeling if applicable, submitted

To facilitate discussion of the PMC, I have scheduled a teleconference for today 1-2pm. Please submit proposed language by 12 noon so we can review it in advance of the teleconference. Should we use the same call-in number for the teleconference?

Please confirm receipt of this request.

Thanks,

Amy

Amy Gomez, RN, MS
Regulatory Project Manager
Division of Biologic Oncology Products

Gomez, Amy

From: Gomez, Amy
Sent: Tuesday, September 18, 2007 10:02 AM
To: 'O'Keefe, Katherine'
Subject: Response to your question re: SPL format

Hi Katie

I received word from the labeling group regarding your question about formatting the cross-references in SPL:

The Sponsor should contact SPL@fda.hhs.gov for technical assistance. Final SPL should be identical to approved draft labeling.

Please let me know if you have any other questions.

Regards,

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Friday, September 14, 2007 1:11 PM
To: Gomez, Amy
Subject: RE: Campath - STN 103948/5070 FDA redlined label

Hi Amy,

We have a question related to the preparation of the SPL. The program that we are using to generate the SPL is giving us some difficulty and we think it is because of the italics that are used in the cross references. We were wondering if it would be acceptable, at least for the initial SPL submission, for the paper documents (WORD/PDF) to have the cross references in italics and for the SPL to have the cross references in regular font. If this is acceptable it would facilitate our ability to submit the SPL more quickly and closer to the action date.

I also wanted to let you know that we will use the same number for today's teleconference that we used last week:

Teleconference Number: (b) (4)
Participant Passcode: (b) (4)

Kind regards,
Katie

Gomez, Amy

From: Gomez, Amy
Sent: Monday, September 17, 2007 8:55 AM
To: 'O'Keefe, Katherine'
Subject: FDA redlined label version date 9/17/07
Importance: High
Attachments: FDA redlined_103948-5070_17sept07.doc

Hi Katie,

We agreed in principle to your redlined version and made a couple of editorial changes (b) (4)

Please confirm these editorial changes are acceptable by sending me a revised label. Let me know if you have any questions about our changes.

Thanks,

Amy

Amy Gomez, RN, MS
Regulatory Project Manager
Division of Biologic Oncology Products

9/17/2007

16 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



T-CON SUMMARY

Applicant: Genzyme

Applicant Participants:

Mark Hayes, Regulatory Affairs
Katie O'Keefe, Regulatory Affairs
Cyndi Sirard (MD), Clinical Research
Jeanne Jones, Clinical Research
Paul Beninger (MD), Pharmacovigilance
Ron Knickerbocker, Biomedical Operations

FDA Participants:

Patricia Keegan, MD, Director, DBOP
Suzanne Demko, PA-C, Clinical Analyst, DBOP
Amy Gomez, RN, MS, Regulatory Project Manager, DBOP
Jeff Summers, MD, Acting Clinical Team Leader, DBOP
Hong Zhao, Ph.D, Clinical Pharmacology Team Leader, DCP 5
Brian Booth, Ph.D., Deputy Director, DCP 5

Number: (b) (4)

Date: Tuesday, September 18, 2007

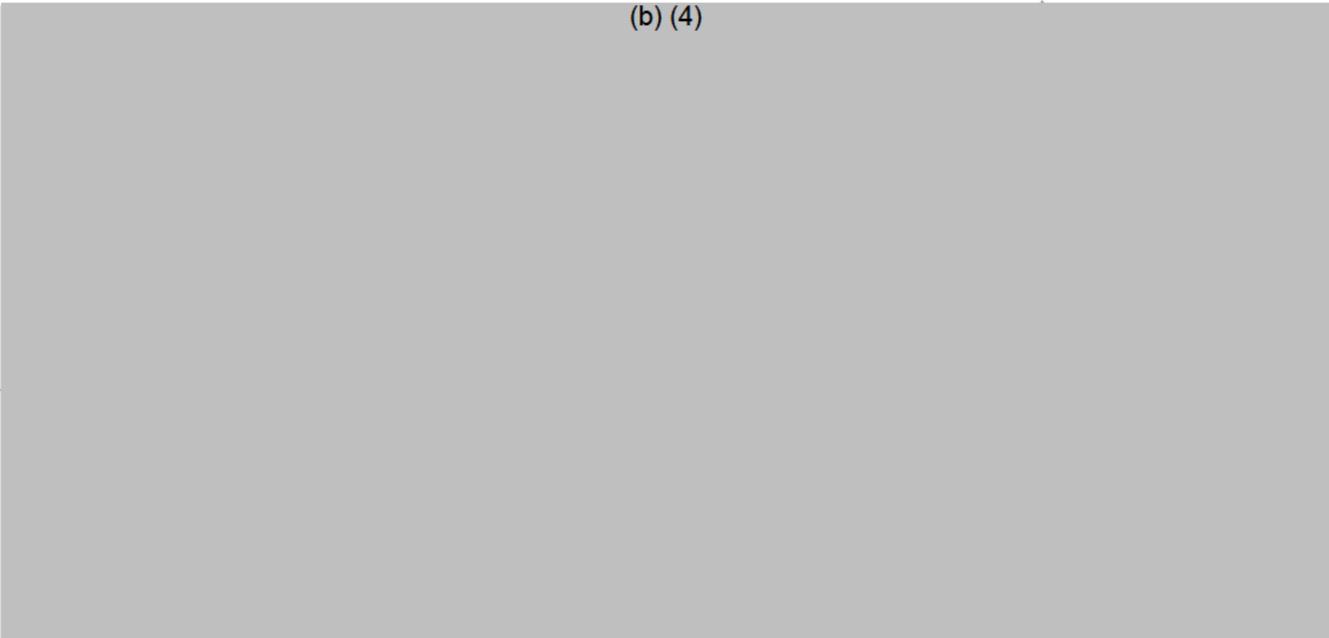
RE: PMC discussion, STN 103948/5070 Alemtuzumab (Campath)

Before the discussion, FDA requested draft language for a PMC to study the effect of Alemtuzumab on QT. Genzyme emailed a response, including draft language (see attached).

Summary:

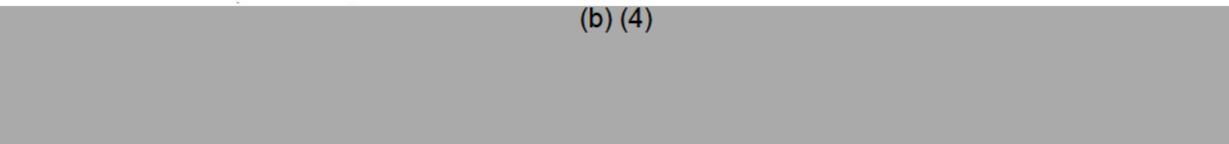
1. FDA stated that a PMC to study effect of Alemtuzumab on QT was appropriate and overdue. The target of the antibody is not a factor in the decision; the division is consistently requesting a QT study for the products it regulates because little is known about the effect of these biologics on QT.
2. FDA stated that it would need a protocol to review and consult with its Interdisciplinary Review Team (IRT) before being able to provide detailed comments on the study design. (b) (4) Typically, the studies would require 40-50 patients. Genzyme can submit a protocol to the IND and the division will consult IRT. Genzyme asked for clarification on how to determine the appropriate number of patients. FDA explained that it would need to be based on a power analysis to determine sample size. In a thorough QT study, the number must be sufficient to rule out a 20 msec increase in QT interval. The IRT will encourage Genzyme to conduct a study as close to the thorough QT study described in ICH as possible. FDA requested that Genzyme propose a timeline based on 40-50 patients, which is more typical of the QT protocols accepted by the division.

(b) (4)

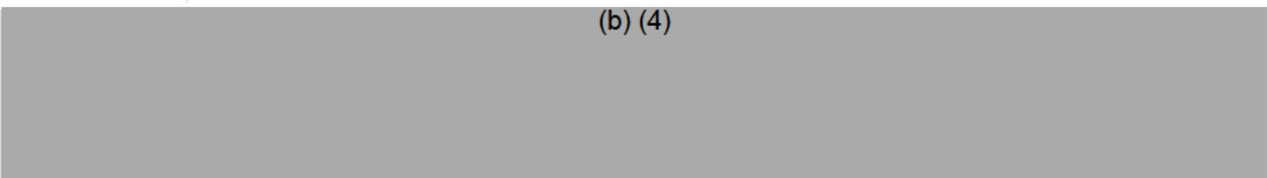


4. Genzyme proposed that, in lieu of listing timelines in the PMC, it could commit to a meeting to discuss options. FDA responded that the timeline for protocol submission as proposed by Genzyme is quite generous and the PMC requires timelines. FDA suggested including timelines in the PMC as proposed and Genzyme could also request a meeting to discuss the protocol before initiation of the study. FDA stated that Genzyme will need to consider how much data are available at the time of the meeting request.

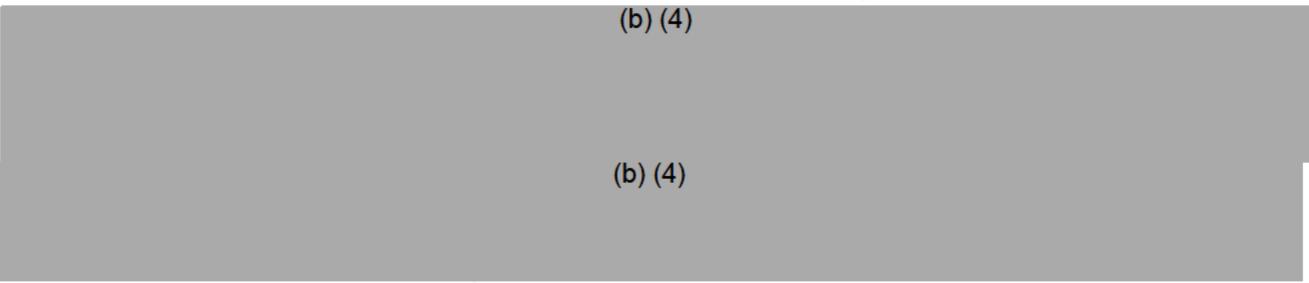
(b) (4)



(b) (4)

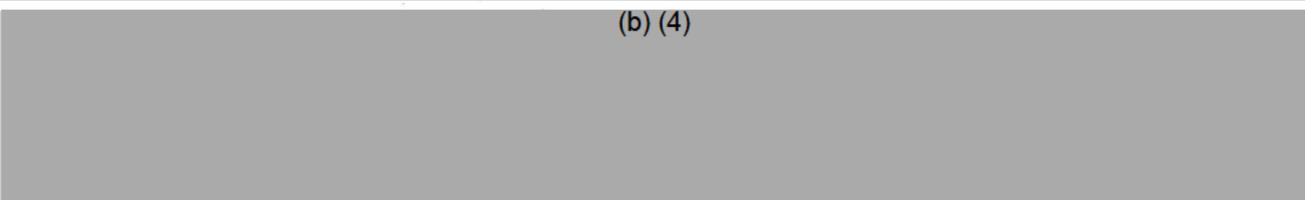


(b) (4)

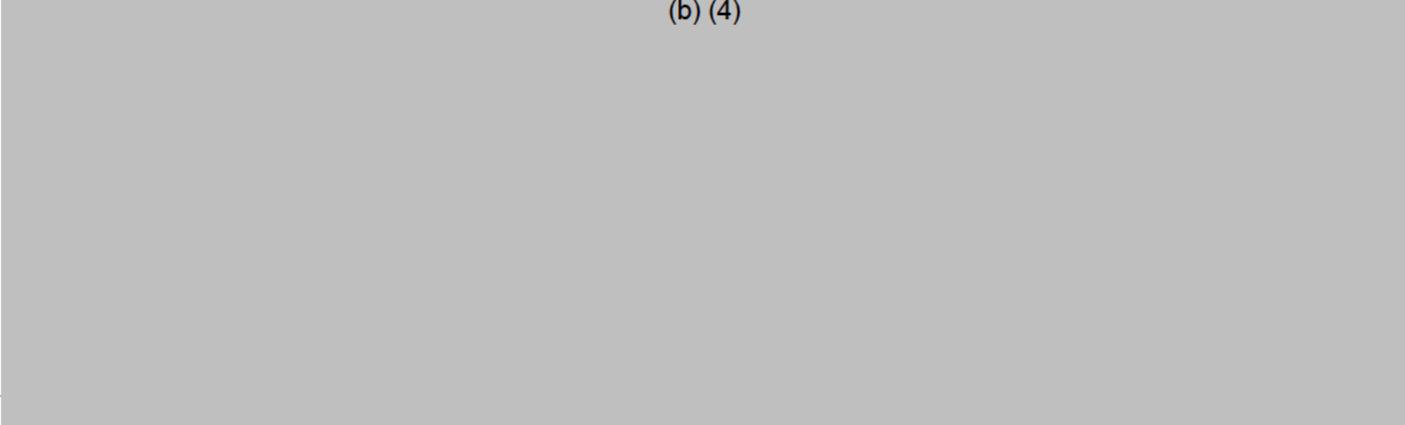


(b) (4)

(b) (4)



(b) (4)



12. Genzyme noted that the timelines proposed may be impacted by design issues. FDA replied that if this occurs, then Genzyme could provide a status explanation in the annual PMC report describing the reason for the change in timelines.
13. FDA agreed that a preliminary conference call to discuss design issues in advance of a formal meeting may be appropriate.

The call concluded.

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #16
Minutes
September 17, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Patricia Keegan, Director, DBOP

Items covered:

Reviewed revised redlined label emailed from Genzyme (version 9/14/07). Made editorial changes to the label.

Action Items:

To email FDA redlined version 9/17/07 to Genzyme

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 15, 2007

TO: Amy Gomez, Regulatory Project Manager, OND/OODP/DBOP
Suzanne Demko, M.D., Medical Officer, OND/OODP/DBOP
Jeff Summers, M.D., Team Leader, OND/OODP/DBOP

THROUGH: Leslie Ball, M.D., Branch Chief, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

FROM: J. Lloyd Johnson, Pharm.D., Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: STN BL 103948/5070

APPLICANT: Genzyme Corporation

DRUG: Alemtuzumab (Campath®, MabCampath®)

CHEMICAL CLASSIFICATION: 6P (New Indication; Priority Review)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Conversion to full approval; expansion of indication to include first-line treatment of B-cell chronic lymphocytic leukemia (B-CLL).

CONSULTATION REQUEST DATE: April 16, 2007

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: August 17, 2007

ACTION GOAL DATE: September 19, 2007

I. BACKGROUND

Genzyme Corporation submitted a sBLA for Alemtuzumab (CAMPATH®, MabCampath®), a humanized monoclonal antibody to CD52 antigen expressed in peripheral blood lymphocytes, monocytes, and macrophages in humans. The product is currently approved for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with an alkylating agent and failed fludarabine therapy. The sponsor is seeking to expand the indication to include the use of alemtuzumab as first-line therapy in the treatment of B-CLL patients and to satisfy the first post-marketing commitment of their initial approval.

Data from a Phase III study, CAM307, was submitted in support of the first line expanded treatment indication in B-CCL patients. The sponsor claims that based on data submitted in Study CAM307, alemtuzumab provides evidence of increased effectiveness and superior progression-free survival (PFS) for previously untreated subjects with B-CLL compared to chlorambucil.

Study CAM307 was the primary focus of the bioresearch monitoring clinical investigator inspections conducted for this BLA supplement submission. The purpose of the inspections was to validate data submitted in support of BLA 103948/5070.

II. RESULTS (by site):

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECTN DATE	EIR-REC'VD	FIELD CLASS.
Prof. Tadeusz Robak (Site 4001)	Lodz	Poland	Study CAM 307	July 23 - 27, 2007	Pending	VAI
Prof Anna Dmoszynska (Study (Site 4006)	Lublin	Poland	Study CAM 307	July 30 - Aug. 03, 2007	Pending	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

VAIr = Deviation(s) from regulations, response requested. Data acceptable

OAI = Significant deviations from regulations. Data unreliable

Pending = Inspection/Report not completed

Investigators:

Study Protocol:

CAM 307: A Phase 3 Study to Evaluate the Efficacy and Safety of Front-line Therapy with Alemtuzumab (Campath) vs. Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia (CAM307).

Basis for site selection: The following sites were selected by the Division of Biologic Oncology Products (DBOP) for inspection because of their relatively high subject numbers and considered essential for the approval of the application. No single site drove the study results; with the exception of increased ratio of protocol violations to subjects at these two sites. DBOP did not identify any specific problems with the study data or specific areas to emphasize during the inspections.

- (1) Prof. Tadeusz Robak (Study CAM 307) (Site 4001) (26 Subjects)
Dept. Hematology
Medical University of Lodz
Copernicus Hospital
2 Ciolkowskiego St.
93-510 Lodz, Poland

Inspection dates: July 23 – 27, 2007.

Methodology: Inspection assignments were issued to the field office.

- a. What was inspected?
Records of 26 subjects randomized in the study were reviewed.
- b. Limitations of inspection: none

General observations/commentary: ATL-DO Field Investigator, Ingrid Zambrana, reported by e-mail that a comprehensive audit comparing the source documents with data listings and completed case report forms was performed for primary efficacy end points, adverse events, serious adverse event, deaths, informed consent documents, and drug accountability records. Subject records were reviewed and compared with sponsor's data listings. ATL-DO is currently preparing the EIR for submission to DSI for evaluation and final classification.

An FDA 483 was issued at the conclusion of the inspection with four observations. Based on the FDA 483 faxed to DSI, the findings are primarily related to not following the protocol procedures in some instances and can be summarized as follows: a) At least 3 study subjects received 4 maintenance doses instead of the 3 maintenance dose per week specified in the protocol during 1 out of the 12 week maintenance treatment period; b) Reporting of some SAEs in 4 subjects were not done within the 24 hour window specified in the protocol; c) chest x-rays and imaging studies were not performed within the 3 weeks prior to randomization in at least 5 subjects; and d) 2 study subjects did not received study drug treatment within 7 days of randomization as required by the protocol.

The observations noted above are based on communication from the field investigator. Further review and evaluation of the observations will be made when the EIR and exhibits are submitted. An inspection summary addendum will be generated if conditions change upon receipt and review of the EIR.

Recommendation: Data from this site are acceptable. Preliminary review does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data

- (2) Prof Anna Dmoszynska (Study CAM 307) (Site 4006) (24 Subjects)
Department of hematology and Bone Marrow Transplantation
Ul. Staszica 11
20-081 Lublin, Poland

Inspection dates: July 30 - August 3, 2007.

Methodology: Inspection assignments were issued to the field office.

- a. What was inspected?
The study records of 24 subjects enrolled in the study were audited.
- b. Limitations of inspection: none.

- c. General observations/commentary: FDA Field Investigator, Ingrid Zambrana, reported by e-mail that a comprehensive audit of this site was also conducted. Source documents were compared with data listings and completed case report forms for primary efficacy end points, adverse events, serious adverse event, deaths, informed consent documents, and drug accountability records.

An FDA 483 was issued with four items. Most of the inspectional observations involved not following protocol procedures in certain cases. The inspectional observations can be summarized as follows: a) Two study subjects received 4 treatments instead of the 3 maintenance dose treatments per week during two weeks of the 12 week maintenance dosing schedule; b) Six SAEs experienced by four subjects were not reported to the sponsor within the 24 hours required by the protocol (reporting of these SAEs range from 20 days to 11 months); c) Some adverse events (i.e., nausea and vomiting, fever, rigors, diarrhea, pain in the left leg, hives, and tingling) experienced by 8 out of 22 subjects were not reported to the sponsor; and d) Forty ampoules of the study drug were shipped below the recommended temperature storage conditions (2 - 8 °C) and were used in the study without notification of the sponsor.

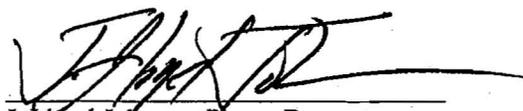
The observations noted above are based on communication from the field investigator. Further review and evaluation of the observations will be made when the EIR and exhibits are submitted. An inspection summary addendum will be generated if conditions change upon receipt and review of the EIR.

Recommendation: Data from this site are acceptable. Preliminary review does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the two study sites inspected, it appears that sufficient documentation to assure that all study subjects audited did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Follow-up action: An inspection summary addendum will be generated if conclusions changes significantly upon receipt and review of the EIRs and evidence exhibits from ATL-DO.



J. Lloyd Johnson, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:

Leslie Ball, M.D.

Leslie Ball, M.D.

Branch Chief, Good Clinical Practice Branch II, HFD-47

Division of Scientific Investigations

DISTRIBUTION:

HFD-47/Johnson

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HFD-45/Program Management Staff (electronic copy)

HFD-45/GD/JS

File HFD-47/LB

DBOP/MO (Suzanne Demko, M.D.)

DBOP/RPM (Amy Gomez)

Filename and path: O: BLA.STN.BL 103948/5070



**BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #15
Minutes
September 14, 2007**

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Joseph Gootenberg, Deputy Director, DBOP
Patricia Keegan, Director, DBOP

Items covered:

Reviewed revised redlined label emailed from Genzyme (version 9/13/07b).

Action Items:

To email FDA redlined version 9/14/07 to Genzyme
To discuss persistent CMV viremia issue with Genzyme at afternoon teleconference (3pm)



T-CON SUMMARY

Applicant: Genzyme

Applicant Participants:

Mark Hayes, Regulatory Affairs
Katie O'Keefe, Regulatory Affairs
Linda Pollitz, Regulatory Affairs - Advertising and Promotion
Cyndi Sirard (MD), Clinical Research
Paul Beninger (MD), Pharmacovigilance
Ron Knickerbocker, Biomedical Operations

FDA Participants:

Patricia Keegan, MD, Director, DBOP
Suzanne Demko, PA-C, Clinical Analyst, DBOP
Amy Gomez, RN, MS, Regulatory Project Manager, DBOP

Number: (b) (4)

Date: Friday, September 14, 2007

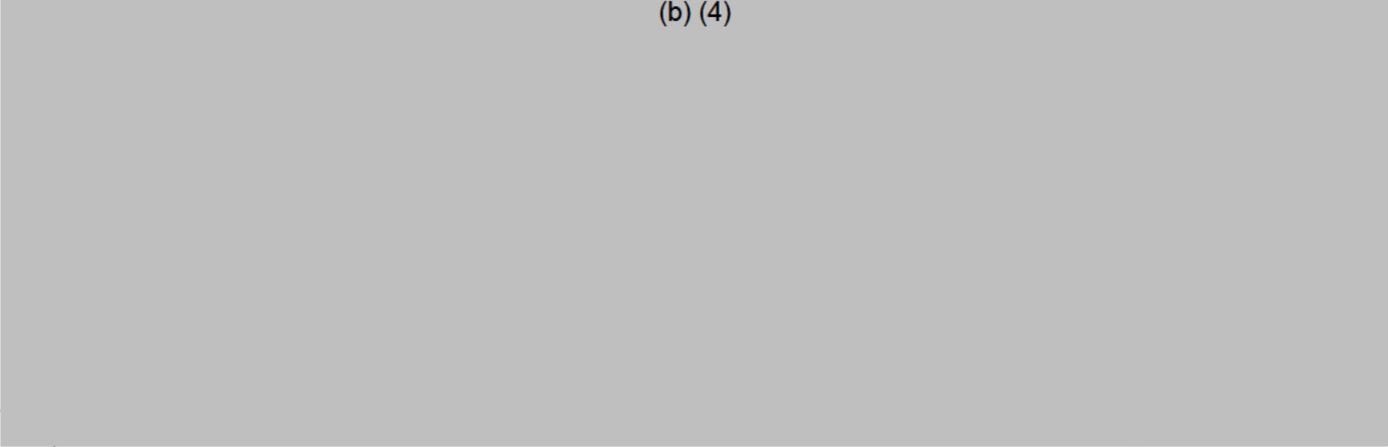
RE: Labeling discussion, STN 103948/5070 Alemtuzumab (Campath)

Summary:

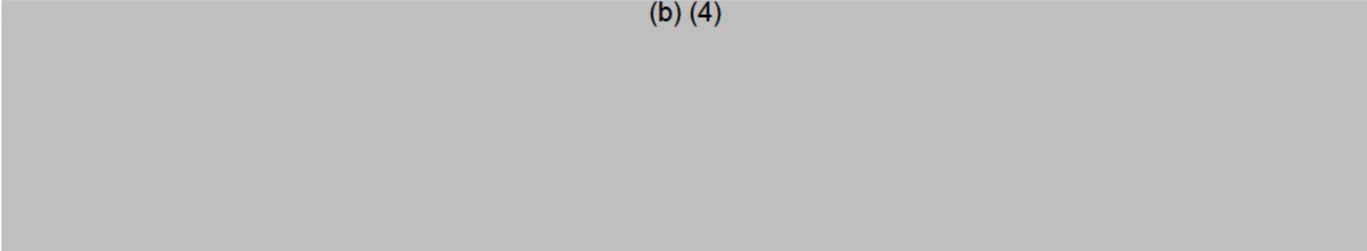
1. Genzyme requested clarification on the rationale for FDA recommending changing the reference for use of irradiated blood products. FDA acknowledged that the circular Genzyme provided as a reference is more widely available but noted that the reference FDA proposed is the text that contains the blood bank standards for the use of irradiated blood products. Not having had the opportunity to review the full text of FDA's proposed reference (b) (4) FDA and Genzyme agreed that the reference to the circular, as originally proposed by Genzyme, would be included in the label.
2. Genzyme stated concern about the language defining "persistent CMV viremia" in lines 109-114. It proposed that the language be "confirmed" instead of "persistent." FDA agreed that the term "persistent" can be changed to "confirmed."

(b) (4)

(b) (4)



(b) (4)



Genzyme stated it would provide revised labeling by close of business Friday, 9/14/07.

The call concluded.

Gomez, Amy

From: Gomez, Amy
Sent: Friday, September 14, 2007 9:21 AM
To: 'O'Keefe, Katherine'
Subject: RE: Campath - STN 103948/5070 FDA redlined label
Importance: High
Attachments: FDA redlined_103948-5070_14sept07.doc

Hi Katie,

We reviewed your revisions and have made a couple of minor changes in the attached redlined label:

1. We added a more updated/appropriate reference for irradiated blood products. Please check the format of the reference.
2. We revised the wording of footnote 3 to Table 1 (I highlighted the change in the footnote so you can see it more easily).

We would like to discuss your comment regarding treatment of persistent CMV viremia at this afternoon's teleconference. I believe participants from this end will be Dr. Keegan, Ms. Demko, and myself. Dr. Gootenberg may also attend.

Regards,

Amy

17 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

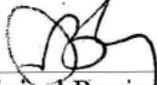
Draft Labeling (b5)

Deliberative Process (b5)



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #14
Minutes
September 13, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Kallappa Koti, Statistical Reviewer
Patricia Keegan, Director, DBOP

Items covered:

Reviewed revised redlined label emailed from Genzyme (received 9/13/07), and Genzyme's justification for changes.

Action Items:

~~Suzanne to confirm with blood bank sources that requiring rather than recommending irradiated~~
blood products for severely lymphopenic patients is appropriate. Will update label accordingly.

To email label to Genzyme with request for revised label by 8am 9/14/07.

Gomez, Amy

From: Gomez, Amy
Sent: Thursday, September 13, 2007 1:15 PM
To: 'O'Keefe, Katherine'
Subject: RE: Campath - STN 103948/5070 FDA redlined label
Importance: High
Attachments: Responses to Genzyme 09 13 07 103948-5070.doc; FDA redlined_103948-5070_13sept07.doc

Hi Katie,

Here is our revised label and responses. There's a page break between the TOC and the FPI that I can't seem to delete. Please see if you can fix that. In reviewing your revisions in the overdosage section, we also made some additional edits to improve the readability.

We look forward to seeing your revised label before tomorrow's internal labeling meeting.

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Thursday, September 13, 2007 11:19 AM
To: Gomez, Amy
Subject: RE: Campath - STN 103948/5070 FDA redlined label

Hi Amy,

We will submit the label/justification to STN 103948/5070. I have a meeting scheduled with the Genzyme team from 2 – 4 to review FDA's comments. Please let me know if you think we will have comments before 2 or if I should adjust the timing of the meeting.

Kind regards,
Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Thursday, September 13, 2007 10:49 AM
To: O'Keefe, Katherine
Subject: RE: Campath - STN 103948/5070 FDA redlined label

As always, please also submit the label/justification to STN 103948/5070. As soon as I have comments back from the reviewers, I will forward them to you. It may be later in the day, however.

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Thursday, September 13, 2007 8:26 AM
To: Gomez, Amy
Subject: RE: Campath - STN 103948/5070 FDA redlined label

Thanks.

9/13/2007

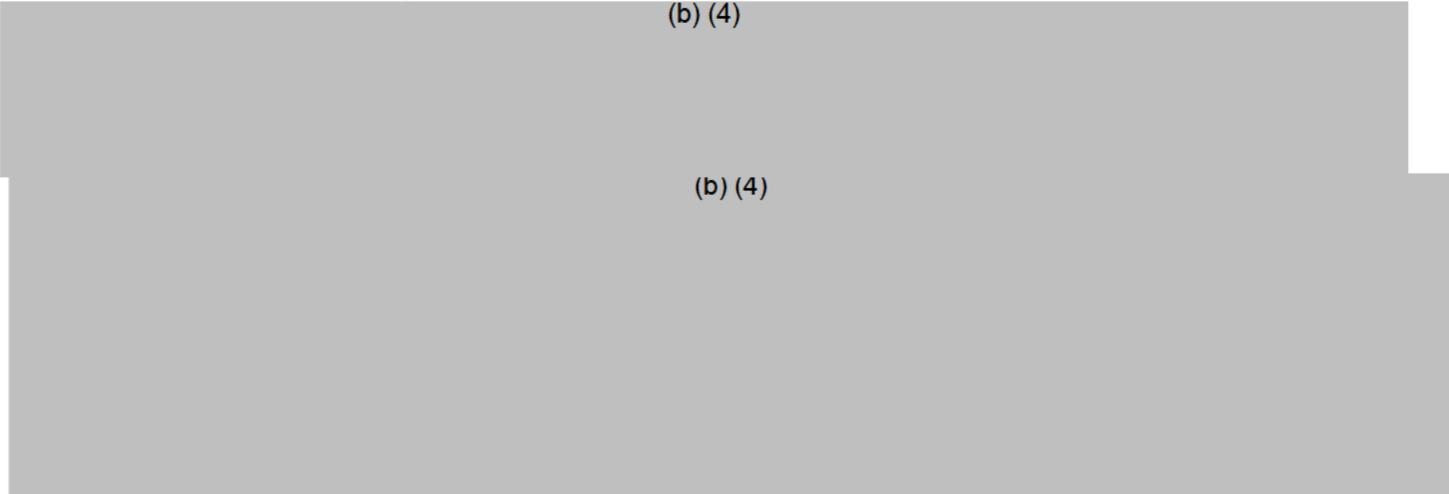
**Responses to Genzyme 103948/5070
September 13, 2007**

Section 5.3 Immunosuppression/Infection

(b) (4)



(b) (4)



(b) (4)

17 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #13
Minutes
September 12, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Kallappa Koti, Statistical Reviewer
Patricia Keegan, Director, DBOP
Anne Pilaro, Acting Supervisory Toxicologist

Items covered:

Reviewed revised redlined label emailed from Genzyme (received 9/6/07), Genzyme's justification for changes, and Genzyme's response to 9/7/07 teleconference. Completed review of label.

Action Items:

To email label to Genzyme with request for revised label by 8am 9/13/07.

Gomez, Amy

From: Gomez, Amy
Sent: Wednesday, September 12, 2007 2:59 PM
To: 'O'Keefe, Katherine'
Subject: RE: Campath - STN 103948/5070 FDA redlined label
Importance: High
Attachments: FDA redlined_103948-5070_09-12.doc

Hi Katie

I was able to schedule an internal labeling meeting today. We have considered your revisions to the label sent 9/6/07 and the cover letter included with the official submission. FDA's redlined label version date 9/12/07 is attached for your review. Where your changes to the label were acceptable, we accepted changes so they no longer appear redlined. There are a couple of comments to you included in the label.

Please send us your revisions by **tomorrow 8:00 am Eastern time** so we can review at tomorrow's internal labeling meeting.

Regarding PLR, we would prefer to receive agreed upon labeling in PLR format by the action date if at all possible. We recognize that might not be possible, given the short turn around time and continued label negotiations.

Please confirm receipt and let me know if you will be able to provide revisions by tomorrow morning.

Thanks!

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Wednesday, September 12, 2007 10:09 AM
To: Gomez, Amy
Subject: RE: Campath - STN 103948/5070 FDA redlined label

Hi Amy,

Thanks for sending the list of FDA participants in the 9/7 teleconference and for letting me know that the next internal labeling meeting at FDA has been scheduled for Thursday and that we probably won't receive feedback until Thursday or Friday.

We are thinking about the preparation/submission of the final agreed upon labeling in the SPL format and were wondering how quickly this needs to be submitted after the labeling language is agreed upon. Please let me know.

Kind regards,
Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Monday, September 10, 2007 8:40 PM
To: O'Keefe, Katherine
Subject: RE: Campath - STN 103948/5070 FDA redlined label

Thanks Katie. I forwarded the cover letter to the team for their review.

9/12/2007

19 Page(s) Withheld

Trade Secret / Confidential (b4)

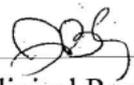
Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #12
Minutes
September 7, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Kallappa Koti, Statistical Reviewer
Patricia Keegan, Director, DBOP
Iris Masucci, SEALD PLR Reviewer

Items covered:

Reviewed revised redlined label emailed from Genzyme (received 9/6/07) and Genzyme's justification for changes/topics for discussion. Reviewed label until section 6.1 neutropenia.

Action Items:

Line 151: Suzanne to check duration of exposure
Line 158: request from Genzyme
Teleconference with Genzyme scheduled for 9/7/07 3 pm.



T-CON SUMMARY

Applicant: Genzyme

Applicant Participants:

- Mark Hayes, Regulatory Affairs
- Katie O'Keefe, Regulatory Affairs
- Brian Conner, Regulatory Affairs - Advertising and Promotion
- Cyndi Sirard (MD), Clinical Research
- Michael Vasconcelles (MD), Clinical Research
- Paul Beninger (MD), Pharmacovigilance
- Michael Wess (MD), Pharmacovigilance
- Elizabeth Trehu (MD), Medical Affairs
- Ron Knickerbocker, Biomedical Operations

FDA Participants:

- Anne Pilaro, PhD, Acting Supervisory Toxicologist, DBOP
- Patricia Keegan, MD, Director, DBOP
- Jeff Summers, MD, Acting Clinical Team Leader, DBOP
- Kallappa Koti, PhD, Statistician, DB5
- Suzanne Demko, PA-C, Clinical Analyst, DBOP
- Amy Gomez, RN, MS, Regulatory Project Manager, DBOP

Number: (b) (4)

Date: Friday, September 7, 2007

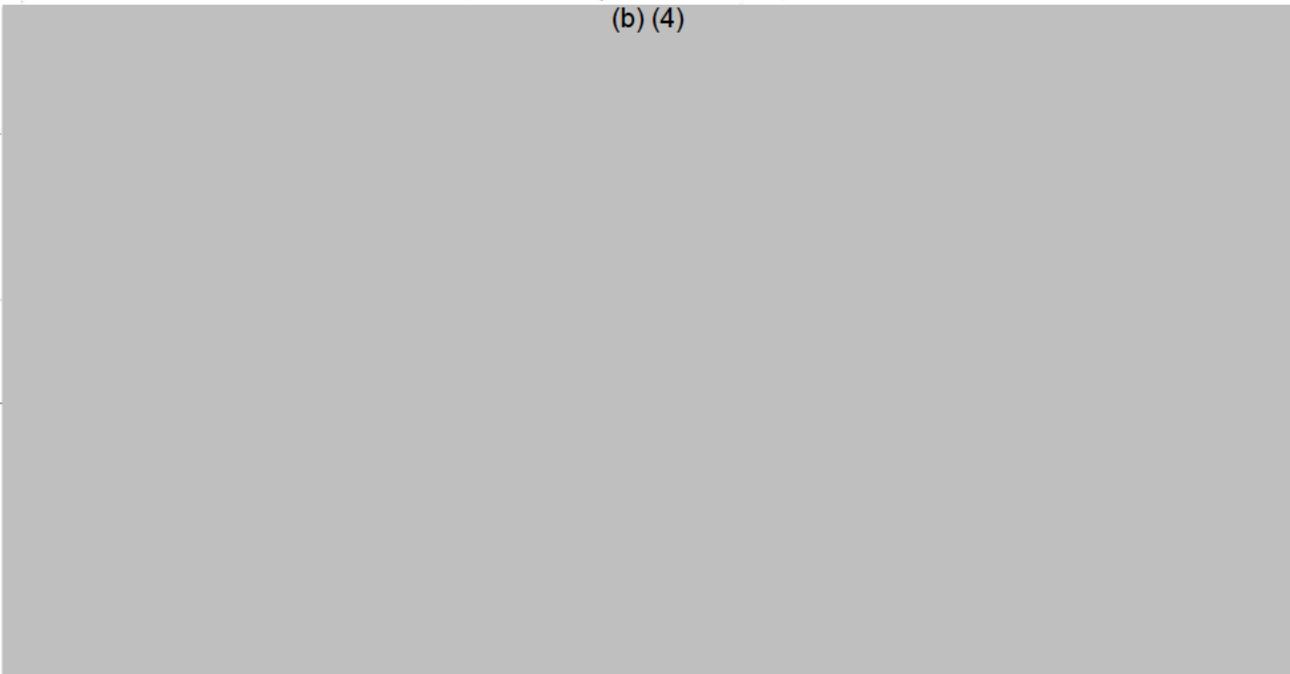
RE: Labeling discussion, STN 103948/5070 Alemtuzumab (Campath)

Summary:

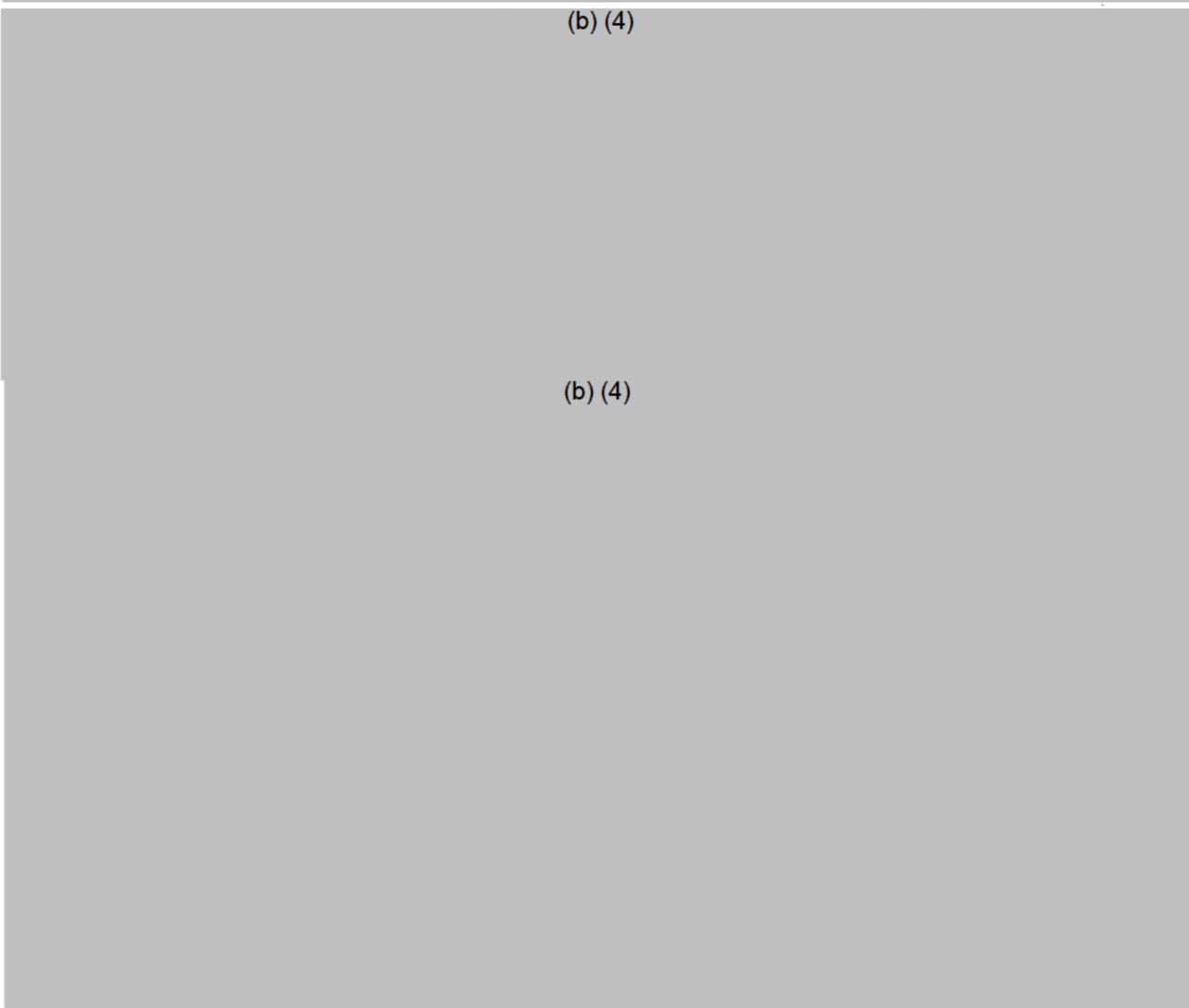
(b) (4)

(b) (4)

(b) (4)



(b) (4)

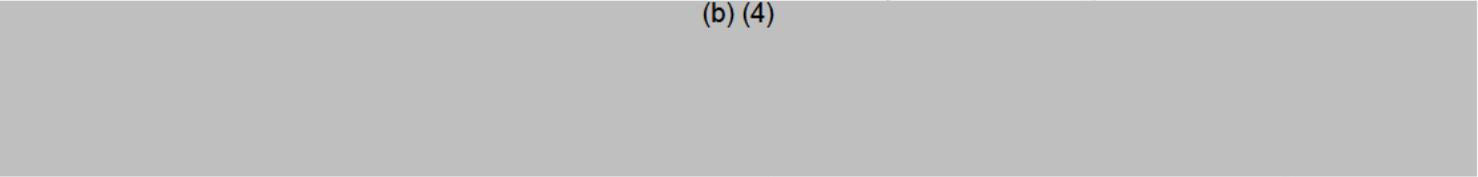


(b) (4)

(b) (4)



(b) (4)



FDA requested that any counterproposal from Genzyme be provided to the RPM as soon as possible so it can be considered as FDA continues internal labeling review.

The call concluded.

Gomez, Amy

From: Gomez, Amy
Sent: Wednesday, September 05, 2007 8:40 AM
To: 'O'Keefe, Katherine'
Subject: FW: Campath signature page

Importance: High

Attachments: CAM 307 Sponsor Signature.doc

Hi Katie,

Please submit an amendment containing the correct signature page for protocol CAM 307, as requested by Ms. Demko (see below).

Thanks,

Amy

From: Demko, Suzanne
Sent: Friday, August 31, 2007 6:06 PM
To: Gomez, Amy
Subject: Campath

Amy:

A signature page from the CSR for the Genzyme's responsible medical officer contains a signature that is reproduced from another study in another disease (See attached, page 2).

Thanks.

Suzanne



CAM 307 Sponsor
Signature.doc ...

Campath® (Alemtuzumab, MABCAMPATH®)
Clinical Study Report: CAM307

16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor's
Responsible Medical Officer

Sponsor Medical Officer: Cynthia Sirard, MD
Medical Director, Clinical Research

Campath® (Alemtuzumab, MABCAMPATH®)
Clinical Study Report: CAM307

Appendix 16.1.5

STUDY TITLE: A Phase II Study of ILX651 Administered Intravenously Daily for Five Consecutive Days Once Every 3 Weeks in Patients with Locally Advanced or Metastatic Non-small Cell Lung Carcinoma

Statistician:

(b) (6)

Signature:

(b) (6)

Date:

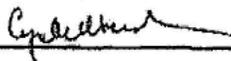
25 Jan 2007

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor Medical Officer:

Cynthia Sirard, MD
Medical Director, Clinical Research

Signature:



Date:

25 Jan 2007

Affiliation:

Genzyme Corporation
55 Cambridge Parkway
Cambridge MA, 02142 USA



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #11
Minutes
August 31, 2007

Attendees:

Amy Gomez, RPM

A handwritten signature in black ink, appearing to be "Suzanne Demko", is written over the name and title of the Clinical Reviewer.

Suzanne Demko, Clinical Reviewer

Jeff Summers, Clinical Team Leader

Anne Pilaro, Pharmacology/Toxicology Reviewer

Kallappa Koti, Statistical Reviewer

Angela Men, Clinical Pharmacology Reviewer

Patricia Keegan, Director, DBOP

Joseph Gootenberg, Deputy Director, DBOP

Iris Masucci, SEALD PLR Reviewer

Items covered:

Reviewed revised label submitted 8/28/07 STN 103948/5070/5006.

Discussed PLR content/format revisions.

Continued review of label and Highlights section.

Action Items:

Send redlined label to Genzyme with comments embedded

F/U on IgG subtypes secreted in breast milk

Kallappa to create Kaplan-Meier curve for time to CD4 recovery to provide estimates in label.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum
Food and Drug Administration
Center for Drug Evaluation and Research Bethesda, MD 20892

Date: August 31, 2007

To: STN103948 File

From: Sean Fitzsimmons, Ph.D. Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies

Through: Patrick Swann, Ph.D., Deputy Director, Division of Monoclonal Antibodies

Subject: Review of STN 103948-5070 Efficacy Supplement eCTD Sequence No. 0014/Supplement 128: Revised Proposed Labeling

Submitted: August 28, 2007

Sponsor:

Genzyme Corporation
4545 Horizon Hill Boulevard
San Antonio, TX 78229-2263

Contact:

Katherine O'Keefe, MPH
Associate Director, Regulatory Affairs
Telephone: (617) 768-6776
Fax: (617) 374-2855

Review of labeling changes:

Genzyme proposed two changes to the label that required my review.

1. In section 2.5 "Incompatibilities", Genzyme removed a statement that Campath is compatible with low binding protein filter sets.

The justification for removing the statement regarding in-line filter compatibility was provided in the cover letter to eCTD sequence number 0013. In-line filters were used because the product was originally packaged in ampoules and there was

a risk of glass particles when the ampoules were opened for use. The product is now packaged in vials, in-line filtration is no longer used.

Removal of the statement regarding filter compatibility is acceptable.

2. In section 7 "Drug Interactions", Genzyme removed the statement "an immune response to Campath may interfere with subsequent diagnostic serum tests that utilize antibodies." Genzyme stated that the wording was added to the label during initial labeling negotiations and that it was never actually documented.

Removal of the statement regarding the potential interference of anti-Campath antibodies with diagnostic serum tests is acceptable.

Campath contains human heavy chain and light chain framework and constant regions and the complementarity-determining regions (CDRs) are of rat origin. A HAHA response to Campath would be directed to the constant or framework regions of the molecule while a HAMA response would be directed to the CDRs. A HAHA response was detected in 11 of 133 (8.3%) first line patients.

It is very unlikely that antibodies developed for diagnostic test kits would be human or humanized, therefore, the risk of HAHA response interference is minimal. Additionally, I consider it unlikely that a HAMA response to Campath CDRs would block or interfere with CDRs of other antibodies that may be components of diagnostic test kits.

33 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Gomez, Amy

From: Gomez, Amy
Sent: Friday, August 31, 2007 4:50 PM
To: 'O'Keefe, Katherine'
Subject: RE: Campath - STN 103948/5070 FDA redlined label
Importance: High
Attachments: FDA redlined 103948-5070 8.31.07.doc

Hello Katie,

We just finished going through the remainder of the label. Please note, because we sent an incomplete label to you last time, the redlines in the highlight section do NOT represent all of the changes we have made since the first FDA redlined label. In the FPI, the redlines are the changes made to the FDA version of the label since the last one sent to you. Your proposed language, if acceptable, is incorporated into this version. Please review the label in its entirety in case there are changes that don't appear redlined.

There are several highlighted comments within the label. A couple are internal comments that you can disregard; the ones directed to you start with "To Genzyme." These include explanations and requests for data.

Also, I corrected the format of the references (e.g. [see *Dosage and Administration (2)*]), please refer to the day 74 letter for explanation of the correct format), but the actual section numbers may need to be updated. Please confirm all of the references are correct.

We look forward to receiving a revised redlined label from you.

Please confirm receipt of this label and let me know when you anticipate you will be able to send a response.

Thanks,

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Thursday, August 30, 2007 2:04 PM
To: Gomez, Amy
Subject: RE: Campath - STN 103948/5070

Hi Amy,

Thanks for letting me know that you're working on a counter proposal and that there will be no teleconference tomorrow. We look forward to receiving the redlined label when you finish your review.

I hope you enjoy the holiday weekend!

Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Thursday, August 30, 2007 2:00 PM
To: O'Keefe, Katherine
Subject: RE: Campath - STN 103948/5070

Hi Katie,

We are working on a counterproposal for the label and thus the team determined that a teleconference tomorrow would be premature. I'll send you the redlined label as soon as we finish our review.

Thanks,

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Wednesday, August 29, 2007 9:18 AM
To: Gomez, Amy
Subject: RE: Campath - STN 103948/5070

Hi Amy,

Thanks for confirming that you received my e-mail and that you will use the WORD document provided yesterday for your labeling meetings. Thanks also for letting me know that we may not know until Thursday afternoon whether we will have a teleconference to discuss labeling on Friday.

Kind regards,
Katie

26 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

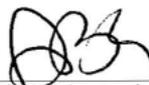
 Draft Labeling (b5)

 Deliberative Process (b5)



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #10
Minutes
August 30, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Anne Pilaro, Pharmacology/Toxicology Reviewer
Kallappa Koti, Statistical Reviewer
Angela Men, Clinical Pharmacology Reviewer
Hong Zhao, Clinical Pharmacology Team Leader
Patricia Keegan, Director, DBOP
Joseph Gootenberg, Deputy Director, DBOP
Sean Fitzsimmons, CMC Reviewer
Iris Masucci, SEALD PLR Reviewer

Items covered:

Reviewed revised label submitted 8/28/07 STN 103948/5070/5006.
Discussed PLR content/format revisions.
Discussed action items from 8/29 labeling meeting with Sean Fitzsimmons.

Action Items:

Continue label review 8/31/07



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #9
Minutes
August 29, 2007

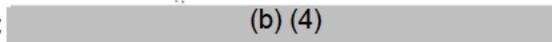
Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Anne Pilaro, Pharmacology/Toxicology Reviewer
Kallappa Koti, Statistical Reviewer
Angela Men, Clinical Pharmacology Reviewer
Hong Zhao, Clinical Pharmacology Team Leader
Patricia Keegan, Director, DBOP
Joseph Gootenberg, Deputy Director, DBOP

Items covered:

Reviewed revised label submitted 8/28/07 STN 103948/5070/5006.
Reviewed sections 1-5, 7-13.

Action Items:

F/U with Sean Fitzsimmons re:  (b) (4)
F/U with Sean Fitzsimmons re: any effect of HAHA on immune serum tests.



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #8
Minutes
August 21, 2007

Attendees:

Amy Gomez, RPM

Handwritten initials, possibly "AG", in black ink.

Suzanne Demko, Clinical Reviewer

Jeff Summers, Clinical Team Leader

Anne Pilaro, Pharmacology/Toxicology Reviewer

Joseph Gootenberg, Deputy Director, DBOP

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002.

Reviewed DDMAC comments and Highlights section

Action Items:

To send label on email for review. Genzyme to submit revised FPI on 8/24/07, to finish review of Highlights section at the next labeling meeting.

Gomez, Amy

From: Gomez, Amy
Sent: Friday, August 17, 2007 10:40 AM
To: 'O'Keefe, Katherine'
Subject: Campath redlined label
Importance: High
Attachments: FDA redlined to Genzyme 103948 5070 8 16 07.doc

Hello Katie,

We will not be holding a teleconference today.

For your review, I am attaching the FDA redlined label for Campath STN 103948/5070. FDA's revisions to the label are in keeping with the spirit of the Physician's Labeling Rule and thus the label has been significantly streamlined. Please note that our internal review of the label is not complete; however, we are sending you these revisions of the "Full Prescribing Information" section so that you have adequate time to incorporate the changes or provide justification for alternative language. We may request additional changes to the label.

Please submit revised redlined labeling by email and to the sBLA STN 103948/5070 by Friday, August 24th. If you have any questions regarding the changes to the label, we would be happy to discuss at our periodic ("standing") weekly teleconference.

Thanks,

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Friday, August 17, 2007 9:42 AM
To: Gomez, Amy
Subject: Campath - Teleconference Today?

Hi Amy,

Does the review team have anything that they would like to discuss with the Genzyme team today?

Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Thursday, August 09, 2007 8:39 AM
To: O'Keefe, Katherine
Subject: RE: No tcon today

Hi Katie,

We're working diligently on the label and I'm hoping we'll be able to send you revisions before September. Of course, this will depend on the review. I'll keep you posted.

If necessary, we can use the standing tcon time for discussion regarding the label.

We currently have no other items to discuss so we won't need to hold the standing tcon tomorrow.

Thanks!

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Friday, August 03, 2007 3:54 PM
To: Gomez, Amy
Subject: RE: No tcon today

Hi Amy,

I hope you enjoyed your vacation!

Thanks for letting me know that the work on the PI is ongoing and there is no need for a teleconference today.

I've been thinking ahead to early September when FDA's labeling comments will be available and anticipating that there will need to be some discussion between FDA and Genzyme about the final labeling content. The Genzyme team members who will need to participate in these labeling discussions are located in a variety of different time zones/countries and I would like to arrange for everyone to be in one place to ensure that these discussions are smooth and efficient. Would it be possible for us to schedule these labeling discussions in advance so that my team can make the necessary travel arrangements?

Kind regards,
Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Friday, August 03, 2007 11:44 AM
To: O'Keefe, Katherine
Subject: No tcon today

Hi Katie,

Our team is continuing to work on the PI; we don't need to have a teleconference today.

Regards,

Amy

38 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #7
Minutes
August 16, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Anne Pilaro, Pharmacology/Toxicology Reviewer
Joseph Gootenberg, Deputy Director, DBOP
Kallappa Koti, Statistical Reviewer
Carole Broadnax, DDMAC Reviewer

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002. Continued review of label, focused on section 6.

Action Items:

Continue label review next meeting 8/21/07.



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #6
Minutes
August 9, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Anne Pilaro, Pharmacology/Toxicology Reviewer
Joseph Gootenberg, Deputy Director, DBOP

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002. Continued review of label.

Action Items:

Ask SEALD regarding what demographic data should be included in the label.
Need further discussion of sections 11 and 12.1



**BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #5
Minutes
August 8, 2007**

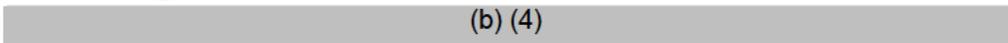
Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Joseph Gootenberg, Deputy Director, DBOP

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002. Continued review of label.

Action Items:

Re-address  (b) (4)
Need clarification on language for pregnancy and lactation from SEALD.



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #4
Minutes
August 3, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Sean Fitzsimmons, Quality Reviewer
Joseph Gootenberg, Deputy Director, DBOP

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002. Continued review of label.

Action Items:

Re-address section 12.1 MOA
Re-address immunogenicity (comment in label)



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #3
Minutes
August 2, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Anne Pilaro, Pharm/Tox Reviewer
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Hong Zhao, Clinical Pharmacology Team Leader
Joseph Gootenberg, Deputy Director, DBOP

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002. Continued review of label.

Action Items:

Re-address the term "recently" in section 5.5
Check the title of section ^{(b)(4)} (infusion reactions)



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration

Center for Drug Evaluation and Research Bethesda, MD 20892

Date: August 1, 2007

To: STN103948 File

From: Sean Fitzsimmons, Ph.D. Laboratory of Molecular and Developmental
Immunology, Division of Monoclonal Antibodies

Sean Fitz 8-1-07

Through: Marjorie Shapiro, Ph.D., Chief, LMDI *Marjorie Shapiro* 8/1/07

Subject: Review of STN 103948-5070 Efficacy Supplement

Submitted: March 19, 2007

**Review
deadline:** August 9, 2007

Sponsor:
Genzyme Corporation
4545 Horizon Hill Boulevard
San Antonio, TX 78229-2263

Contact:
Katherine O'Keefe, MPH
Associate Director, Regulatory Affairs
Telephone: (617) 768-6776
Fax: (617) 374-2855

Recommendation: *The assays used to monitor CD52 expression, anti-Campath antibodies and neutralizing antibodies were adequate and appropriately validated.*

Overview:

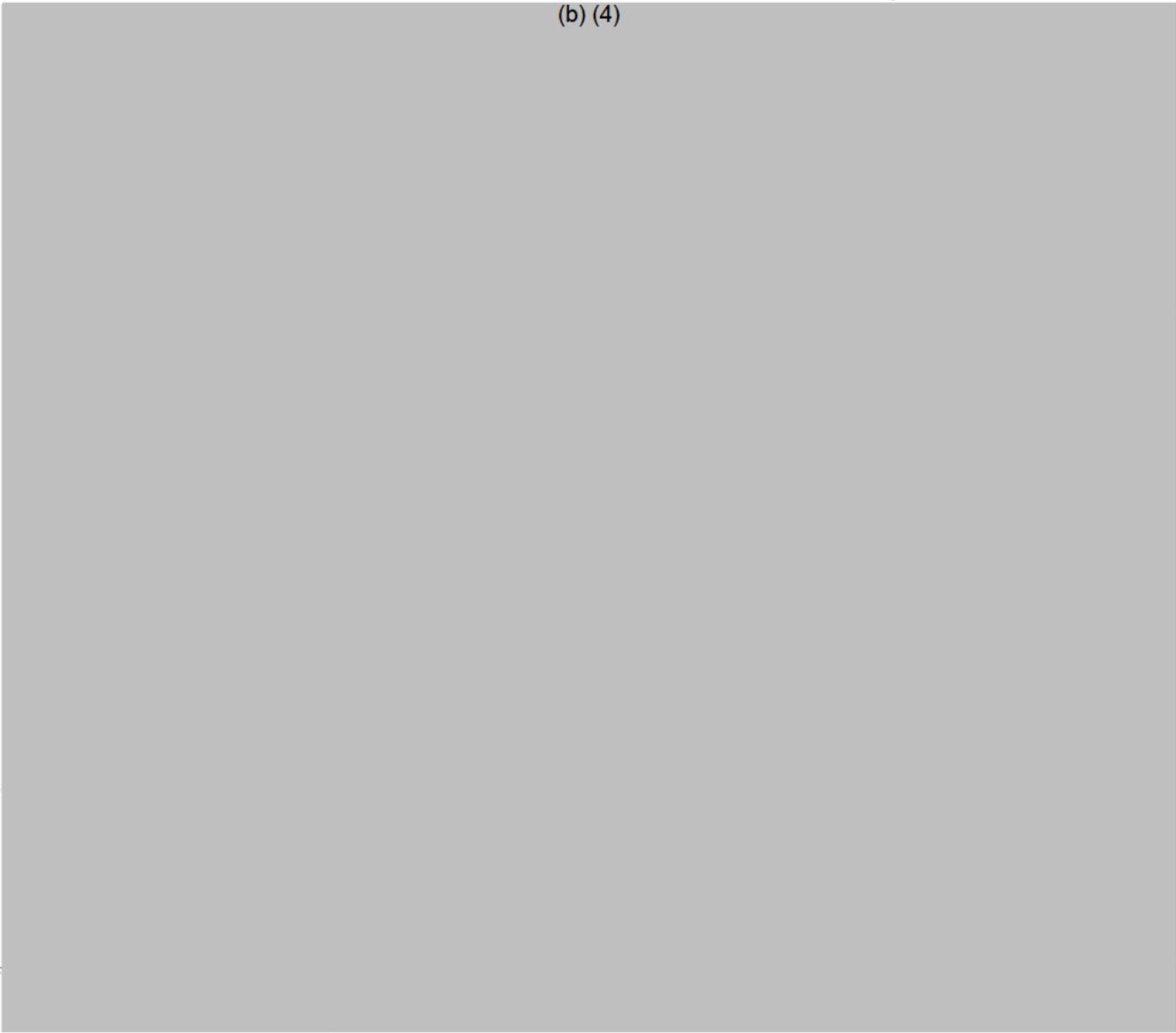
Campath (alemtuzumab, MABCAMPATH) is a genetically engineered humanized IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52). Campath causes the lysis of lymphocytes by binding to CD52, a highly expressed, non-modulating antigen which is present on the surface of essentially all B and T-cell lymphocytes as well as monocytes, thymocytes, and macrophages. The antibody mediates the lysis of lymphocytes via complement fixation and antibody-dependent cell

mediated cytotoxicity. Induction of apoptosis may also play a role in the cytotoxic effect of Campath.

The supplement under review contains data from study CAM 307, a phase III study that evaluated Campath for use as front-line therapy in patients with progressive B-cell CLL to support a change in the labeled indication.

Final study reports were submitted for the assessment of loss of CD52 expression at time of relapse or disease progression during or following Campath therapy and for the quantitative analysis of the incidence and magnitude of HAHA and anti-idiotypic antibodies at study entry and following exposure to Campath. For samples that were positive for HAHA, the neutralizing activity of the antibodies was assessed using a flow cytometry-based neutralization assay. Both the CD52 expression assay and the HAHA assay were previously validated. The only new assay described in this submission is the neutralization assay.

(b) (4)



4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Gomez, Amy

From: Kiel, Hea S
Sent: Monday, July 23, 2007 4:45 PM
To: Gomez, Amy
Cc: CDER-TB-EER
Subject: FW: Request for compliance check STN 103948/5070

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the TB-EER request below. There are no pending or ongoing compliance actions to prevent approval of STN 103948/5070 at this time.

(b) (4)



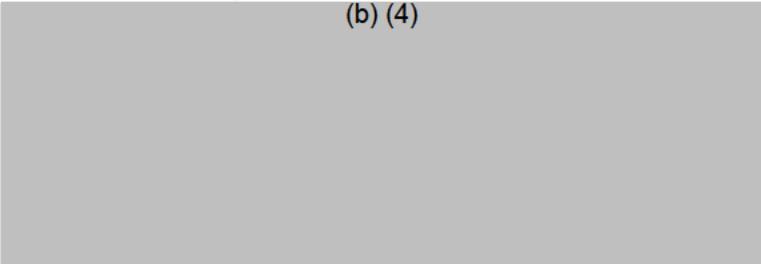
HeaSuk

From: Gomez, Amy
Sent: Friday, July 20, 2007 9:09 AM
To: CDER-TB-EER
Subject: Request for compliance check STN 103948/5070

Please perform a compliance check for the following:

Applicant: Genzyme Corporation

(b) (4)



U.S. License 1596

Product: Campath® (alemtuzumab, MabCampath®)

STN: 103948/5070

Proposed indication: for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) (PMC#1 under 103948/0)

PDUFA Action Due Date: September 19, 2007 (please complete by August 17, 2007)

8/14/2007

Amy,

Amy Gómez, RN, MS
Regulatory Project Manager
Division of Biologic Oncology Products

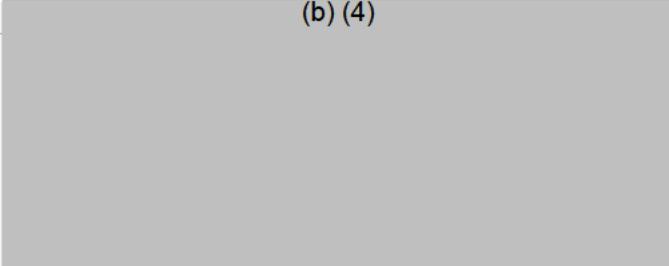
Gomez, Amy

From: Gomez, Amy
Sent: Friday, July 20, 2007 9:09 AM
To: CDER-TB-EER
Subject: Request for compliance check STN 103948/5070

Please perform a compliance check for the following:

Applicant: Genzyme Corporation

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill, obscuring the applicant's name and other identifying information.

U.S. License 1596

Product: Campath® (alemtuzumab, MabCampath®)

STN: 103948/5070

Proposed indication: for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) (PMC#1 under 103948/0)

PDUFA Action Due Date: September 19, 2007 (please complete by August 17, 2007)

Amy

Amy Gomez, RN, MS
Regulatory Project Manager
Division of Biologic Oncology Products

8/14/2007



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #2
Minutes
July 19, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Hong Zhao, Clinical Pharmacology Team Leader
Patricia Keegan, Director, DBOP

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002. Continued review of label.

Action Items:

To continue label review @ next meeting 8/2/07.



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Labeling Meeting #1
Minutes
June 28, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Sean Fitzsimmons, Product Reviewer
Joseph Gootenberg, Deputy Director, DBOP
Patricia Keegan, Director, DBOP

Items covered:

Reviewed revised label submitted 6/22/07 STN 103948/5070/5002. Discussed indication statement and revised label sections 2-4.

Action Items:

Dr. Keegan to discuss indication statement with Dr. Pazdur (Director, OODP).

Amy to send revisions of sections 2-4 to Genzyme for review.



103948/5070
Campath (Alemtuzumab)
Genzyme Corporation
License 1596
Midcycle Review Minutes

Meeting Date: June 12, 2007 11:00 am – 12:30 pm

Attendees:

Aloka Chakravarty
Suzanne Demko
Kathy Fedenko
Sean Fitzsimmons
Amy Gomez 
Karen Jones
Patricia Keegan
Kallappa Koti
Ginny Kwitkowski
Angela Men
Lee Pai-Scherf
Richard Pazdur
Mark Rothmann
Marjorie Shapiro
Jeff Summers
Karen Weiss
Hong Zhao

Background:

sBLA 103948/5070 received March 20, 2007, data from CAM 307 to support conversion to full approval and fulfill PMC #1; also new indication first-line B-CLL.

Review Team:

Amy Gomez, RPM
Suzanne Demko, Clinical Reviewer
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Sean Fitzsimmons, Product Reviewer
J Lloyd Johnson, DSI Reviewer

Proposed Indication:

for the treatment of B-cell chronic lymphocytic leukemia (B-CLL)

Agenda:

Review of Milestones	Amy Gomez	5 Minutes
Clinical Review and Statistical Review	Suzanne Demko and Kallappa Koti	45-60 Minutes
Clinical Pharmacology Review	Angela Men	10 Minutes
Product Review (Immunogenicity Assay)	Sean Fitzsimmons	5 Minutes
Discuss Labeling: Major Issues		10 Minutes
Upcoming Meetings/ Path Forward		5 Minutes

Milestones (priority review):

- a. Committee Assignment: Complete
- b. First Committee Meeting: Held April 6, 2007
- c. Filing Meeting: Held May 4, 2007
- d. Filing Action Letter: May 19, 2007
- e. Deficiencies Identified (Day 74) Letter: issued June 2, 2007
- f. **Action Letter: Due September 19, 2007**

DSI Update:

DSI has issued the inspection assignments for the two study sites in Poland. ORA's International Office is now working on getting a Field Inspector assigned and is working on the necessary foreign government clearances to get the inspections scheduled. Inspection dates have not been firmed up yet. DSI expects to have the inspections scheduled and completed hopefully in July or August.

Upcoming meetings (scheduled thus far):

- a. Team Meeting: Thursday, June 28, 2007 11:30am-12:00pm
- b. First Labeling Meeting: Thursday, June 28, 2007 12:00-1:30pm
- c. Team Meeting: Friday, July 13, 2007 8:30-9:00am
- d. Second Labeling Meeting: Thursday, July 19, 2007 11:30am-1:00pm
- e. Team Meeting: Thursday, August 2, 2007 11:30am-12:00pm
- f. Third Labeling Meeting: Thursday, August 9, 2007 11:30am-1:00pm
- g. Weekly teleconferences with Genzyme (as needed) Fridays 3:00-4:00pm

Discussion:

Milestones were discussed and presentations were given by all team members, except J. Lloyd Johnson, regarding their reviews to date. DSI update was provided in writing as noted above because J. Lloyd Johnson could not attend the meeting.

Labeling was not discussed due to time limitation, but it was noted that the day 74 Deficiencies Identified letter issued to Genzyme contained comments based on review of PLR format and broad labeling issues.

The meeting adjourned.

Gomez, Amy

From: Gomez, Amy
Sent: Tuesday, July 03, 2007 11:39 AM
To: 'O'Keefe, Katherine'
Subject: RE: Campath - Revised Proposed Labeling (eCTD Sequence 0008)
Attachments: FDA draft labeling redlined to Genzyme 6.28.07.doc

Hi Katie,

Here is the redlined label for sections 2-4. The entire label is included, but the only changes made thus far are to sections 2-4.

The reviewers are continuing to evaluate the remainder of the label. Unfortunately, I can't be more specific at this time regarding timing of additional comments. I'll keep you posted.

Have a happy 4th.

Amy

From: O'Keefe, Katherine [mailto:Katherine.OKeefe@genzyme.com]
Sent: Thursday, June 28, 2007 3:59 PM
To: Gomez, Amy
Subject: RE: Campath - Revised Proposed Labeling (eCTD Sequence 0008)

Hi Amy,

Thanks for letting me know that we won't need to hold the teleconference tomorrow. I have notified the team accordingly. We look forward to receiving the comments on the boxed warning and sections 2-4 of the label. Do you know when we might receive feedback from the review team on the other sections of the label?

Kind regards,
Katie

37 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Team Meeting Minutes
May 31, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Angela Men, Clinical Pharmacology Reviewer
Kallappa Koti, Statistical Reviewer
Joseph Gootenberg, Deputy Director
Patricia Keegan, Director

Items covered:

1. Potential Review Issues:

- a. Datasets submitted, change by a couple of subjects
- b. Issues with CMV viremia infection dataset

2. Discussion:

- a. Infection prophylaxis was discussed
- b. DDRE: no need for DDRE consult and no need for RiskMAP identified
- c. Reviewed statistical reviewer's midcycle presentation slides.

3. Follow up:

- a. Amy to follow up with Sean re: slide for midcycle meeting (assay review)



T-CON SUMMARY

Sponsor: Genzyme

Sponsor Participants: (b) (6) Cyndi Sirard, Jay Qu, Mark

Hayes, Katie O'Keefe

FDA Participants: Suzanne Demko, Jeff Summers

Number: (b) (4)

Date: May 14, 2007

RE: sBLA 103948/5070 Campath

Summary: FDA put questions to the sponsor about identified data discrepancies in the CAM 307 datasets in an effort to understand the structure and meaning of the datasets. We focused largely on the analysis dataset termed EFF1 by the sponsor. Specifically, we noted that there were a number of subjects who were confirmed by the IRRP as RAI stage I-II and who were noted to have "unconfirmed eligibility" elsewhere in the datasets. In an attempt to work through some data manipulations with the sponsor it became clear that the sponsor had different numbers than FDA had working in the same dataset with the same sequence of manipulations. The sponsor was able to answer some of our questions with regard to the organization and meaning of data, but informed us that they would look into the apparent discrepancy in the numbers.

Additionally the sponsor confirmed that they would set aside time each Friday to discuss any questions that may arise during the review, beginning May 25. Details to be worked out.

The call concluded.

May 17, 2007 In follow up to the above Tcon, the following email was received from the sponsor with an attachment further explaining the error and corrections to be made:

Suzanne and Jeff,

In response to your questions during our teleconference, the CAM307 team would like to provide clarification regarding the discrepancy in the number of patients with Rai Stage I-II and unconfirmed eligibility. In addition, we would like to provide a written explanation of the datasets/variables used to determine PFS.

The Tables, Listings, and Figures provided in the CAM307 sBLA were generated using pre-submission ready datasets rather than the submission ready datasets that were provided in the sBLA. The discrepancies in numbers that were noted during our discussion on Monday are a result of errors in the programming used to create the submission ready datasets. These errors do not impact the information presented in the Module 5, Module 2 summary documents or draft labeling. Additional detail regarding the RAIIRRP variable in the EFF1 dataset is provided in the attached document.

Genzyme anticipates that updated datasets in which these errors have been corrected can be submitted to FDA next week and recommends that FDA wait to perform additional analyses on the CAM307 data until these datasets are received.

If you have any questions about the information provided in the e-mail or attachment, please let me know.

Kind regards,
Katie

Attachment:

Clarification on the RAIIRRP Variable in EFF1 Dataset and Patient Eligibility

EFF1 dataset is the analysis dataset that contained the primary and secondary efficacy variables as well as their supporting data.

Included in the EFF1 dataset are variables named as PFS1 to PFS7. PFS2 is the primary variable using the IRRP determined date of progression and Rai stage. PFS2 is derived the same way as PFS1 except that unconfirmed Rai I-IV patients (n=9, 5 Rai 0 and 4 unconfirmed for BCLL diagnosis) were censored at day 1. PFS2 is the primary variable for the efficacy endpoint. In PFS1, the last follow up date or event date for these 9 patients were included, serving as a sensitivity analysis to test the effect of excluding patients with unconfirmed eligibility from the primary analysis. The other PFS3-PFS7 variables were also derived as sensitivity analyses of the primary variable of PFS2. The description of each of these variables can be found in the tip sheet.

The variable RAIIRRP (Rai Stage group by IRRP I-II vs. III-IV) is the variable that can be used to determine whether a patient has been confirmed by the IRRP as Rai I-IV to be treated with study drugs. RAIIRRP is derived from RAI_IRRP (Rai Stage by IRRP), which is also kept in the EFF1 dataset. In the updated datasets the number of patients who had missing values for RAIIRRP is 9.

The difference in 9 missing rows of RAIIRRP in the Errata datasets vs. 13 missing rows in the original submission were these: patient 4001-1025, 4002-1012, 4006-0007, 4006-0023. These 4 patients were incorrectly left as missing in the original submission due to a subsetting statement in the SAS program that left values missing for patients excluded from the safety population. The safety population was defined as patients who received at least 1 dose of study drug. Patients 4001-1025 and 4002-1012 were randomized but did not receive study drug, both had minimal follow-up data. Patients 4006-0007 and 4006-0023 were screen failures, they were not randomized, did not receive study drug, and had no follow-up data. This error will not affect the effort to reproduce a Kaplan-Meier curve using PFS2 since these patients had minimal follow-up data. In terms of the number of patients who were not confirmed to be Rai I-IV at study entry, the number is 9 as was summarized in Table 11-2 of the CSR. Data handling of missing Rai Stage assessment by the IRRP was included in Section 9.8.3 of the CSR. Source information on the IRRP's review can be found in Listing 16.2.6-2, 16.2.6-3 and 16.2.6-4 in Appendix 16 of the CSR.

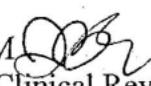
Regarding the situation where patient(s) who were unconfirmed for Rai Stage I-IV to be eligible for study treatment but still have response and date of progression assessment by the IRRP, this happened because the IRRP review did not occur in a timely manner when a patient was enrolled

by the study investigator. Four IRRP review meetings occurred during the course of the study. The IRRP meeting dates were 4-5 November 2004, 24-25 June 2005, 16-17 October 2005, and 1-4 May 2006 (see Section 11.4.1 of CSR). Due to logistical and practical reasons, the IRRP could not have reviewed response, date of progression, eligibility for the same patient at different review meetings. In fact, the review of eligibility for most of the patients was completed at the last review meeting in May 2006 after the retrieval of immunophenotyping data. Thus, there were situations that patients who were unconfirmed for Rai I-IV but still have a response assessment or date of progression by the IRRP.



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
Filing Meeting Minutes
May 4, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Angela Men, Clinical Pharmacology Reviewer
Hong Zhao, Clinical Pharmacology Team Leader
Kallappa Koti, Statistical Reviewer
Sean Fitzsimmons, Product Reviewer
Joseph Gootenberg, Deputy Director

Items covered:

1. Filing Issues and Potential Review Issues:

- a. CMC: no filing or potential review issues identified
- b. Clin Pharm: no filing or potential review issues identified
- c. Clinical: no filing or potential review issues identified
- d. Statistics: no filing or potential review issues identified
- e. Project Management: no filing or potential review issues identified

- 2. Review Priority:** Amy to follow up with Dr. Keegan after filing meeting. Post meeting note: Dr. Keegan confirmed this supplement will be granted priority review status.

3. Milestones Reviewed:

- a. Filing action letter: due May 19, 2007. It was decided that a day 60 filing letter will be issued without additional comments and deficiencies (e.g. PLR format) will be included in the day 74 deficiencies identified letter.
- b. Deficiencies identified letter: Due June 2, 2007. Team reminded to provide deficiency comments 2 weeks in advance of due date.
- c. Action Letter: Due September 19, 2007.

4. Upcoming Meetings (through June):

- a. Team Meeting: Friday May 18, 2007: 8:30 - 9:00 am
- b. Team Meeting: Thursday, May 31, 2007: 11:30 am - 12:00 pm
- c. Midcycle Meeting: Tuesday, June 12, 2007: 11:00 am - 12:30 pm
- d. Team Meeting: Thursday, June 28, 2007: 11:30 am - 12:00 pm
- e. First Labeling Meeting: Thursday, June 28, 2007: 12:00 - 1:30 pm



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: May 4, 2007

FROM: Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

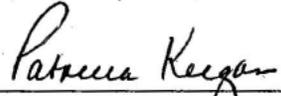
SUBJECT: Designation of BLA efficacy supplement review status
Sponsor: Genzyme Corporation
Product: Alemtuzumab
Indication: Treatment of B-cell chronic lymphocytic leukemia (B-CLL)

TO: BLA file STN 103948/5070

The review status of this file submitted as a BLA application is designated to be:

Standard (10 Months)

Priority (6 Months)



Patricia Keegan, M.D.

BLA/BLS Regulatory Filing Review

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy. An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 103948/5070 Product: Alemtuzumab Applicant: Genzyme

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 5/4/07 Committee Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

RPM: [Signature]
(signature/date)

Attachments:

Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

1 Part A - RPM

1 Part B - Product/CMC/Facility Reviewer(s): FITZSIMMONS

Part C - Non-Clinical Pharmacology/Toxicology Reviewer(s): _____

3 Part D - Clinical (including Pharmacology, Efficacy, Safety, and Statistical)

Reviewers DEMYO MEN LOTT

Memorandum of filing recommendation:

1 Part B - Product/CMC/Facility Reviewer(s): _____

Memo of Filing Meeting

STN 103948/5070Product Alemtuzumab

Part A Page 1

Applicant:	<u>Genzyme</u>
Short Summary:	<u>for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) (PMC #1 under 103948/0)</u>
RPM:	<u>Anly Gomez</u>
Office/Division:	<u>OODP/DBOP</u>

Filing worksheet Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<input checked="" type="radio"/> Y <input type="radio"/> N	
Form 356h completed	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	Y <input type="radio"/> N ^{N/A}	N/A
Comprehensive Table of Contents	Y <input checked="" type="radio"/> N	<u>eCTD folders clearly labelled</u>
Debarment Certification with correct wording (see * below)	<input checked="" type="radio"/> Y <input type="radio"/> N	
User Fee Cover Sheet	<input checked="" type="radio"/> Y <input type="radio"/> N	
User Fee payment received	Y <input type="radio"/> N	<u>N/A orphan designation</u>
Financial certification &/or disclosure information	<input checked="" type="radio"/> Y <input type="radio"/> N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/> Y <input type="radio"/> N	<u>Amendment recd 3/28/07</u>
Pediatric rule: study, waiver, or deferral	Y <input checked="" type="radio"/> N	<u>N/A orphan designation</u>
Labeling:	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI - non-annotated	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI - annotated	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI (electronic)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Medication Guide	Y <input type="radio"/> N	N/A
<input type="checkbox"/> Patient Insert	Y <input type="radio"/> N	N/A
<input type="checkbox"/> package and container	Y <input type="radio"/> N	N/A
<input type="checkbox"/> diluent	Y <input type="radio"/> N	N/A
<input type="checkbox"/> other components	Y <input type="radio"/> N	N/A
<input type="checkbox"/> established name (e.g. USAN)	Y <input type="radio"/> N	} <u>already established</u>
<input type="checkbox"/> proprietary name (for review)	Y <input type="radio"/> N	

* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. 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 the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?		If not, justification, action & status
<input type="checkbox"/> legible	(Y)	N	
<input type="checkbox"/> English (or translated into English)	(Y)	N	
<input type="checkbox"/> compatible file formats	(Y)	N	
<input type="checkbox"/> navigable hyper-links	(Y)	N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	(Y)	N	
<input type="checkbox"/> summary reports reference the location of individual data and records	(Y)	N	
<input type="checkbox"/> protocols for clinical trials present	Y	(N)	Cross referenced in Appendix of cover letter
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	(Y)	N	
companion application received if a shared or divided manufacturing arrangement	Y	N	N/A
if CMC supplement:			N/A
<input type="checkbox"/> description and results of studies performed to evaluate the change	Y	N	
<input type="checkbox"/> relevant validation protocols	Y	N	
<input type="checkbox"/> list of relevant SOPs	Y	N	
if clinical supplement:			
<input type="checkbox"/> changes in labeling clearly highlighted	(Y)	N	CDISC to be provided mid-May
<input type="checkbox"/> data to support all label changes	(Y)	N	
<input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	(Y)	N	
if electronic submission:			
<input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	Y	(N) N/A	Gateway submission fully electronic.

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
 If yes, review committee informed? No

Does this submission relate to an outstanding PMC? Yes PMC 1 STN 103948/0
PMC (b) (4) 4 require submission of final study report.

STN 103948/5070

Product Alemtuzumab

Part A Page 3

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: _____

Recommendation (circle one): File RTF

RPM Signature: [Signature]

Chief, Project Management Staff concurrence: Karen D. Jones

Part B – Product/CMC/Facility Reviewer(s)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum of Filing Review

STN:	<u>103948/5070</u>
Applicant:	<u>GENZYME CORPORATION</u>
Product:	<u>CAMPATH</u>
Short Summary:	<u>SBLA TO SUPPORT A CHANGE IN THE LABELED INDICATION</u>
Reviewer:	<u>SEAN FITZSIMMONS</u>
Office/Division:	<u>OTRR/ DMA</u>

I have conducted a filing review of the above referenced BLA supplement to determine whether it is sufficiently complete to permit a complete review.

Brief description of the change:

The following was submitted in support of the change (check all that apply):

<input checked="" type="checkbox"/>	A detailed description of the proposed change
<input checked="" type="checkbox"/>	Identification of the product(s) involved
<input type="checkbox"/>	A description of the manufacturing site(s) or area(s) affected
<input type="checkbox"/>	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
<input type="checkbox"/>	The data derived from such studies
<input checked="" type="checkbox"/>	Relevant validation protocols and data
<input type="checkbox"/>	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues):

Recommendation:

<input checked="" type="checkbox"/>	I recommend that this supplement be filed.
<input type="checkbox"/>	I recommend that this supplement be refused for filing for the reasons stated above.

Reviewer: Sean Fitzsimmons 4-31-07 Type (circle one) Product (Chair) Facility (DMPQ)
(signature / date)

Concurrence:
Team Leader/Lab Chief: Maryoune Shapiro Division Director: LaVonne Clouse
(signature / date) 5/4/07 (signature / date) 5/4/2007

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3]	Y N	<i>Not applicable. sBLA was to support a change in the labeled indication</i>
<input type="checkbox"/> Drug Substance	Y N	
<input type="checkbox"/> Drug Product	Y N	
<input type="checkbox"/> Facilities and Equipment	Y N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	
<input type="checkbox"/> Novel Excipients	Y N	
<input type="checkbox"/> Executed Batch Records	Y N	
<input type="checkbox"/> Method Validation Package	Y N	
<input type="checkbox"/> Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y N	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
<input type="checkbox"/> description of manufacturing process	Y N	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
<input type="checkbox"/> control of materials	Y N	
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y N	
o justification of specifications		
o analytical method validation		
o reference standards		
o stability		
<input type="checkbox"/> process validation (prospective plan, results, analysis, and	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>conclusions)</p> <p><input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)</p> <p><input type="checkbox"/> characterization of drug substance</p> <p><input type="checkbox"/> control of drug substance</p> <ul style="list-style-type: none"> <input type="checkbox"/> specification <ul style="list-style-type: none"> <input type="checkbox"/> justification of specs. <input type="checkbox"/> analytical procedures <input type="checkbox"/> analytical method validation <input type="checkbox"/> batch analyses <ul style="list-style-type: none"> <input type="checkbox"/> consistency (3 <u>consecutive</u> lots) <input type="checkbox"/> justification of specs. <p><input type="checkbox"/> reference standards</p> <p><input type="checkbox"/> container closure system</p> <p><input type="checkbox"/> stability</p> <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	<p>Y N</p>	<p><i>Not applicable</i></p>
<p>Drug Product [3.2.P]</p> <p><input type="checkbox"/> description and composition</p> <p><input type="checkbox"/> pharmaceutical development</p> <p><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</p> <p><input type="checkbox"/> batch formula</p> <p><input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</p> <p><input type="checkbox"/> controls of critical steps and intermediates</p> <p><input type="checkbox"/> process validation including aseptic processing & sterility assurance:</p> <ul style="list-style-type: none"> <input type="checkbox"/> 3 <u>consecutive</u> lots <input type="checkbox"/> other needed validation data <p><input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of</p>	<p>Y N</p>	<p></p>

STN 103948 | 5070

Product CAMPATH

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <input type="checkbox"/> human/animal origin <input type="checkbox"/> control of drug product (justification of specifications; analytical method validation) <input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF <input type="checkbox"/> closure integrity <input type="checkbox"/> administration device(s) <input type="checkbox"/> stability 	<p>Y N</p> <p>Y N</p> <p>Y N</p>	<p>Not applicable</p>
<ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 		
<p>Diluent (vials or filled syringes) [3.2.P']</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> 3 consecutive lots <input type="checkbox"/> other needed validation data <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) <input type="checkbox"/> reference standards 	<p>Y N</p>	

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF <input type="checkbox"/> closure integrity <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 	Y N Y N	Not applicable
Other components to be marketed (full description and supporting data, as listed above): <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit) 	Y N Y N	
Appendices for Biotech Products [3.2.A] <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation and storage <input type="checkbox"/> sterilization of equipment and materials <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	Y N Y N Y N	
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <ul style="list-style-type: none"> <input type="checkbox"/> method validation package <input type="checkbox"/> comparability protocols 	Y N Y N Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	Y N	NOT APPLICABLE

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	Y N	
<input type="checkbox"/> legible	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="checkbox"/> N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y N	Not applicable
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y N	
includes data demonstrating consistency of manufacture	Y N	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
certification that all facilities are ready for inspection	Y N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y N	

Examples of Filing Issues	Yes?		If not, justification, action & status
<input type="checkbox"/> LAL instead of rabbit pyrogen	Y	N	Not applicable
<input type="checkbox"/> mycoplasma	Y	N	
<input type="checkbox"/> sterility	Y	N	
<input type="checkbox"/>			
<input type="checkbox"/>			
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y	N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y	N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

most of the items listed above are not applicable to this submission since the sBLA under review was for a change in the labeled indication. Sufficient information regarding the CBS2 expression assay, neutralizing Ab assay, and anti-CAMPYH assay was provided.

Recommendation (circle one): File RTF

For BLA Applications: Were any potential review issues identified? Yes No

Reviewer: Sam Felt 4-31-07 Type (circle one): Product (Chair) Facility (DMPQ)
(signature/ date)

Concurrence:

Team Leader/Lab Chief: Morgan Shapiro Division. Director: Kathleen Clouse
(signature/ date) 5/17/07 (signature/ date) 5/4/2007

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical)

Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="checkbox"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="checkbox"/> Y N	
Clinical overview [2.5]	<input checked="" type="checkbox"/> Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="checkbox"/> Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="checkbox"/> Y N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="checkbox"/> Y N	
Study Reports and related information [5.3]	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Biopharmaceutic	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Pharmacokinetics (PK) <i>NA</i>	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Pharmacodynamic (PD) <i>NA</i>	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Postmarketing experience	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Case report forms	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Individual patient listings (indexed by study)	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="checkbox"/> Y N	
Literature references and copies [5.4]	<input checked="" type="checkbox"/> Y N	

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Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> legible	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> compatible file formats	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="checkbox"/> Y N	<i>a few are missing navigability, but easily worked around</i>

*Table 14.3.3-1
Summary of Safety
Narratives
p 673*

STN 103748/5070

Product *Campath*

Examples of Filing Issues	Yes?	If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y <input type="radio"/> N	
statement for each clinical investigation:		
<input type="checkbox"/> conducted in compliance with IRB requirements	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	<input checked="" type="radio"/> Y <input type="radio"/> N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	<input checked="" type="radio"/> Y <input type="radio"/> N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	<input type="radio"/> Y <input type="radio"/> N	<i>NA</i>
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	<input checked="" type="radio"/> Y <input type="radio"/> N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	<input type="radio"/> Y <input type="radio"/> N	<i>NA</i>
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	<input checked="" type="radio"/> Y <input type="radio"/> N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	<input checked="" type="radio"/> Y <input type="radio"/> N	
drug interaction studies communicated as during IND review as necessary are included	<input type="radio"/> Y <input type="radio"/> N	<i>NA</i>
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	<input type="radio"/> Y <input type="radio"/> N	<i>NA</i>
comprehensive analysis of safety data from all current world-wide knowledge of product	<input checked="" type="radio"/> Y <input type="radio"/> N	

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Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	<input checked="" type="radio"/> Y <input type="radio"/> N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/> Y <input type="radio"/> N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/> Y <input type="radio"/> N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	<input type="radio"/> Y <input type="radio"/> N	NA
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	<input type="radio"/> Y <input type="radio"/> N	NA
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/> Y <input type="radio"/> N	Have asked sponsor for data to support Δ in CMV recommendation

Have asked sponsor for data to support Δ in CMV recommendation

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
<i>CAM 307</i>	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None

Is clinical site(s) inspection (BiMo) needed?

yes, consult requested

Is an Advisory Committee needed?

No

Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

Reviewer: [Signature] Type (circle one): Clinical Clin/Pharm Statistical

Concurrence: 05-04-07

Branch Chief: [Signature]
acting TL (signature/ date)

Division Director: [Signature]
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical)

Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	Y N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	Y N	
<input checked="" type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Clinical Safety	Y N	
<input checked="" type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y N	
Study Reports and related information [5.3]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Biopharmaceutic	Y N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y N	
<input type="checkbox"/> Pharmacodynamic (PD)	Y N	
<input checked="" type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Postmarketing experience	Y N	
<input type="checkbox"/> Case report forms	Y N	
<input type="checkbox"/> Individual patient listings (indexed by study)	Y N	
<input checked="" type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y N	
Literature references and copies [5.4]	Y N	

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Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y N	
<input checked="" type="checkbox"/> legible	<input checked="" type="radio"/> Y N	
<input checked="" type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y N	
<input checked="" type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y N	
<input checked="" type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y N	
<input checked="" type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?	If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	(Y) N	
<input type="checkbox"/> protocols for clinical trials present	(Y) N	
<input type="checkbox"/> all electronic submission components usable	(Y) N	
statement for each clinical investigation:		
<input type="checkbox"/> conducted in compliance with IRB requirements	(Y) N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	(Y) N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

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Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	<input checked="" type="radio"/>	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/>	N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/>	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	<input checked="" type="radio"/>	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	<input checked="" type="radio"/>	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/>	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
<u>CAM307</u>	<input checked="" type="radio"/>	N	Y	N	NR	<input checked="" type="radio"/>	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

NONE

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

NO

Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

Reviewer: Kallappa Iyer Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date) 4/26/07

Concurrence:

Branch Chief: _____ Division Director: Alaka Chakravarty
(signature/ date) (signature/ date) 4/26/07

Office of Clinical Pharmacology
sBLA Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	103948/5064	Brand Name	Campath®
OCP Division	5	Generic Name	alemtuzumab
Medical Division	Biologic Oncology	Drug Class	Recombinant DNA-derived humanized monoclonal antibody to CD52
OCP Reviewer	Angela Yuxin Men, M.D., Ph.D.	Indication(s)	B-cell chronic lymphocytic leukemia (B-CLL)
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	30mg/mL solution per vial
		Dosing Regimen	Initial 3 mg/day → 10 mg/day; Maintenance dose: 30 mg/day, 3 times/week on alternate days for up to 12 weeks
Date of Submission	March 19, 2007	Route of Administration	2-hr IV infusion
Estimated Due Date of OCP Review	End of July, 2007	Sponsor	Genzyme
PDUFA Due Date	September 19, 2007	Priority Classification	Priority
Division Due Date	Mid-August, 2007		

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.	x			
Tabular Listing of All Human Studies	x			
HPK Summary				
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	2		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I/II) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
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:				
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 (CD52 expression)		
Population Analyses -				
Data rich:				
Data sparse:				
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:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Immunogenicity	X	1		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	Yes			
Comments sent to firm?	No			
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Angela Men, 05/03/07 <i>Angela Men</i> 5/3/07			
Secondary reviewer Signature and Date	Hong Zhao, 05/04/07 <i>Hong Zhao</i>			



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103948/5070

APR 09 2007

Genzyme Corporation
Attention: Katherine O'Keefe
Associate Director, Regulatory Affairs
4545 Horizon Hill Boulevard
San Antonio, TX 78229-2263

Dear Ms. O'Keefe:

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

STN	Name of Biological Product
BL 103948/5070	Alemtuzumab / Campath

Reason for the submission: For the treatment of B-cell chronic lymphocytic leukemia (B-CLL).

Date of Supplement: March 19, 2007

Date of Receipt: March 20, 2007

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
<http://www.fda.gov/oc/datacouncil/spl.html>

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Amy Gomez, R.N., M.S., at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



BLA STN 103948/5070
Campath (Alemtuzumab), Genzyme
First Committee Meeting Minutes
April 6, 2007

Attendees:

Amy Gomez, RPM 
Suzanne Demko, Clinical Reviewer
Jeff Summers, Clinical Team Leader
Angela Men, Clinical Pharmacology Reviewer
Hong Zhao, Clinical Pharmacology Team Leader
Kallappa Koti, Statistical Reviewer
Sean Fitzsimmons, Product Reviewer
Marjorie Shapiro, Product Team Leader
Karen Jones, CPMS
Patricia Keegan, Director, DBOP

Items covered:

1. Review Priority: will be determined at filing meeting.
2. Milestones (assuming priority review)
 - a. Committee Assignment: Complete
 - b. First Committee Meeting: Complete
 - c. Filing Meeting: due May 4, 2007; scheduled for May 4, 2007
 - d. Filing Action Letter: due May 19, 2007
 - e. Deficiencies Identified (Day 74) Letter: due June 2, 2007
 - f. Action Letter: Due September 19, 2007
3. Upcoming meetings
 - a. Applicant Orientation: Thursday, May 3, 2007 9:00-10:00 am
 - b. Filing Meeting: Friday, May 4, 2007 3:00-4:00 pm
 - c. Midcycle Meeting: Tuesday, June 12, 2007 11:00 am- 12:30 pm
4. Consultants needed
 - a. Anne Pilaro will provide pharm/tox feedback on label, if necessary. She is invited to all meetings.
 - b. SEALD team will be invited to midcycle and labeling meetings,
 - c. OSE: will obtain DDRE consult once initial review of the data provided is performed so a directed AERS database search can be requested.
 - d. DDMAC: will request since the label revision is extensive.
 - e. DSI: will request, Suzanne to provide site information.
5. Additional meetings to be scheduled

- a. Labeling meetings
- b. Decision regarding setting up weekly standing teleconferences with Genzyme will be made later.
- c. Biweekly ½ hour team meetings will be scheduled, first meeting in approx 1 month.

Discussion:

1. Any issues that have been identified during review to date (e.g. navigating eCTD) or need to request additional information
 - a. CMC: Environmental assessment (categorical exclusion) was provided in an amendment. CMC will review the assay information and claim for categorical exclusion.
 - b. Clinical: Hyperlinks missing in SAE death table. Narratives for deaths within 30 days were provided, will request narratives for all deaths within 180 days.
 - c. Project Management: redlined label in MS Word format was provided in an amendment
 2. Other issues
 - a. PMCs: need to submit FSR in addition to supplement to determine if PMCs are fulfilled. Amy to follow up.
 - b. Will include label edits in day 74 letter (what needs to be deleted, format issues).
-



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: March 23, 2007

FROM: Amy Gomez, RN, MS 
Regulatory Project Manager
Division of Biologic Oncology Products

SUBJECT: Request for information
Sponsor: Genzyme Corporation
Product: Alemtuzumab
Indication: Treatment of B-cell chronic lymphocytic leukemia (B-CLL)

TO: BLA file STN 103948/5070

On March 23, 2007, I requested that Genzyme provide an environmental assessment or claim for categorical exclusion. See attached.

Gomez, Amy

From: O'Keefe, Katherine [Katherine.OKeefe@genzyme.com]
Sent: Monday, March 26, 2007 2:48 PM
To: Gomez, Amy
Subject: RE: Campath sBLA 103948/5070

Hi Amy,

Thank you for sending your questions regarding the CAM307 sBLA via e-mail. The claim for categorical exclusion and the redline version of the label were inadvertently omitted from the submission. We will submit these as amendments to the supplement later this week or early next week. When we submit the amendment, should I address related submissions to you since you will be the project manager for this supplement or should I continue to address all submissions to Monica?

Please let me know if you have any other questions.

Kind regards,
Katie

-----Original Message-----

From: Gomez, Amy [mailto:Amy.Gomez@fda.hhs.gov]
Sent: Friday, March 23, 2007 3:56 PM
To: O'Keefe, Katherine
Subject: RE: Campath sBLA 103948/5070

Hi Katie,

Since you're traveling today and I'll be working from home Monday, I decided that email may be the easier way to contact you regarding the submission. I can not locate the environmental assessment or a claim for categorical exclusion. Where would I find it? Also, I see you provided a word version of the label, but we will also need a word version of the redlined label for our review and label discussions.

Thanks,

Amy



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103948/5064

Genzyme Corporation
Attention: Katherine O'Keefe
Associate Director, Regulatory Affairs
4545 Horizon Hill Boulevard
San Antonio, TX 78229

Dear Ms. O'Keefe:

Please refer to your biologics license application (BLA) submitted under the Public Health Service Act for Alemtuzumab (Campath).

We also refer to the meeting held on October 12, 2006, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact me at (301) 796-2320.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Monica Hughes".

Monica Hughes, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Meeting Summary
Attendee list
Genzyme's presentation



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: November 9, 2006
From: Monica Hughes, M.S.; DBOP/OODP/CDER
Subject: Meeting Minutes to BLA 103948/5064 (Prior to the meeting, draft FDA comments to Genzyme's questions were provided by facsimile on October 10, 2006). These final meeting minutes incorporate the draft comments and additional discussion from the meeting.

Meeting Type: Type B
Meeting Category: Pre-BLA 103948/5064
Meeting Date and Time: April 27, 2006: 1:00PM-2:00PM EST
Meeting Format: Face to Face
Product: Alemtuzumab (Campath®)
Meeting Requestor/Sponsor: Genzyme Corporation

Background: On August 10, 2006, Genzyme Corporation requested a type B pre-sBLA meeting to discuss protocol CAM307. The meeting packages were received September 11, 2006.

A biologics license was granted May 7, 2001 for alemtuzumab (Campath®). The approved indication is the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. As detailed in the May 7, 2001, approval letter, marketing approval of the product was granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as a basis for approval of products intended for serious or life-threatening conditions. The clinical post-marketing commitments (PMCs) to be addressed by protocol CAM307 are as follows:

PMC 1/Accelerated Approval: Verification of clinical benefit by conducting protocol CAM307 "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Campath (alemtuzumab) versus Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia", submitted on March 16, 2001, and revised on April 20, 2001. As described in your letters of April 12 and May 7, 2001, completion of patient accrual will occur in June 2004, completion of the study will occur in February 2006, and the final study report including SAS datasets and applicable revised labeling will be submitted in November 2006. It is understood

October 12, 2006: Pre-BLA 103948/5064 Face to Face MTG with Genzyme

that, to fulfill the requirements of accelerated approval, the study must be conducted with due diligence and must demonstrate that Alemtuzumab provides superior disease-free survival, as compared to chlorambucil, with comparable or acceptable toxicity.

PMC 2: Immunological assessment of the effect of Alemtuzumab therapy on responses to vaccinations for infectious diseases.

PMC 3: Assessment of the incidence of loss of CD52 expression at the time of relapse or disease progression during or following Alemtuzumab therapy.

PMC 4: A quantitative analysis of the incidence and magnitude of HAMA and anti-idiotypic antibodies at study entry and following exposure to Alemtuzumab.

Regarding PMC 2, Genzyme noted that CAM307 was completed before the full number of patients in the immunological assessment cohort could be accrued (b) (4)

CAM307 was a Phase 3, open-label, multicenter, randomized, comparative study of alemtuzumab versus chlorambucil as first line therapy in patients with progressive B-CLL. The primary objective of the study was to demonstrate that alemtuzumab is superior to chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression free survival (PFS). Secondary objectives were to evaluate: complete response (CR) and overall response rates using 1996 NCI working group (WG) criteria, duration of response, time to alternative treatment, survival, safety, and time to treatment failure. Enrollment in CAM307 was completed with a total of 297 patients in July, 2004.

Table 1.6.2.4-4 of the briefing document summarized analysis of the primary endpoint, progression free survival (intent-to-treat):

- Overall, the Kaplan-Maier (KM) median PFS for Campath [N=149] was 14.7 months (95% CI 12.4, 22.3); the KM median PFS for chlorambucil [N=148] was 11.7 months (95% CI 9.9, 13.2). The log rank P value (unadjusted) of the PFS difference was .0001. The adjusted hazard ratio for PFS was 0.57 (95% CI 0.427, 0.763) favoring Campath; the unadjusted hazard ratio was 0.57 (95% CI 0.424, 0.758).
- For Rai Stage I-II, the KM median PFS for Campath [N=93] was 21.7 (95% CI 14.2, Not reached); the KM Median PFS for chlorambucil [N=96] was 12.5 (95% CI 10.9, 14.8), with a P value 0.007 (unadjusted log-rank test). The unadjusted hazard ratio was 0.53 (95% CI 0.365, 0.768) favoring Campath.
- For Rai Stage III-IV, the KM median for Campath [N=50] was 11.1 (95% CI 8.6, 18.1); the KM median for chlorambucil [N=49] was 8.6 (95% CI 4.7, 12.9), with P value 0.0503 (unadjusted log rank test). The unadjusted hazard ratio was 0.63 (95% CI 0.397, 1.005) favoring Campath.

October 12, 2006: Pre-BLA 103948/5064 Face to Face MTG with Genzyme

Meeting Purpose: To discuss the data from CAM307 and its ability to fulfill PMCs 1^{(b)(4)} and 4 and support an expansion of the indication to include Campath as first line therapy in B-CLL.

Sponsor Submitted Questions and FDA Response:

QUESTIONS:

CAM307 Clinical Questions:

1. **Based on the CAM307 data described in the information package, does FDA agree that the data from CAM307 demonstrate that alemtuzumab provides superior progression free survival, as compared to chlorambucil, with at least comparable or acceptable safety profile?**

FDA Response Faxed on 10-10-06: Based on data presented in the pre-BLA meeting package, the improvement in progression free survival in patients treated with Campath versus chlorambucil appears to support the filing of a sBLA. A final decision regarding the safety and effectiveness of Campath will be determined during the review.

Discussion During Meeting: Genzyme had no additional comments regarding FDA's response.

2. **Genzyme would like to obtain FDA concurrence regarding our plan to specify a date of disease progression for the purposes of our final statistical analysis in situations when the Independent Response Review Panel (IRRP) determined progression but there was a lack of confirmation due, for example, to initiation of alternative therapy.**

FDA Response Faxed on 10-10-06: Genzyme's plan to include unconfirmed progressions as events in the primary analysis supported by a sensitivity analysis censoring these patients is acceptable. FDA will perform additional analyses to assess the robustness of the results. In order to be included in the primary analysis, these patients should have met the protocol specified criteria for progression. The use of the initial date of disease progression in these cases is acceptable.

Discussion During Meeting: Genzyme agreed to include the sensitivity analysis in the sBLA submission and acknowledged that FDA will perform additional analyses on the data provided in the sBLA submission.

Regulatory Questions:

3. **Does FDA agree that the sBLA should receive priority review classification?**

FDA Response Faxed on 10-10-06: This decision will be made at the time of filing.

October 12, 2006: Pre-BLA 103948/5064 Face to Face MTG with Genzyme

Discussion During Meeting: Genzyme asked for further clarification regarding the criteria FDA will use to make its determination during the initial sBLA review. FDA stated that the data submitted will be required to show significant improvement compared to marketed products.

4. **Based on the CAM307 data described in the information package, does FDA agree that the data from CAM307:**

a. **Are sufficient to satisfy the first post-marketing commitment identified in our approval letter of May 7, 2001?**

b. **Support conversion from accelerated to regular approval of alemtuzumab?**

FDA Response Faxed on 10-10-06: The summary data provided suggest that it is appropriate to file the sBLA application. The final decisions regarding FDA acceptance of these data to satisfy the first post-marketing commitment and conversion from accelerated to regular approval will be determined during the review of the application.

Discussion During Meeting: Genzyme had no additional comments regarding FDA's response.

(b) (4)



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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

(b) (4)



8. **In the sBLA, Genzyme proposes to include completed CRFs only for those patients who died or were discontinued due to AEs during the clinical study (CAM307). For each of these patients we intend to submit all case report form pages and all data clarification forms that result in database changes. Please confirm that this is acceptable.**

FDA Response Faxed on 10-10-06: Please include case report forms for each patient who died during the clinical study, with any of the following: while receiving study drug, after cessation of study drug but with persistent toxicity, or without confirmation of disease progression by the independent evaluators. In addition to including CRFs for patients who discontinued the study drug due to AEs, please include completed CRFs for all patients who discontinued the study drug for any reason other than toxicity, or IRRP documented disease progression. Please note that CRFs for any patient must be available if requested during the course of the review.

October 12, 2006: Pre-BLA 103948/5064 Face to Face MTG with Genzyme

Discussion During Meeting: Genzyme agreed to FDA's request.

9. **Genzyme plans to submit the sBLA electronically in CTD format. Please confirm that this is acceptable.**

FDA Response Faxed on 10-10-06: We agree that the submission of the sBLA in the electronic CTD format is acceptable. Please clarify why tabulation datasets and subject profiles for CAM307 will not be included in the submission. Please confer with FDA regarding the electronic re-submission of certain materials included in earlier paper submissions.

Discussion During Meeting: Genzyme stated that SDTM datasets would not be included because Genzyme is using the database structure that was in place at the time the trial was designed (prior to the SDTM initiative), and that Genzyme wants to provide the data in the same format to allow FDA to perform their own separate analyses of the data. FDA stated they need to review the structure of the datasets and current guidance documents before commenting further. FDA and Genzyme agreed to an additional meeting to work out details of database design.

In addition, FDA stated that there may be some difficulty accessing files from the original BLA filing and that Genzyme should include all cross-referenced information in this sBLA filing. FDA will look at the original application in the CBER EDR to test the accessibility of the data.

CAM307 Labeling Questions

10. **Does FDA agree that the data collected in CAM307 will support the following:**

- a. **Expansion of the indication to include first line therapy for B-CLL?**

FDA Response Faxed on 10-10-06: The FDA considers this to be a review issue. To support expansion of the indication, an independent blinded review of radiographs should be performed for all patients who were judged to progress based on radiological criteria alone.

Discussion During Meeting: Genzyme stated that the established and protocol-specified criteria for evaluation of disease progression did not require radiographic imaging and that IRRP determination was based on a blinded assessment of the totality of clinical data for each patient (per IRRP Charter, radiology films were not evaluated). FDA asked what information was provided to the IRRP (physical exams, CBCs, radiographs). Genzyme stated that data was not collected in a manner in which only the radiograph could be used to determine disease progression, as only disease site was confirmed by radiographs. Genzyme stated that all data was provided to the IRRP and that Genzyme is not sure which data were used by the IRRP to determine disease progression. FDA expressed concern regarding the degree of independence of the review conducted.

October 12, 2006: Pre-BLA 103948/5064 Face to Face MTG with Genzyme

Genzyme agreed to provide the patient datasheets provided to the IRRP to allow FDA to perform its own analyses. Genzyme stated that no internal IRRP records are available.

b. Other proposed labeling changes described in the concept below?

FDA Response Faxed on 10-10-06: If approved, the final labeling changes will depend on the review of the submitted data. We have some preliminary comments:

- i. In order to support the inclusion of complete response in the label, a blinded review of bone marrow slides will be necessary. Please confirm whether the central laboratory review of bone marrow histopathology slides was blinded.

Discussion During Meeting: Genzyme confirmed the central laboratory review of bone marrow histopathology slides was blinded.

(b) (4)



1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

(b) (4)



Additional FDA Comments Faxed on 10-10-06:

Statistics

14. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the BLA submission.

Discussion During Meeting: Genzyme confirmed SAS programs will be included in the sBLA submission.

October 12, 2006: Pre-BLA 103948/5064 Face to Face MTG with Genzyme

15. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

Discussion During Meeting: Genzyme confirmed this information will be included in the sBLA submission.

16. The protocol states that patients who do not receive study drug will be censored on the date of randomization. If these patients were followed for progression, their actual progression data should be included in the primary analysis. Please provide sensitivity analyses that assess the effect on study results of patients withdrawn from study prior to receipt of study drug.

Discussion During Meeting: Genzyme confirmed this occurred in only 3 patients, one of whom was followed for 12 days. Genzyme agreed to perform a sensitivity analysis.

Action Items:

17. Regarding the discussion that occurred around question 9, FDA agreed to a follow up meeting with Genzyme to review the structure of the databases to be submitted in the upcoming CAM307 sBLA. This meeting has been set up for December 7, 2006.
18. Regarding the discussion that occurred around question 9, FDA agreed to review the accessibility of the original Campath BLA application (103948/0) and to follow up with the CBER EDR IT personnel regarding any issues identified with the accessibility of the original application. Currently, DBOP is not able to access the original submission roadmap in the CBER EDR; however, DBOP is able to access the information associated with the original application as individual files not in the roadmap structure. CDER personnel are currently working with CBER personnel to correct the roadmap and accessibility issues within the CBER EDR and will follow up with Genzyme regarding the outcome. However, it may be necessary to readily allow the CDER DBOP reviewers access to the original BLA application, for DBOP to request Genzyme submit the information contained in the original BLA application along with the CAM307 sBLA submission, perhaps as a CD-ROM desk copies of the original BLA application and its associated amendments.

October 12, 2006: Pre-BLA 103948/5064 Face to Face MTG with Genzyme

Attendees:

FDA Attendees:

Monica Hughes, M.S., DBOP/ODDP, Regulatory Project Manager
Wen-Yi Gao, M.D., Ph.D., DBOP/ODDP, Pharmacology-Toxicology Reviewer
Amy Gomez, R.N., M.S., DBOP/ODDP Regulatory Project Manager
Steven Lemery, M.D., DBOP/ODDP, Medical Officer
Joseph Gootenberg, M.D., Medical Officer Team Leader
Hong Zhao, Ph.D., OTS/OCP, Pharmacologist
Sean Fitzsimmons, Ph.D., OPS/DMA, Quality/CMC Reviewer
Angela Men, Ph.D., OTS/OCP, Pharmacologist
Kallapa Koti, Ph.D., OTS/OB/DBV, Statistical Reviewer
Richard Pazdur, M.D., OODP, Office Director
Patricia Keegan, M.D., DBOP/ODDP, Division Director
Kevin Shannon, M.D., DBOP/ODDP, Medical Officer
Cathryn Lee, MSN, CRNP, AOCN, DBOP/ODDP, Nurse Consultant
Victor Santana, M.D., DBOP/ODDP
Vinni Juneja, M.D., DBOP/ODDP, Medical Officer
Karen Weiss, M.D., DBOP/ODDP, Office Deputy Director

Sponsor Attendees:

Genzyme Corporation Attendees

Mark Hayes	Vice President, Regulatory Affairs
Katherine O'Keefe	Associate Director, Regulatory Affairs
(b) (6)	Senior Associate, Regulatory Affairs
Michael Vasconcelles, MD	Vice President, Clinical Research
Mark Davison, MD	Associate Medical Director, Clinical Research
Paul Beninger, MD	Vice President, Pharmacovigilance
Ron Knickerbocker	Vice President, Biomedical Operations
(b) (6)	Senior Biostatistician, Biomedical Operations
Linda White	Manager, Clinical Research
(b) (6)	Principal Medical Writer, Biomedical Operations

(b) (4)

MEETING ATTENDANCE LIST

Meeting between Genzyme Corporation and
the Center for Drug Evaluation and Research.

DATE: October 12, 2006 TIME: 11:00 -12:30 AM ROOM: WO, 1419

NAME - Please print	AFFILIATION
Monica Hughes	RPM - CDER/DBOP
WEN-YI GAO	Pharm/tox - CDER/DBOP
AMY GOMEZ	RPM - DBOP
Mark Hayes	Genzyme
Katie O'Keefe	Genzyme
(b) (6)	Genzyme
Ken Knickerbocker	Genzyme
PAUL BENINGER	GENZYME
M. DAU WON	GENZYME
M. Mascione	Genzyme
(b) (4)	
(b) (6)	GENZYME
Lionel White	Genzyme
(b) (6)	Genzyme
Steven Lemery	FDA medical officer (DBOP)
Hong Zhao	FDA/OCP
SEAN FITZSIMMONS	FDA
Angela Men	FDA/OCP
Kallappa Keti	FDA/DBV
R PAZDUR	FDA
Patricia Keegan	FDA/OODP/DBOP
Jane Mackinnon	Patient consultant
Joe Gootenberg	FDA/DBOP
Kevin Shannon	FDA/DBOP
Robert Kane	FDA/DBOP
JOANN MINOR	FDA/OSHI
Cathryn Lee	OODP/DBOP
Victor Santara	Visitor - OODP
VINU JENUJA	
KAREN WEISS	



Our STN: BL 103948/0

JAN 06 2006

Genzyme Corporation
Attention: Mark P. Hayes, Ph.D.
Vice President, Regulatory Affairs
4545 Horizon Hill Boulevard
San Antonio, TX 78229-2263

Dear Dr. Hayes:

On November 8, 2005, in a presentation to the Oncologic Drugs Advisory Committee, Dr. Cynthia Sirard of your firm made statements to the Committee and the public regarding the regulatory history of post-marketing commitment #1 under Biologics License Application 103948/0 for Alemtuzumab. These statements were not consistent with the facts as documented by FDA communications and gave an inaccurate characterization of FDA's advice regarding this required post-marketing commitment.

The intent of this letter is: 1) to identify aspects of Dr. Sirard's presentation which led to the incorrect characterization of FDA's advice by the members of the ODAC; 2) to present a summary of FDA's communications on this issue; and 3) to describe corrective action requested of Genzyme.

1. In her remarks before the committee, Dr. Sirard characterized the selection of a comparator arm for CAM307 in the following manner:

"One of the problems with oncology trial design is coming up with the appropriate comparator arm. We had many discussions with the FDA in regards to this comparator arm and what would be pertinent to the study design...As the sponsor, we had actually gone to the FDA several times trying to utilize Fludarabine as the control agent because of the Kanti Rai paper. This Kanti Rai paper looked at fludarabine versus chlorambucil versus the combination. In fact, fludarabine at that stage was actually shown to have superior response rates to chlorambucil. However, since chlorambucil was the only approved single first-line agent for B-CLL at this stage, it was thought that chlorambucil was the appropriate comparator."

Dr. Sirard stated that "the sponsor had gone to FDA several times" with a proposal to use fludarabine in the comparator arm in CAM307. Some members of the ODAC incorrectly concluded that FDA refused to accept a fludarabine control arm and mandated use of chlorambucil in the control arm in CAM307 as evidenced by the following statements made during the ODAC discussion:

"It seems to me the company was forced to conduct this trial with one hand behind their back when fludarabine was really the comparator drug rather than chlorambucil. Why did the FDA refuse the company's, I am sure impassioned, plea to use fludarabine which would have made this a quicker study, a clinically more valuable study because the comparison of the two is really what we want and need to know, and insist on a historically relic of a drug, chlorambucil?"

This mischaracterization of FDA's position was not acknowledged nor corrected by Ms. Sirard.

2. Based on FDA communications records, it is clear that FDA advocated consistently for a frontline study of Alemtuzumab versus fludarabine and did not suggest, much less mandate, that Millennium & Ilex Partners, LP, utilize a study design employing chlorambucil in the control arm. These records are outlined below:

a. The FDA's briefing package for the December 14, 2000, ODAC meeting contained question (#3) that clearly presents the FDA's and Millennium & Ilex Partners, LP's positions regarding the potential designs for CAM307:

"If CAMPATH receives accelerated approval, please discuss the types of confirmatory studies that should be conducted. Among these, please comment on the following study designs:

- Millenium proposed Phase 4 study: Multi-center, randomized study of CAMPATH (vs. no additional therapy) in patients who have achieved a CR or PR to fludarabine therapy;
- FDA recommended Phase 4 study: Multi-center, randomized study of fludarabine vs. CAMPATH in patients with CLL who have not yet received fludarabine
- Multi-center, randomized study of CAMPATH versus supportive care (no additional therapy) in patients who have failed fludarabine;

Please comment on the preferred primary study endpoint (e.g., survival, progression-free survival). Please comment on the acceptability of the criteria for progression proposed by Millenium versus the NCI WG criteria."

b. In a February 9, 2001, facsimile to (b) (6) of Millennium & Ilex Partners, LP, FDA recommended a frontline study of Alemtuzumab versus fludarabine.

(b) (4)

(b) (4)

- f. In a February 26, 2001, facsimile, (b) (6) proposed CAM307, designed to demonstrate the superiority of Alemtuzumab versus chlorambucil in the front-line setting. (b) (4)

(b) (4) the sample size for the proposed CAM 307 trial would be 280 patients.

3. In order to provide relevant and accurate advice to FDA on matters of public health and policy, Advisory Committees must have access to reliable information. Dr. Sirard's presentation had two significant deleterious effects on the day's proceedings. First, it undermined the credibility of the Advisory Committee process. Second, it sidetracked the committee members, who may have offered policy advice based in part on erroneous information.

FDA recommends that Genzyme undertake the following corrective actions:

- a. To investigate the reasons why these statements, which misrepresented FDA's advice, were made at the November 8, 2005, ODAC proceedings.
- b. To report to FDA any pertinent findings from this investigation and to describe any changes in corporate governance Genzyme may wish to undertake in its medical and regulatory affairs divisions.
- c. To provide members of ODAC with a written summary of the events and discussions leading to the design of the required post-marketing study verifying the clinical benefit of Alemtuzumab, inform the members of the investigation's results and the proposed corrective actions.

We request that Genzyme respond, in a letter submitted to the BLA, STN BL 103948, to these recommendations within 30 days of receipt of this letter.

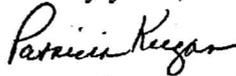
Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Monica Hughes, at (301)796-2320.

Sincerely yours,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: April 6, 2001
From: Sharon Sickafuse, OTRR/DARP ^{SXS}
Subject: March 12, 2001, telephone conversation with Millennium and ILEX (M&I)
regarding the Phase 4 confirmatory study for CAMPATH
To: STN 103948
IND 4294
Attendees

Background

This telephone conversation is a follow-up to previous conversations (December 22, 2000 and February 15, 2001) on this topic. It references the sponsor's February 26, 2001, submission to their BLA and March 2, 2001, submission to their IND which contained a draft version of protocol CAM307 "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Campath (alemtuzumab) vs Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia". It also references the sponsor's March 5, 2001, submission, to their BLA which contained, among other things, a proposed timeline for conducting the confirmatory study, a proposed protocol to study the impact of CAMPATH on immune function, and a proposed protocol to determine the incidence of loss of CD52 following treatment with CAMPATH in patients being considered for a second course of treatment.

The FDA stated that protocol CAM307 was acceptable as the confirmatory study, but that some revisions and additional information were necessary:

- M&I clarified that the chlorambucil treatment schedule is 40mg/m² every 28 days for up to 12 months. The FDA agreed that this schedule is acceptable.

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling