

**Briefing Package for
Oncologic Drugs Advisory Committee (ODAC) Meeting
8 November 2005**

PRODUCT: Alemtuzumab, Campath®, MabCampath®

BLA: 99-0786

IND No: 4,294

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DATE ISSUED: 5 October 2005

BACKGROUND AND EXECUTIVE SUMMARY

On 22 July 2005, the Division of Biologic Oncology Products sent notice to the Sponsor, Genzyme Corporation (Genzyme), inviting participation in an open session at the 8 November 2005 meeting of the Oncologic Drugs Advisory Committee (ODAC). Genzyme was asked to provide an update on the status of Phase IV post-marketing commitments for Campath® (alemtuzumab).

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody that is directed against the 21-28 kD cell surface glycoprotein, CD52. CD52 is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and tissues of the male reproductive system.

Alemtuzumab is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated previously with alkylating agents and who have failed fludarabine therapy. The safety and efficacy of alemtuzumab were evaluated in a multicenter, open-label, noncomparative study (CAM211) of 93 patients with B-cell chronic lymphocytic leukemia (B-CLL) who had been previously treated with alkylating agents and had failed treatment with fludarabine. Two supportive, multicenter, open-label, noncomparative studies of alemtuzumab enrolled a total of 56 patients with B-CLL. These patients had been previously treated with fludarabine or other chemotherapies. Determination of the effectiveness of alemtuzumab was 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 completed. Background summaries on chronic lymphocytic leukemia, treatment options, approved therapies, and alemtuzumab are provided in Appendix A.

Alemtuzumab received marketing approval under 21 CFR § 601.40, Subpart E (accelerated approval regulations) on 7 May 2001 (approval letter included as Appendix B). There were nine post-marketing commitments (PMC) assigned as part of the accelerated approval and are described herein.

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Appendix B: Approval Letter

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Accelerated Approval Clinical Phase IV Commitments

1. GENERAL INFORMATION

1.1 Sponsor Name:

Genzyme Corporation

1.2 Drug Name:

Campath[®] (alemtuzumab, MabCampath[®])

1.3 Indication:

B-Cell Chronic Lymphocytic Leukemia in adults who have been treated with alkylating agents and who have failed fludarabine therapy

1.4 Accelerated Approval Date:

7 May 2001

2. DESCRIPTION OF POST-MARKETING COMMITMENTS

There were nine post-marketing commitments (PMC) assigned as part of accelerated approval of alemtuzumab. Five of the commitments are complete (see Table 5.1, Summary of the Status of All Post-marketing Commitments). Three of the commitments (described below) will be fulfilled with the completion of the required Phase IV clinical study, CAM307. One remaining commitment (PMC No. 2) will be completed under a separate Genzyme-sponsored study.

2.1 Post-Marketing Commitment No. 1:

Sponsor must commit to conduct the clinical study, CAM307, titled "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with alemtuzumab (Campath[®])

MabCampath[®]) vs Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia”.

To fulfill the requirements of accelerated approval, the study (CAM307) 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.

In point of fact, the primary objective of CAM307, as accepted for this commitment, is to demonstrate that alemtuzumab is superior to chlorambucil as front-line therapy in patients with B-CLL as measured by *progression-free survival (PFS)*.

2.2 Post-Marketing Commitment No. 2:

Immunological assessment of the effect of alemtuzumab therapy on responses to vaccinations for infectious diseases.

PMC No. 2 was not satisfied as part of CAM307 and is still outstanding. As recently discussed with the Division of Oncology Drug Products (29 July 2005) Genzyme will fulfill this commitment in a separate new study (CAM203).

2.3 Post-Marketing Commitment No. 3:

Assessment of the incidence of loss of CD52 expression at the time of relapse or disease progression during or following alemtuzumab therapy.

The results for PMC. No. 3 will be reported in the CAM307 final study report (on target for completion in November 2006).

2.4 Post-Marketing Commitment No. 4:

A quantitative analysis of the incidence and magnitude of human-anti-humanized-antibody (HAHA) and anti-idiotypic antibodies at study entry and following exposure to alemtuzumab.

The results for PMC No. 4 will be reported in the CAM307 final study report (on target for completion in November 2006).

3. POST-MARKETING STUDY

3.1 Essentials of Study Design: CAM307 Study

A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with alemtuzumab (Campath[®], MabCampath[®]) vs Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia

CAM307 is a Phase III, open-label, multicenter, randomized, comparative study designed to assess the effectiveness and safety of alemtuzumab versus chlorambucil as front-line therapy in patients who have progressive B-CLL.

3.1.1 Summary of Study Sites (Geography, Number):

The original CAM307 protocol was based on enrollment at 25 to 30 sites. Amendment 1 (4 June 2001) allowed for additional sites (25 or more). A total of 73 study sites were selected, with 48 European and 25 U.S. sites. Amendment 3 (9 February 2004) allowed for enrollment into the sub-cohort for the immune function testing (post-marketing commitment 2) at sites outside the U.S. sites. However, as noted, immune function testing was not completed as part of CAM307, and will be performed in a separate trial, CAM203, which is designed to assess the safety and efficacy of alemtuzumab delivered by the subcutaneous route of administration.

3.1.2 Patient Population (Inclusion/Exclusion Criteria):

Previously untreated patients requiring treatment for the progression of their B-CLL (Rai stage I-IV disease)

3.1.2.1 Inclusion Criteria:

- Histopathologically confirmed diagnosis of B-CLL with CD5, CD19, or CD23 positive clone

- Rai Stage 1 through IV disease with evidence of progression as evidenced by the presence of one or more of the following:
 - Disease-related B symptoms
 - Evidence of progressive bone marrow failure
 - Progressive splenomegaly
 - Progressive lymphadenopathy
 - Progressive lymphocytosis
- Received no previous chemotherapy for B-CLL
- WHO Performance status of 0, 1, or 2
- Serum creatinine $\leq 2.0 \times$ the institutional upper limit of normal
- Adequate liver function with total bilirubin, AST and ALT $\leq 2 \times$ the institutional ULN value, unless directly attributable to the disease

3.1.2.2 Exclusion Criteria:

- ANC $< 0.5 \times 10^9/L$ or platelet count $< 10 \times 10^9/L$
- Autoimmune thrombocytopenia
- Active infection
- Patients with serious cardiac or pulmonary disease
- Central nervous system (CNS) involvement with CLL
- Positive quantitative CMV by PCR assay

3.1.3 Objectives

3.1.3.1 Primary Objective:

- 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).

3.1.3.2 Secondary Objectives:

- To compare overall survival times
- To compare CR and overall response rates
- To compare duration of response
- To compare time to treatment failure
- To compare time to alternative treatment
- To compare the safety of the two treatment arms

3.1.4 Treatment Schema (Dosage):

Patients were randomized on a 1:1 basis to receive either alemtuzumab (30 mg/day IV three times per week up to a total of 12 weeks) or chlorambucil (40 mg/m² PO once every 28 days up to a maximum of 12 cycles).

For patients who were randomized to receive alemtuzumab, the starting dose was 3 mg. When the 3 mg daily dose was tolerated, the daily dose could be escalated to 10 mg and continued until tolerated. When the 10 mg dose was tolerated the maintenance dose (30 mg) could be initiated. All subsequent doses of alemtuzumab was to be 30 mg IV three times a week (every other day) for a maximum of 12 total weeks of alemtuzumab therapy, inclusive of any dose escalation periods. Patients were randomized to receive chlorambucil at a dose of 40 mg/m² PO once every 28 days. Treatment was to be repeated monthly for a maximum of 12 cycles.

3.1.5 Efficacy and Safety Monitoring:

Safety data is monitored on a monthly basis by the Sponsor's Medical Monitor. An independent Data Safety Monitoring Board (DSMB) was to provide periodic monitoring of study safety as well as review interim efficacy data at pre-specified intervals.

3.1.5.1 Data Safety Monitoring Board

The DSMB that oversees CAM307 consists of three members, including one biostatistician and two clinicians with expertise in B-CLL. The DSMB periodically reviews study results, evaluates the treatments for excess adverse events, determines whether the basic study assumptions remain valid, evaluates whether the overall integrity and conduct of the study remain acceptable, and makes recommendations to the sponsor. The objective of the DSMB was to evaluate overall mortality and safety (SAE rates). The planned interim analyses are described below:

- The first interim analysis to assess safety was conducted after 50 patients per arm had reached 4 months following randomization. The primary purpose of this analysis was to evaluate overall mortality and SAE rate both in absolute terms for the study as a whole and in a comparative fashion with the control arm.

- The second interim analysis to assess safety and efficacy was conducted after 95 patients had progressed in order to detect marked differences in PFS, survival, CR rate, or toxicity.

The DSMB has met frequently throughout the study. Dates of the meetings are listed below. The next planned meeting of the DSMB is 8 November 2005. At this meeting, in addition to ongoing review, the DSMB will consider whether release of response rate data is appropriate prior to final analysis of the trial.

- 19 August 2005
- 28 July 2005 – Interim analysis of efficacy data
- 23 February 2005
- 21 April 2004 – Interim analysis of safety data
- 17 December 2003
- 16 September 2003
- 05 March 2003
- 11 September 2002
- 26 June 2002
- 04 December 2001

3.1.5.2 Independent Response Review Panel

An Independent Response Review Panel (IRRP), blinded to treatment arm, was assigned to the CAM307 study to objectively determine confirmation of eligibility, response to treatment, with specific reference to the following parameters:

- Date of response and response confirmation
- Date of disease progression

3.1.6 Statistical Design:

- Primary endpoint
 - Assumes 50% improvement in PFS
 - Final analysis will be conducted after a total of 190 failures, regardless of treatment arm
- Sample Size
 - 284 patients (142 per treatment arm)

- Randomization
 - Minimization method to optimize balance between treatment arms with respect to six prognostic factors (center, Rai stage, age, ECOG, sex, and lymph node size)
 - Controlled by IVRS
- Primary analysis population
 - Intent-to-treat population
- An Independent Response Review Panel
 - Blinded to treatment assignment
 - Objective assessment of response, date of relapse
- Data and Safety Monitoring Board
 - Interim monitoring of the study

3.1.7 Date of Initiation (First Patient Enrolled):

The first patient was enrolled in November 2001, slightly later than the planned date of September 2001.

3.1.8 Accrual (Last Patient Enrolled):

Patient accrual was expected to be completed by the end of June 2004. The last patient was enrolled in July 2004. Total enrollment exceeded the planned number of 284 patients (142 per arm). A total of 297 patients (149 on the alemtuzumab arm; 148 on the chlorambucil arm) were enrolled on study. Actual patient accrual by country is described in Table 3.1.8.

Table 3.1.8: Accrual Distribution by Country

Country	No. of Patients	Country	No. of Patients
Croatia	47	Netherlands	9
Czech Republic	39	Poland	117
Estonia	2	Serbia	28
France	4	Slovakia	12
Ireland	1	Slovenia	0
Italy	3	United Kingdom	3
Lithuania	8	United States	24

3.1.9 Estimated Timeline for Study Completion

Table 3.1.9 describes the study timeline accepted by the Division for completion of the CAM307 study.

Table 3.1.9: CAM307 Study Timeline

Milestone	Target Date	Actual Date
Submission of Protocol Amendment to FDA	05/2001	06/2001
Final Approved Case Report Form Available	07/2001	09/2001
Initiation Visits	08/2001	08/2001
First Patient Enrolled	09/2001	11/2001
Interim Safety Analysis	12/2003 ^a	04/2004
Interim Analysis Performed	<i>After 95 patients have progressed</i>	08/2005 ^b
Last Patient Enrolled	06/2004	07/2004
Last Patient Follow-up (Active Phase)	12/2005	
Last Patient Follow-up (Extended Follow-Up)	TBD	
Database Lock	02/2006	
Final Clinical Study Report	11/2006	

^a After 50 patients/arm have reached 16 weeks following randomization

^b Genzyme submitted the final Statistical Analysis Plan on 19 July 2005 prior to the interim analysis.

3.1.10 Estimated Timeline for Submission of Study Results

The final CAM307 clinical study report is on target for completion in November 2006, as addressed in the FDA approval letter of 7 May 2001.

4. DIFFICULTIES ENCOUNTERED IN CONDUCT, ACCRUAL, AND COMPLETION OF TRIAL(S)

4.1 Patient Enrollment - Overall

As reported in the CAM307 *Post Marketing Study Annual Progress Report* submitted 16 July 2002, the study's status was categorized as delayed due to slow enrollment. In spite of the fact that chlorambucil was the only approved first line therapy for B-CLL, additional first line therapeutic options have emerged in recent years that provided challenges to enrollment in this trial in countries where these options were available.

In the CAM307 *Post Marketing Study Annual Progress Report* submitted 1 July 2003, the study was upgraded to ongoing as the study had progressed markedly with a total of 101 of 284 (36%) planned patients randomized. The increase in enrollment was largely attributed to the opening of the originally planned sites in Poland and the Czech Republic as well as the addition of new sites in Croatia. To further ensure that enrollment was completed on schedule, ILEX (now Genzyme) activated additional sites in Serbia, Slovakia, Slovenia, Lithuania and Estonia.

4.2 Patient Enrollment – Subcohort for Immune Function Testing

In order to increase the patient enrollment into the sub-cohort for fulfilling the second post-marketing commitment (PMC No. 2, the immunological assessment of the effect of alemtuzumab therapy on responses to vaccinations for infectious diseases) a protocol amendment, CAM307-A3, was submitted as Serial No. 438 to BBIND 4,294 on 11 February 2004. Amendment 3 allowed for selecting patients for the immune function evaluation from sites outside of North America as patient accrual was higher in Europe.

Overall patient recruitment was completed before the full number of patients in the immunological function assessment cohort in the CAM307 study could be accrued. Therefore, the post-marketing commitment (PMC No. 2) for the immunological assessment of the effect of alemtuzumab therapy on responses to vaccinations for infectious diseases is still outstanding. In a recent discussion with the Division of Oncology Drug Products (29 July 2005) Genzyme proposed to fulfill this commitment in a new study (CAM203), which is designed to assess the safety and efficacy of alemtuzumab delivered by the subcutaneous route of administration.

5. CONCLUSION

5.1 Status of All Post-marketing Commitments

Alemtuzumab has emerged as an important treatment option for patients with CLL. Ongoing clinical development by the Sponsor is exploring the utility of alemtuzumab in

additional hematologic malignancies as well as in multiple sclerosis. In addition, a clinical development program to assess the efficacy and safety of alemtuzumab administered by the subcutaneous route are underway. The completion of the Subpart E commitments described herein should provide definitive demonstration of clinical benefit in B-CLL patients and further inform the most appropriate safe and effective use of this agent in this population. Table 5.1 summarizes the status of all post-marketing commitments.

Table 5.1: Summary Of The Status Of Postmarketing Commitments (PMC)

PMC No.	Description	Status
1	To fulfill the requirements of accelerated approval, the study (CAM307) must be conducted with due diligence and must demonstrate that alemtuzumab provides superior disease-free survival (note, this was since clarified as progression-free survival), as compared to chlorambucil, with comparable or acceptable toxicity.	Ongoing Enrollment Complete
2	Immunological assessment of the effect of alemtuzumab therapy on responses to vaccinations for infectious diseases	Outstanding ^a
3	Assessment of the incidence of loss of CD52 expression at the time of relapse or disease progression during or following alemtuzumab therapy	Ongoing Results To Be Reported in CAM307 Final Study Report
4	A quantitative analysis of the incidence and magnitude of HAHA and anti-idiotypic antibodies at study entry and following exposure to alemtuzumab	Ongoing Results To Be Reported in CAM307 Final Study Report
5	Submission of the final study report for protocol CAM213: "A Phase II Study, Including Pharmacokinetics, of Campath-1H in Patients with B-Cell Chronic Lymphocytic Leukemia Who Have Received Treatment with a Purine Analogue" in August 2001 (STN: 103948-5006)	FDA Released 15 DEC 2003
6	Submission of the validation plan for the human-anti-humanized antibodies (HAHA) assay in July of 2001 and the validation report in September 2001 (STN: 103948-5008)	FDA Released 28 JAN 2003
7	Submission of the validation plan for the FACS based immune assay in July of 2001 and the validation report in September 2001 (STN: 103948-5005)	FDA Released 28 JAN 2003
8	To evaluate data from the CMCL potency assay (QA10379) and the monomer content assay (QA 10371) performed for lot release of bulk drug substance and drug product over the year following approval (or the next ten lots) and to tighten the lot release specifications appropriately with submission of a manufacturing supplement by June 2002 (STN: 103948-5031)	FDA Released 20 MAY 2003
9	To evaluate data from the residual Protein A assay (QA10370) performed for lot release of bulk drug substance and drug product over the year following approval (or the next ten lots) and to tighten the lot release specifications appropriately with submission of a manufacturing supplement by June 2002 (STN: 103948-5031)	FDA Released 20 MAY 2003

^a Patient recruitment was completed before the full number of patients in the immunological function assessment cohort in the CAM307 study could be accrued. In a discussion with the Division of Oncology Drug Products (9 June 2004), ILEX agreed to provide alternative options to evaluate the immunological function in patients treated with alemtuzumab and discuss these options with the FDA. In a recent discussion with the Division of Oncology Drug Products (29 July 2005) Genzyme proposed to fulfill this commitment in a new study (CAM203).

Appendix A

Background Summaries:

**Chronic Lymphocytic Leukemia (CLL), Treatment of CLL, Approved Therapies,
and Alemtuzumab**

1. CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most prevalent form of adult leukemia in the Western world. In 2005, an estimated 9,730 Americans are expected to develop CLL and 4,600 are expected to die from the disease.¹ The median age at diagnosis of CLL is approximately 70 years, with about one-third of the patients being younger than 60 years of age. The disease occurs predominantly in males with a male to female ratio of 2:1.² The clinical course of CLL is variable; some patients achieve a normal life span whereas others die within 5 years of diagnosis. The overall median survival from diagnosis is approximately 6 years with little change in this outcome during the past 30 years.^{3,4}

CLL is a neoplastic disorder characterized by increased numbers of clonal leukemic 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.^{3,5} The diagnosis of CLL is based on the detection of lymphocytosis in the blood and bone marrow. A threshold peripheral blood lymphocyte count greater than $5 \times 10^9/L$ has been recommended by the NCIWG⁶ as a diagnostic criterion for CLL.

Morphologically, the lymphocytes must appear mature and there must be less than 55% immature cells. Other cellular characteristics include the following: the B-cell markers (CD19, CD20, and CD23) are expressed as well as the CD5 antigen in the absence of other pan-T-cell markers; the B-cell is monoclonal with regard to expression of either κ or λ ; and the surface immunoglobulin is of low density. Although the bone marrow is involved in all patients, a bone marrow aspirate and biopsy are generally not necessary to make the diagnosis of CLL. When available, the aspirate smear must show at least 30% of all nucleated cells to be lymphoid.

The survival of CLL patients greatly varies with the stage of their disease. In one large series, patients with low-risk disease (Rai stage 0) had a median survival of 14.5 years compared to 2.5 years for patients with high-risk disease.

In addition to staging, other variables provide prognostic information. Among patients with early stage CLL, a shorter survival is expected for those with a pattern of diffuse bone marrow infiltration and/or rapidly increasing lymphocytosis compared to patients without these features^{3,7} A similar discriminating power has been claimed for various serum markers, among which β_2 -microglobulin seems to have an established value.⁸

2. TREATMENT OF CLL

Patients with B-CLL who have progressive disease as evidenced by progressive marrow failure, progressive lymphadenopathy, splenomegaly or hepatomegaly, progressive lymphocytosis, autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy, or disease-related symptoms require treatment. There are three agents approved for the treatment of CLL in the US: chlorambucil, fludarabine phosphate, and alemtuzumab. Historically, initial treatment for patients with B-CLL typically included an alkylating agent such as chlorambucil either alone or in combination with steroids or other chemotherapy agents.⁹ Chlorambucil has been the standard front-line treatment for patients with CLL, with or without corticosteroids. Fludarabine phosphate, a purine analog, is indicated for second-line treatment in the US of CLL patients who have not responded to or whose disease has progressed during treatment with an alkylating agent. Fludarabine phosphate is indicated for first-line treatment of CLL patients in Europe.^{10,11} Recent studies have shown improved efficacy with combination regimens including fludarabine, cyclophosphamide and rituximab as initial therapy or treatment for relapsed CLL.^{12,13} Alemtuzumab is indicated in the treatment of B-CLL in patients who have been treated with alkylating agents and who have failed Fludara therapy.¹⁴

2.1 Approved Therapies

The only agent approved in the United States for the front-line treatment of CLL is chlorambucil. In a cooperative group study conducted by Rai et al, chlorambucil used as front-line therapy resulted in a complete response rate (CR) of 4% and a partial response rate (PR) of 33% (overall response rate 37%), and a PFS of 14 months.¹⁵ However,

chlorambucil is a carcinogen, and probable mutagen and teratogen. It has also been associated with secondary malignancy and acute leukemia.

Fludarabine, currently approved as a second-line treatment for CLL in the U.S. and as first-line therapy in Europe, is a more effective front-line therapy than chlorambucil or other alkylating-agent-based regimens as measured by response rate and progression free survival.^{15,16,17} When fludarabine was compared to chlorambucil as front-line therapy in a cooperative group study, the CR rate for fludarabine was 20% and the PR rate was 43% (overall response rate 63%), with a PFS of 20 months. Two other cooperative group studies from Europe demonstrated similar results^{16,17} Based upon these studies, the use of fludarabine as front-line therapy is common in the United States and Europe and is increasing.

The safety and efficacy of alemtuzumab were evaluated in a pivotal, multicenter, open-label, non-comparative study (CAM211) of 93 patients with advanced B-CLL who had been previously treated with alkylating agents and had failed treatment with fludarabine (see Appendix C). These patients, who were extensively previously treated, represented a severely ill patient population. In addition, two supportive, multicenter, open-label, noncomparative studies of alemtuzumab[®] were conducted in a total of 56 patients with B-CLL [Study 125-005 (n = 32) and Study 125-009 (n = 24)]. This population of patients with advanced CLL who had been previously treated with fludarabine or other chemotherapies was similar to patients enrolled in the pivotal study. The approval of alemtuzumab in May 2001 was based on CAM211 and the two supportive studies described above.

3. ALEMTUZUMAB (CAMPATH[®], MABCAMPATH[®])

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a cell surface protein expressed at high density on most normal and malignant lymphocytes, B-cells, and T-cells¹⁸ but not on hematopoietic stem cells.¹⁹

a small modification to the first framework region of the heavy chain. Compared to Campath-1G, alemtuzumab has equal potency for in vitro C'-mediated lysis and 2 to 4 times greater potency in ADCC assays with normal and malignant human lymphocytes.

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Appendix B

Approval Letter

Appendix C

CAM211 Reference