

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103948/0

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: September 18, 2001^{SKS}
From: Sharon Sickafuse, OTRR/DARP
Subject: SBA Equivalent
To: STN 103948

The SBA Equivalent is composed of the following reviews:

CMC	May 31, 2000; April 24, 2001; April 25, 2001; May 2, 2001
Facilities	November 24, 2000; April 25, 2001
Clinical	April 30, 2001; June 4, 2001
Biostatistics	June 9, 2000; April 2, 2001
Pharm/Tox	April 27, 2001
BIMO	October 26, 2000

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Tuesday, May 01, 2001 6:01 PM
To: 'K. Tate'; 'M. Recupero'
Subject: Campath PI

Here it is gentlemen, the long awaited package insert. The red changes are items that I have previously relayed to you. The blue changes are Dr. Siegel's which I just received today. Please call me tomorrow if problems.



CampathPI.doc

3 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Telecon

Date: Apr 25, 2001
Sponsor: Millennium and ILEX Partners, LP (mand I)
Ref no: 103948/0.5021
CBER: Kurt Brorson, Ph.D. *KB*
Firm: Millennium Pharmaceuticals- Lee Brettman, Robert Pietrusko, Michael Recupero; ILEX Oncology- Kelly Tate, Sonny Fong

mand I was called to settle issues regarding the immunogenicity assay.

1) Regarding the immunogenicity (HAHA) assay:

a) Please commit to amending the assay SOP to specify that HAHA+ samples should be _____

Response: M&I agrees to amend the assay SOP to specify that when a

7 **Reviewer's note:** This response is adequate.

b) Please commit to submitting a validation plan with pre-specified acceptance criteria for the validation data.

i) [_____]

Response: _____

c) Please commit to submitting the validation report when the validation is complete.

Response: The sponsor agrees. The validation report will be submitted

2) [_____]

Response: The sponsor agrees. The validation plan will be submitted in

b) [

]

Response: [

]



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: April 20, 2001
From: Sharon Sickafuse, OTRR/DARP ^{SKS}
Subject: April 18, 2001, telephone conversation with Mr. Kelly Tate from ILEX
Oncology regarding the trade name for Alemtuzumab
To: STN 103948

Background:

On November 24, 1998, the sponsor submitted a request for review of the proposed trade name "CAMPATH". A letter was issued on April 13, 1999, accepting the name.

In the BLA submission, the trade name on the carton and vial labels was "Campath" while the trade name in the package insert was "CAMPATH". Comments on the carton and vial labels were returned to the sponsor on March 31, 2000. The sponsor made the requested changes and submitted final draft labeling for review (vial and 3 ampoule carton on April 19, 2000, and 12 ampoule carton on August 4, 2000). On August 23, 2000, the sponsor was informed that the final draft labeling for the vial, 3 ampoule carton, and 12 ampoule carton was acceptable.

In April of 2001, it was noted that the trade name was not presented consistently through out the labeling. At a meeting on April 11, 2001, between the sponsor and the FDA to discuss the package insert, the sponsor stated that they had printed the carton and vial labels with "Campath".

After internal discussion between DCTDA, DARP, DMA, and APLB on the sponsor's options, I spoke to Mr. Tate on April 18, 2001.

Conversation of April 18th:

I told Mr. Tate that the presentation of the trade name had to be consistent throughout all the labeling. There is no regulation that requires the trade name to be in all capital letters, although many trade names are in all capital letters.

The sponsor's options are:

1. Use the carton and vial labels they had already printed with "Campath" and revise the package insert.
2. If they want the name in all capital letters now, they will need to submit revised draft vial and carton labels for review for prominence issues.

Page 2 – April 18, 2001, telephone conversation with Mr. Tate regarding Alemtuzumab.

I also said that if the sponsor decides on option 1, if in the future, they decide to change to all capital letters, they can submit such a request for change in the annual report.

Mr. Tate said that Millennium and ILEX would use the carton and vial labels that they had already printed and would submit a revised package insert using “Campath”.

3 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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 ^{SKS}
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.

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-
-

✓

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Our STN: BL 103948/0

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Michael A. Recupero, R.N.
Senior Regulatory Affairs Associate
Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139

March 27, 2001

Dear Mr. Recupero:

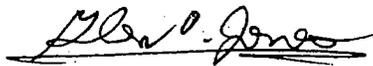
We acknowledge receipt on March 19, 2001, of your March 16, 2001, resubmission to your license application for Alemtuzumab.

This resubmission contains the final version of the confirmatory study, CAM307. We also acknowledge receipt of your March 5, 2001, submission which contained a revised package insert, a proposed schedule for CAM307, and a proposed schedule for study _____ entitled "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," submitted in response to our February 20, 2001, complete response letter.

We consider this a complete, class 1 response to our action letter. CBER intends to review this submission and take action on it by May 19, 2001.

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 827-5101.

Sincerely yours,



Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: HFM-515/P. Harris
HFM-555/K. Webber
HFM-555/K. Stein
HFM-561/K. Brorson
HFM-110/RIMS
HFM-500/J. Siegel
HFM-588/S. Sickafuse
HFM-570/K. Weiss
HFM-570/P. Keegan
HFM-573/G. Schechter
HFM-579/M. Green
HFM-215/C. Gnecco
HFM-650/L. Johnson
HFM-675/W. Lange

OTRR:DARP:Sickafuse:3-23-01:amw:3-26-01
(S:/Sickafuse/Campath/resubmission letter2.doc

MILESTONE - COMMUNICATION TYPE:
LETTER: Acknowledgement Letter (ACK)
Summary Text: Class 1 Resubmission

Division	Name/Signature	Date
DARP	Sickafuse	3-26-01
DARP		3-26-01
DARP	A. Williams	3-27-01

3 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 19, 2001 *SKS*
From: Sharon Sickafuse, OTRR/DARP
Subject: Telephone conversation with Kelly Tate of ILEX Oncology and Jackie Cinicola of Millennium Pharmaceuticals
To: STN 103948

1. I stated that Dr. Dave Green, the pharm/tox reviewer, had tried to contact the pharm/tox people at Millennium to discuss the differences observed in the FDA's and Millennium's pk analysis of Campath, but was having difficulty getting through to the right people. I asked Ms. Cinicola to call Dr. Green and to make arrangements for a telecon with him and whomever is necessary from Millennium. Ms. Cinicola said that she would do so.
2. I asked for an update on the status of their Phase 4 study proposals. Ms. Cinicola said that the proposals would be submitted next week.
3. I advised the sponsor that the FDA is working on the package insert labeling. An internal meeting is scheduled for January 24th and I anticipate that I would be able to send to the sponsor the FDA's proposed revisions approximately 1 week after that meeting. I advised the sponsor that the revisions will be significant.
4. Ms. Cinicola stated that an updated ISS which consists solely of tables will be submitted today.
5. Ms. Cinicola also stated that the protocol, assay method, and assay validation for the pk study being conducted in the UK will be submitted to the IND next week.
6. I advised the sponsor that I would follow-up with Drs. Keegan and Schechter regarding contact with OVRP as to an appropriate vaccine for the patient population that can be used to characterize the immune response of patients who have received Campath.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 9, 2001
From: Sharon Sickafuse, OTRR/DARP ^{SKS}
Subject: December 22, 2000, telephone conversation with ILEX and Millennium regarding Phase 4 commitments for the Campath BLA.
To: STN 103948

The purpose of this telecon was for FDA to relay to the sponsor our expectations of what will be required as Phase 4 commitments prior to the issuance of an approval letter.

1. The commitment will need to include a proposed schedule including dates of study initiation, accrual, completion, and submission of the final study report to the FDA.
2. The sponsor was advised to propose one or two studies for the confirmatory trial for efficacy. Please include in the proposal, the patient population, number of patients to be enrolled, and the primary endpoint. The sponsor stated that they already have sites lined up for the confirmatory trial.
3. Regarding the safety issue of pharmacokinetics, to try and resolve the differences between the FDA and the sponsor in the analysis of the datasets, FDA agreed to supply to the sponsor the FDA dataset and output.

The sponsor stated that they currently have a trial ongoing ~~_____~~ designed to collect pk data on 20 patients refractory to fludarabine. The non-IND study is being done in the UK and has been ongoing for about one year. The sponsor expects to have data within two months. They will submit to the IND the protocol, assay methodology, and assay validation.

4. Regarding the safety issue of immunogenicity to infectious disease antigens, sponsor stated that CCL patients are already immunocompromised and those who have received Campath have a poor response to hepatitis, tetanus, and influenza vaccines. Dr. Keegan said that she or Dr. Schechter will consult with OVRP to recommend to the sponsor an appropriate vaccine for the patient population to characterize the immune response. We would prefer a study over a registry evaluation as a study we think that better collection of data will occur in a study.

Attendees

Center for Biologics Evaluation and Research

Division of Application Review and Policy
Sharon Sickafuse, M.S.

Division of Clinical Trial Design and Analysis
Patricia Keegan, M.D.

ILEX Oncology

Kelly Tate

Millennium Pharmaceuticals

Lee Brettman, M.D.
Jacqueline Cinocola

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

TELECON MINUTES: BLA #99-0786

DATE: November 7, 2000
TIME: 10: 30 – 11:40 AM EST
ATTENDEES: Dr. Lee Brettman, M.D. Millennium
Jackie Cinacola, Millennium
Barbara Brasher, Millennium
Kelly Tate, Ilex
Dr. Patricia Keegan, M.D., FDA
Dr. Clare Gnecco, Ph.D.
Dr. Genevieve A. Schechter, M.D. *BMS 11/7/00*

Summary: The following issues of the sponsor's briefing document were discussed during this telecon.

- A copy of whatever information that is available for reference #18 will be provided to the agency.
- The sentence on page 30 regarding "intent to treat" needs to be revised since the Study 005 population was selected.
- Response rates and efficacy information available for the studies mentioned on page 14, Table 1 should be included along with the safety information probably as a separate table with safety information in Table 2.
- Problems with the clinical benefit assessment were discussed. The sponsor was advised to show benefit in tumor associated symptoms, reduction in transfusions, decrease in rate of infections in responders. Improvement in survival is not a benefit unless improvement over a comparator is observed. Time to alternative therapy is also not a benefit as this was not defined a priori and no comparator arm exists.
- The adverse event section needs to include more information:
 - Information on all the adverse events for the other patients (93) from Study 005 used needs to be included in tabular form.
 - A table of SAEs for patients enrolled Protocol 016, 212, and the current international compassionate use protocol (similar dosing schedule) needs to be included (~ 119 patients).
 - A table of the SAEs for the patients enrolled on protocols used for non-malignant indications should be included as well as table of all adverse events if available. The sponsor should include all the information available, state the number of patients treated on the study, and state that information may not be complete
 - Information with regard to tumor lysis, vascular leak syndrome, and pancytopenia is particularly important and should be include in the briefing document (and package insert).
- A more correct title for Table 16 is "Response and Time to Event Parameters".
- In Figures where rates are shown, the numbers should be included on the graft for each week so the reader can appreciated the percentages.
- Use of median concentrations or counts over time for describing hematological parameters can be very misleading., however, information about changes is important.

- The sponsor was encouraged to use Figure 20 to provide information about CD4 counts.
- The sponsor was advised that the briefing document and the package insert should contain more information about the dose concentration / toxicity effect at doses over 30 mg TIW. The briefing document should contain information as serious toxicities that can occur when therapy is initiated at doses > 10 mg.

As soon as directives are released with regard to the release of the agency's review, the sponsor will be advised. The sponsor was advised that this division would contact Karen Templeton-Somers and advised her that the sponsor's final briefing documents would be delayed. The sponsor will contact the agency with a tentative date for re-submission.

MINUTES OF A TELECON: BLA 99 – 0786

DATE: October 16, 2000
TIME: ~ 4:00 PM
ATTENDEES: Dr. Lee Brettman, M.D.
Jackie Cinacola
Dr. Genny Schechter, M.D. *MS
10/16/00*

Dr. Schechter contacted Dr. Brettman and Ms. Cinacola in order to provide further information about issues discussed in a telecon held earlier today.

- The Campath presentation to the advisory committee has been rescheduled for December 14 in the morning.
- Dr. Schechter advised Dr. Brettman that a joint presentation would be possible with Dr. Brettman presenting the efficacy data and Dr. Schechter the safety data (CLL and other diseases) and summary. The details will be worked out in November after the briefing documents are distributed.
- Dr. Keegan agrees that a discussion of the definition of progression after objective response would be an interesting point of discussion with the CLL experts and ODAC panel members giving opinions, rationales for definition of progression. This will be discussed further at a later time.
- Dr. Brettman was advised that CBER does review the briefing document prior to distribution to ensure that the sponsor and the agency are in agreement about major issues and claims. The sponsor will attempt to submit the document to CBER in early November for review. Dr. Schechter noted that CBER has not formally adopted the CDER timelines but that every effort will be made to get the FDA document out in a timely fashion.
- Dr. Brettman was advised that the sponsor should have submitted a proposal for a post-marketing commitment with the planned schedule for completion of the proposed commitment prior to the ODAC meeting in case ODAC decides to give limited approval for Campath.
- The sponsor was advised that official action regarding the Campath application might be possible before the end of the calendar year 2000 depending on how many difficulties are encountered with regard to the labeling. Dr. Keegan will attempt to locate the information on aplasia.

MINUTES OF A TELECON: BLA 99-0786

DATE: October 16, 2000
TIME: 2:30 PM EST
ATTENDEES: Kelly Tate, ILEX Oncology
L. Brettman, MD Millennium
J. Cinacola, Millennium
B. Balsler, Millennium
G. Schechter, M. D., FDA
Paula Lincoln-Smith, FDA

BSL
10/16/00

The following issues were discussed:

- Dr. Schechter stated that her review was coming along but she was unsure exactly when it would be completed. The ODAC date is set for December 13 in the afternoon.
- It was agreed that there is no need for an October 26th meeting.
- Dr. Schechter stated that she would forward a copy of the efficacy data sets and reason for the differences to the sponsor for review and comparison with the sponsor's data set. Dr. Schechter requested that the sponsor forward a copy of their statistical analyses for comparison with Dr. Gnecco's data. Dr. Schechter stated that as far as she could tell the database was error free but could not guarantee it.
- The definition of treatment failure was discussed and the sponsor will compare their treatment failure dates with the FDA dates. The sponsor was advised that there was no need to submit revised data.
- With regard to use of the independent review panel assessments for objective response, Dr. Brettman stated that he was concerned that Dr. Simon, the statistician, might question the response if different. Dr. Schechter stated that the partial responders had been reviewed and the Dr. Simon would not challenge the agency's assessment of objective responder.
- With regard to progression Dr. Schechter noted that two patients (one in 009 and one in 005?) had almost reached an ALC 5000/ul and was considered to have progressed on that date since there was no further follow-up.
- Dr. Schechter stated that the definition of progression used by the agency was the same as applied initially and based on the 1996 NCI-WG definition for progressive disease. Dr. Schechter stated that a discussion of the definition of progression after response in CLL (duration of response) might be an interesting addition to the ODAC meeting. Dr. Brettman stated that Dr. Keating, Dr. Rao, and Dr. John Bennett would be attending. Dr. Brettman stated that Millennium was considering inviting Dr. Cheson also. Dr. Schechter stated that she had send Dr. Cheson an E-mail about definition of progression after response and that Dr. Cheson had forwarded it to Dr. Rao, Dr. Bennett, Dr. Monserrat, and Keating and had received varied responses. Perhaps part of the ODAC meeting could be used as a forum to reach a consensus about definition for progression after response to provide guidance for future studies.

- Dr. Schechter stated that she had not discussed a joint presentation any further with Dr. Keegan but would do so and let everyone know.
- Dr. Schechter noted that the agency would use the clinical benefit assessment defined by the agency. Use of time to alternative treatment, a benefit proposed by the sponsor, was not defined prior to enrollment and bias is introduced in this analysis. This claim probably could not be used in labeling. Most of the labeling review will be completed after ODAC.
- Dr. Schechter stated that she was unsure if approval would be possible during the year 2000 but she would try.
- Dr. Brettman asked about the box warning for _____ Dr. Schechter stated that she would discuss this further with Dr. Keegan to determine if this occurred in the NHL or in the RA patients. Dr. Schechter advised Dr. Brettman to submit the label without the box warning and let the agency add it. Dr. Schechter advised that sponsor that the label should be modeled after Rituxan and Herceptin. Dr. Schechter is not aware of any class labeling with regard to monoclonals at this point in time.

The telecon ended at 3:15 PM.

SEP 01 2000

Our STN: BL 103948 (replaces 99-0786)

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

Dear Ms. Cinicola:

We acknowledge receipt on August 21, 2000, of your August 18, 2000, resubmission to your license application for Alemtuzumab.

This resubmission contains additional clinical information regarding studies CAM-211, 005, and 009 submitted in response to our June 23, 2000, complete response letter.

We consider this a complete, class 2 response to our action letter. CBER intends to review this submission and take action on it by February 20, 2001.

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

FILE
COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP	Sickafuse	8-31-00						
DARP	Sickafuse	8-31-00						
DARP	G. Jones	8-31-00	DARP	D. W. Jones	9-01-00			

cc: HFM-515/P. Harris
HFM-555/K. Webber
HFM-555/K. Stein
HFM-561/K. Brorson
HFM-110/RIMS
HFM-500/S. Risso
HFM-500/J. Siegel
HFM-585/G. Jones
HFM-588/S. Sickafuse
HFM-570/K. Weiss
HFM-570/P. Keegan
HFM-573/G. Schechter (Comment received 8-31-00)
HFM-579/M. Green
HFM-215/C. Gnecco
HFM-650/L. Johnson
HFM-675/W. Lange

OTTR:DARP:Sickafuse:8-31-00:dixon:8-31-00
(S:/Sickafuse/Campath/resubmission letter.doc)

**CORR: ACKNOWLEDGMENT LTR FOR CLASS 2 RESPONSE
MILESTONE: CLASS 1/2 RESUBMISSION - (1R/2R)**

MINUTES OF A TELECON: BLA 99-0786

DATE: August 8, 2000

TIME: 3:00 PM EDT

ATTENDEES:

Millennium Dr. Lee Brettman, M.D.

Jackie Cinacola

ILEX Kelly Tate

FDA Dr. Genevieve A. Schechter, M.D.

Ms. Paula Lincoln-Smith

*WKS
8/9/00*

SUMMARY:

- The clinical benefit graphs provided in a fax from ILEX were reviewed. The graphs are adequate. Performance status will be graphed and as will all parameters mentioned in the "Completed Review" letter. Days to response and days to progression will be calculated and included in a list at the end of the clinical benefit section to aid in reviewing these graphs.
- The filing date for the resubmission has been moved back to August 18 or 19th. If no serious problems are encountered during the review, presentation at the December ODAC is planned. The sponsor was advised to request a meeting or telecon in mid October (~October 16th) when the review has been completed.
- The sponsor indicated that they had spoken with Ms. Templeton-Summers about the new requirements with regard to ODAC briefing documents. The sponsor was advised that at the present time these rules do not apply to submissions from CBER to the ODAC committee. Dr. Schechter stated that these requirements could be instituted for some / all centers at any time.
- A joint presentation remains an option at this time and will depend on the Office Director's decision.
- Areas in each study report, that are revised, will be marked clearly in the index for each study report. The sponsor will submit both electronic and printed formats. The statistical data will be submitted on CDs. Changes in the data base will be submitted. For each revised table a "key" which lists all the changes will be provided. The key will be separate from the table. The sponsor was advised that only an electronic submission is required.
- The revised adverse event tables for the label and the revised label will not be included in the August 18 – 19th submission. Dr. Schechter stated that this was acceptable. The sponsor is revising the Integrated Summary of Safety to include information from all studies. This will be included in the same submission with the revised labeling. The sponsor was advised that a request for a revised Integrated Summary of Safety was not included in the Completed Review letter. When the revised summary is submitted, it will be reviewed.
- The sponsor was advised that a 120 Day Safety Update will need to be submitted. A acceptable / unacceptable length of delay in the submission will be discussed with Dr. Keegan. Dr. Schechter will appraise the sponsor as to the results of this discussion.

- Patient #006-0024 was discussed. The sponsor will fax all three bone marrows. The sponsor states that the investigator's impression of progression was based on a "drop" in platelet count which was actually a return to baseline in platelet count. The sponsor was advised that Dr. Schechter would review the data and, if everything checks out, accept the "partial response designation.
- The sponsor stated that they were able to demonstrate clinical benefit for patients with regard to several of the parameters designated as clinical benefits. This information will be reviewed by the agency. The sponsor was again advised that demonstration of clinical benefit is required in single arm studies as objective response, in and of itself, is not proof of clinical benefit.
- The sponsor was advised that teleconferences will be arranged through Kelly Tate as needed during the review of the resubmitted application.

MINUTES OF A TELECON: BLA 99-0786

DATE: July 19, 2000
TIME: 2:30 PM – 4:10 PM EDT
ATTENDEES: Lee Brettman, M.D. Millennium
Jackie Cinacola, Millennium
Kelly Tate, ILEX
Genevieve Schechter, M.D., FDA
Paula Lincoln-Smith, FDA

*bms
7/24/00*

SUMMARY:

DEMONSTRATION OF CLINICAL BENEFIT

A draft copy of the sponsor's proposed description of clinical benefit response was forwarded to Dr. Schechter for review and comment on July 15, 2000. The sponsor was advised that individual graphs for each parameter mentioned in the Completed Review Letter should be submitted for each partial responder as part of the demonstration of clinical benefit. The graphs may be in black / white. The graphs should have the appropriate scale and appropriate annotations on the graph as well (i.e. on the graph of hemoglobin values the timing / number of RBC transfusions and the use of EPO; on the ANC graft use of growth factors and infections) and should cover the time period from initiation / enrollment or earlier until the patient relapses. The draft clinical benefit grafts submitted for review were very difficult to read and interpret.

The patient's clinical course should be concisely presented as in the boxed outline following the graphs as shown in the draft. The sponsor has agreed that all data used to construct clinical benefit will be verified prior to inclusion in the clinical benefit summary. The sponsor was advised that the dates used should be their dates not dates as determined by the agency. Only one response (the sponsor's final assessment of response) should be included in this outline.

A short discussion of the clinical benefit should be included. Extraneous material should be removed from the discussion of clinical benefit. The sponsor should remember that resolutions of symptoms and decrease in adenopathy, splenomegaly, and improvement in lymphocyte count are part

of the definition of partial response and are not individual clinical benefits per se. Information about changes in disease status would be better included in the boxed outline of the patient's clinical course.)

A summary discussion with use of summary descriptive statistics for different clinical benefit parameters (i.e. % of patient's demonstrating a particular benefit) may be included. The agency agrees that more complicated statistical assessments would not be performed since the demonstration of clinical benefit is based on a post-hoc analysis. Inclusion of the patient summary sheets (All the data for each patient used for the clinical benefit analysis and audited for accuracy.) with each patient's assessment of clinical benefit is most helpful for review.

ISE, ISS:

The sponsor does not need to submit a revised integrated summary of efficacy (ISE) every one hundred and twenty days. An update of the safety information must be submitted every 120 days during the review cycle. This update should show any new information about deaths and serious adverse events and update all pertinent adverse event tables. If an increase in incidence of a specific adverse event is noted over the previous reporting cycle, this should be discussed briefly. If any concerns about the safety of the product is raised on review of the data this should be discussed. For this safety summary the sponsor indicates that follow-up through February, 2000 will be available.

The complete response to the Completed Review Letter may contain an updated ISE if the sponsor so desires.

REPONSE TO COMPLETED REVIEW LETTER:

All issues in the Completed Review letter must be addressed in the submission. The completed review focuses on each study and the corrected information that must be submitted for each study. A revised summary of the "corrected, updated, revised" study reports would constitute an integrated summary of efficacy, but revision / updating on the ISE is not a requirement.

The sponsor was advised that all databases should be corrected. The updated statistical sets should be in SAS compatible format. The revised study report should be concise and the sections of the protocol that are revised should be

clearly delineated in the index or by some other method to indicate a change in study report. A new study report will be submitted for 005. The same numbering system should be used as in the original study report so that the old and new study reports can be compared [for Study 211 and 009]. Tables should be numbered and titled the same in the revised as in the original reports. Any additional information requiring a new subsection should have a numerical extension added so that the basic numbering is not changed. Titles to specific sections should not be changed. With regard to specific subparts of the study report some areas will not change such as objectives. The sponsor noted that Sections 10 –13 will be the sections of the study report that require revision.

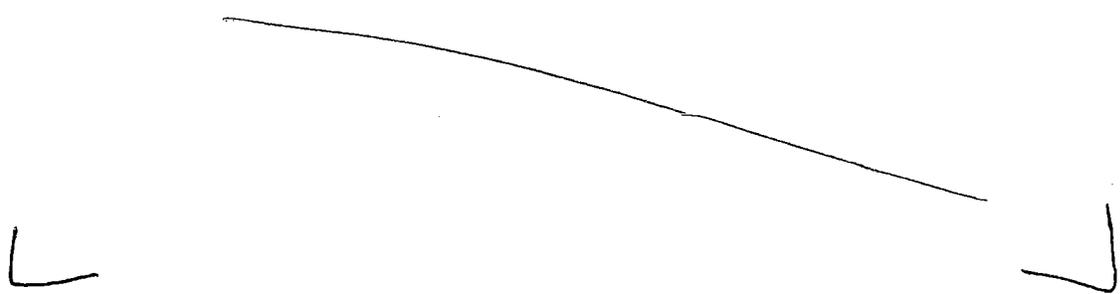
The sponsor was advised that their submission in response to Completed Review would be on a six-month review clock. If problems were discovered on the review of the resubmission, an another “completed review” letter would be issued. If there are no problems on review (The database is corrected; the reissued study reports contain the appropriate analyses; and, no other significant safety problems are observed.), the application would probably go to ODAC in December 2000. All action on the application must be resolved by the clock date (? February 2000), hopefully sooner.

The sponsor will cancel the August 10 meeting. Plans were made to hold a telecon in early October to discuss any problems with the resubmission and future plan of action. The Federal Register notice must be submitted eight weeks in advance which requires that the submission be reviewed by that date.

Label:

The sponsor was advised that a revised proposed label did not have to be submitted with the response to the Completed Review letter but could be submitted at a later time. Major problems were noted in the draft label that the sponsor forwarded. 

The sponsor was advised that in the Clinical Section the initial sentence should include information on the total number of patients (all diseases) who received Campath followed by the a sentence on with information for the



Information on time to recovery of CD4+ counts should be included in the appropriate section. Information about CD4 count and correlation with infection should be included. In the adverse event section a table of adverse events occurring in > 5% of patients treated on other protocols for other disease states besides CLL (including the Burroughs-Wellcome information) must be included. A listing of all serious adverse events that occurred in one or more patients should be included by body organ system starting with body as a whole. The sponsor was advised that the overdose section should be expanded to include some idea of the type and incidence of toxicity with a specific Campath dose over time (i.e. toxicities with Campath 240 mg over five days).

With regard to drug administration a statement about the minimal safe time for infusion should be included in this section along with a precaution that too rapid administration may cause severe hypotension and allergic reactions. References to the _____ of administration must be removed from the label until the sponsor has submitted an efficacy supplement to demonstrate the subq route is as safe or safer than the IV route with similar or superior efficacy. Single arm studies such as the one in Finland would support the efficacy / safety of this product but do not take the place of a PK or other type of controlled efficacy study. The final label will contain FDA statistics and is likely to be rewritten extensively by the agency.

Dr. Schechter advised the sponsor that she would provide them with a copy of her minutes. If the sponsor had corrections, the sponsor should submit a copy of the 'sponsor's minutes' to the FDA.

BLA 99-0786: MINUTES OF TELECON

DATE: July 13, 2000
TIME: 3:20 PM – 4:45 PM
ATTENDEES: Dr. Lee Brettman, M.D., Millennium
Kelly Tate, ILEX Oncology
Dr. Genevieve A. Schechter, M.D. *BAS 7/13/00*
Paula Lincoln-Smith, Administrative Assistant

Dr. Brettman began the telecon by stating that they were hard at work checking on all source documents and the 211 database would contain an additional twenty thousand pages. All CRFs and all lab data would be updated. An error was found in the 120-Day Safety Update where lymphocyte counts were entered as percentages rather than the absolute value. The database would be corrected and the corrections flagged. In Study 005 the hemoglobin data from some study sites was entered as mmol% rather than gm%. This table will be corrected. The study reports will be revised.

With regard to demonstration of clinical benefit, the sponsor will send a “mock up” for several patients for critique. A telecon will be held early next week to discuss the data presentation. The sponsor is anxious to have everything completed and hopes to submit the entire complete response at the end of the first week of August. The sponsor was advised that an ODAC presentation in October was very unlikely since the Federal register notice has been published approximately eight weeks prior to the meeting and the resubmitted data would not be completely reviewed by the time that the notice would have to be issued.

A more likely scenario would be presentation at the December ODAC, and, if the ODAC committee voted for approval, prompt issuance of an approval letter possibly before the advent of the New Year.

Dr. Schechter stated that it was extremely important to have an accurate idea of the toxicities. Dr. Brettman commented that the number of prior therapies that a patient received appears to increase the severity of the toxicity that the patient experiences during Campath therapy. The sponsor will look analyze toxicity by the number of prior treatments to demonstrate the effect of previous treatment on the Campath toxicity profile.

With regard to a joint ODAC presentation Dr. Schechter stated that this would have to be discussed at the division / office level, but was a possibility. She will discuss the issue with Dr. Keegan prior to the August telecon.

The definition of treatment failure was discussed. The agency considers treatment failure as progression, discontinuation of treatment for adverse events for reasons other than progression, or death. A median treatment failure duration that is markedly shorter than the median progression time suggests study drug toxicity as a reason for treatment discontinuation rather than disease related causes. Dr.

Schechter noted that a patient may be a treatment failure, but still is a partial responder with a long duration of response. One patient on 211 withdrawn for an adverse event had a long duration of response (time to progression).

With regard to progression, Dr. Brettman is concerned about the definition of progression and cited a case where a cervical node 2 cm in diameter was reported (and considered as evidence of progression by the medical reviewer) at one visit but not at subsequent visits. Dr. Schechter noted that she would be glad to discuss / provide reasons for any cases where disagreement occurred. Once the revised database is submitted then difference in dates will be noted and reviewed. Usually if progression was observed at one site, then progression was observed at other sites in the near future. Dr. Schechter also noted that perfect agreement on all patients was probably not possible.

The sponsor will also analyze some patients with regard to progression over time specifically patients who lymphocyte count rose to 5000/ul and then declined to 4000/ul on next visit. Dr. Schechter advised the sponsor to identify all patients who would be included in this category.

Database issues that were discussed included:

- The database for 005 will include only 32 patients who have B-CLL. This is a selected group of patients from a larger study.
- One patient on 005 [006-102] reported by the sponsor as alive is dead.
- Dr. Schechter will review the new databases and compare with her database and the CRF or line listings. Once her databases are updated and checked for error and the statistical analyses done using these databases, the databases will be provided to the sponsor. Until the databases are reviewed for error based on the corrected data to be submitted by the sponsor the databases will not be released. The revised databases will be provided in a SAS compatible format.
- The NCI CTC criteria will be used to grade the laboratory toxicities for study 005. Dr. Schechter noted that the letter stated WHO criteria, but that NCI CTC grading was far more acceptable.
- With regard to the 009 database one patient with T-CLL was included and three patients who appear to have other B-cell malignancies. Since an ITT population will be used for the label, the inclusion of patients who may have other B-cell malignancies is probably not an important issue.

With regard to other efficacy analyses Dr. Schechter stated ITT analyses would be used in the briefing document, at ODAC, and for the label. An exploratory subgroup analysis including B-CLL patients who were fludarabine refractory and had advanced disease requiring treatment was done prior and presented at the midcycle to demonstrate efficacy in the group

Dr. Schechter asked the sponsor to submit a copy of the draft label to discuss areas that should be expanded or added in order to facilitate labeling review. It would be best to have the label in final format at the time of the ODAC meeting.

With regard to response rate Dr. Schechter noted a different assessment of objective response in one patient on 211 and one patient on 009. For the patient 006-0024 on Study 211 the sponsor needs to submit the bone marrow, CBC and reason why the investigator stated that the patient was progressing in the progress notes. Dr. Schechter suggested that Dr. Brettman review the progress notes. For patient 002-0014 did not have follow-up assessment of hepatosplenomegaly after baseline. Other differences in assessment for stable disease, progression, and not evaluable were briefly discussed.

With regard to the 120 Day Safety Update the sponsor was advised to submit the previous safety profile with any new adverse events reported during this 120 day period. Of interest to the reviewer is the difference in the incidence of adverse events over the time period of interested. For example _____ . No information on efficacy needs to be submitted in the safety update.

The sponsor was asked to consider whether an additional telecon would be need in August with Dr. Keegan since many of the issues to be discussed during the proposed telecon were discussed today. A telecon will be held next week to discuss the clinical benefit response and the label. Dr. Schechter stated that she would fax a copy of the minutes to Kelly Tate.

**Appears This Way
On Original**

TELECON MINUTES FOR MAY 18, 2000: BLA 99-0786

BLA: 99-0786
DATE: May 18, 2000
TIME: 11:00 – 11:30 AM EST

ATTENDEES:

Millennium: Lee Brettman, M.D.
ILEX: Gayle Cook
Kelly Tate
FDA: G. Schechter, M.D.
P. Lincoln-Smith

*Per review of Schechter
5/18/00*

Dr. Brettman and Kelly Tate acknowledged receipt of the fax where data tables had missing patient numbers. Dr. Brettman stated that for the Table 16.2.9.6 entitled "Follow-Up" information that the data was not actually missing. According to Dr. Brettman five patients numbers do not appear on this table. Three patient numbers were for deaths on study 1-0040, 5-0045, 6-0016 and so these patients were omitted from the table since follow-up pages on the CRF were not filled out. For patient 3-095 no follow-up was available due to problems at the study site so the patient number was omitted from the table. Dr. Brettman did not discuss the fifth patient. Dr. Brettman admitted that the inclusion of a table entitled "Follow-Data" could cause confusion if follow-up was defined as continuing information on all patients enrolled on study. Dr. Brettman agreed to supply to the agency with corrected tables for follow-up information. Dr. Schechter advised that the completed review letter would include this request.

With regard to the table entitled "Blood Product Use on Treatment" Dr. Brettman stated that a revised table was not included in the 120 Day safety update. Only certain tables with data revision are included in the 120 safety update. Section 9.0 of the update includes information on any changes to any of the tables, but the revised table was not included in its entirety in the Safety Update. Dr. Schechter stated that the completed review letter will include information on which data tables must be corrected and resubmitted in their entirety (contain information on all patients).

Dr. Brettman stated that the Adverse Event Listings have been updated in the 120 Safety Review and is complete.

With regard to steroid usage (Table 16.2.9.3B entitled "Concomitant Corticosteroids") Dr. Schechter noted that topical and nasal steroid use was included in this table. She also noted a difference in her analysis of the information included in this table. Her analysis is as follows:

- Eight patients had steroid requirement prestudy which continued during study
- One patient began premedication three days prior to study.
- Forty-nine additional patients had not previous history of systemic steroid usage received steroids during study. Seventeen patients had less than five doses.

Other than the bone marrow reports for 6-0094 Dr. Schechter replied that no further information was need. Kelly Tate asked if this relieved the sponsor of the obligation to provide all the information requested in the request for information letter. Dr. Schechter replied absolutely not. The sponsor needs to provide the information for review so that disposition and profile for some patients can be completed. As for example the patient who stopped treatment due to pancytopenia and died in [] Did this patient recover? What were blood counts at hospitalization? The information was requested in order to complete a safety and efficacy profile on each patient. Schechter reminded the sponsor that this application is not based on a large number of patients, that the studies are single arm studies, and that information has to be accurate to have an accurate safety profile.

Appears This Way
On Original

MINUTES OF A TELECON: BLA 99 -0786

DATE: May 17, 2000
TIME: 10:00 AM - ~ 10:30 AM
ATTENDEES:

ILEX: Kelly Tate
P. SantaBarbara, M.D.
Bret Wachter, Statistics
Gayle Cook
Millinneum: Lee Brettman, M.D. *Genevieve A. Schechter*
Jackie Cinacola *5/17/2000*
J. Balser, Ph.D.
B. Balser, Ph.D.
FDA: Patricia Keegan, M.D., Deputy Director, DCTDA
Richard Steffen, M.D., Branch Chief - Oncology
Genevieve A. Schechter, M.D., Reviewer

A discussion of the problems with the evaluation of data submitted with for review for this BLA was held. The FDA advised the sponsor that significant problems have been encountered with omission of data from tables and discrepancies with regard to information in certain tables. The sponsor has provided information to indicate that some tables in the NDA were 'unlocked' and not audited or updated. Other tables which were "locked" (updated and audited) were used to generate analyses. The sponsor asked for specific examples of data omissions. Dr. Schechter stated that she would fax the certain data tables to the sponsor for review. Dr. Keegan advised the sponsor that correction of the database was the responsibility of the sponsor. The medical reviewer's job was to review the data. If significant omissions or errors are found, the database must be corrected.

Dr. Schechter stated that she had difficulty determining the staging. No staging is included in the electronic database. The staging evaluations that she used were in Appendix E. The sponsor stated that the data in appendix E was used for the independent review and had not been updated. With regard to correct staging the sponsor stated that the staging used in the study for any data tabulations would be found in Table 16.2.6.12.

Dr. Schechter advised the sponsor that the audit of adverse events might be necessary since the seriousness of the adverse event with regard to patient 003-0095 was underestimated. Dr. Brettman stated that this patient was an unusual case in that the follow-up had been difficult. He stated that the attempts at follow-up had become more aggressive after a discussion of this patient's course with Dr. Schechter. Dr. Brettman agreed that the grading of the SAE was difficult since the patient had organ involvement (systemic Candidiasis) but was not hospitalized for treatment so the infection could be grade II or Grade III using the NCI CTC. Dr. Keegan stated that inclusion of a SAE report but failure to include the patient in the tables caused problems, as this appeared to be a serious event. Dr. Schechter advised that the adverse events would be carefully reviewed and additional information on some patients including complete histories may be requested from the sponsor to ensure accuracy with regard to grading of adverse events.

The telecon ended with Dr. Schechter stating that she would fax the information to the sponsor on this day and arrange for a telecon to discuss the fax to be held in the near future.

MINUTES OF TELECON: MAY 11, 2000

TIME: 11:15 AM – ~ 12:15 PM
ATTENDEES: L. Brettman, M.D., Millennium
J. Cinicola, Millennium
J. Balsler, Ph.D. Millennium
P. Santabarbara, M.D., Ilex
Bret Wacker, Ilex
Gayle Cook, Ilex
Patrick Shannon, Ilex
Kelly Tate, Ilex
G. Schechter, M.D., FDA
C. Gnecco, Ph.D., FDA
G. Schechter, M.D., FDA
P. Lincoln-Smith, FDA

*G. Schechter
5/11/2000*

Summary:

There were multiple interruptions during the telecon due to problems with the phone connection. The sponsor reported difficulty in hearing the FDA.

With regard to objective responses, after review FDA agrees that 003-0095 is considered a partial response. Dr. Schechter will fax a short review with the date of response and date of progression. Dr. Schechter noted that the information contained in Appendix E in Vol. 3.30 is not correct with regard to this patient. Information on 006-0024 was faxed today by Ilex. Dr. Schechter will review and fax her comments to the sponsor. *[Addendum: A entire list of complete and partial responders will be faxed to Ilex by Dr. Schechter to ensure agreement on this issue.]*

The information in the latest submission package with regard to staging will be reviewed. FDA comments will be forwarded to the sponsor. The sponsor was advised that the material in the patient summaries in Appendix E is not consistent with the material in Table 16.2.8.1, hence making the determination of eligibility difficult. The agency usually reviews the source documents and compares to summaries and tables derived from them.

With regard to fludarabine refractoriness, the following three patients (11-009, 7-008, 6-094) did not have a second course of fludarabine but were treated with 2-CDA. One patient (8-036) had duration of 6 months, 3 days for partial remission. Dr. Schechter requested that information be provided on an additional patient (16-0080 to determine date of progression after a partial response to fludarabine therapy. Dr. Schechter agreed that the information provided by the sponsor proves that these patients were fludarabine refractory. The five patients in question will be noted in the review and the committee can decide their "refractoriness". Dr. Schechter noted that the information included in the BLA did not demonstrate the patients' refractoriness.

Demonstration of clinical benefit was discussed with Dr. Gnecco and Dr. Schechter. At the midcycle meeting the consensus was that clinical benefit had not been adequately demonstrated. For all objective responders (complete and partial) clinical benefit should be described by the following for *each* patient. Information that should be included:

- study number,
- stage at entry
- response duration and dates of response
- survival information
- individual patient plot of performance status at baseline, during study, and post study until progression
- individual patient plot of hemoglobin at baseline, during study, and post study until progression with transfusion history clearly indicated, also duration of use of Procrit if used
- individual patient plot of ANC at baseline, during study, and post study until progression with use of growth factor and duration of growth factors indicated
- individual patient plot of platelet counts at baseline, during study, and post study until progression with platelet transfusion history clearly indicated
- individual patient plot of ALC counts at baseline, during study, and post study until progression
- individual patient plot of CD₄ counts at baseline, during study, and post study until progression
- information on all infections from baseline, during study, and post study until progression
- information on other adverse events during study at baseline, during study, and post study until progression including infusion related events
- Information on parental or oral steroid usage during study (with pre and post study information if necessary). Dr. Schechter noted that the use of steroids probably did not affect the response rate, but the information has to be included for review and
- A discussion of clinical benefit in this patient.

The sponsor was advised that this would be one of the issues addressed in the 'completed review' letter. This information should not be submitted to the FDA until the letter is received. The sponsor inquired if the same information would be helpful for stable disease patients. Dr. Schechter stated that the advisory committee would probably not consider this information of benefit.

Dr. Schechter asked the sponsor why the adverse event information about the systemic candidiasis infection (hepatic and splenic involvement which required multiple liver biopsies and six months of difulcan) in patient 003-0095 was not listed in the on-study or post study serious adverse event tabulations, discussed in the text, or reported in the 120 day safety update. The sponsor replied that it was not considered a serious adverse event as "the investigator considered it a grade 1 infection". Dr. Schechter stated that the failure to grade adverse events appropriately presents a major problem.

Dr. Schechter noted that the use of steroids may have influenced the tolerance to drug therapy. The sponsor advised that they would review this information.

The information on CD₄ counts as provided in the study report (means at specific time points) is not informative as the dropout rate is high and recovery can not be appreciated. The sponsor was advised to provide information based on the length of follow-up for each mutual exclusive group of patients (i.e. x patients with baseline and follow-up CD₄ counts for X months). This type of analysis will eliminate patients who go off study early due to progression or AE. This information is important in terms of labeling and need for prophylaxis. This information will be requested in the "completed review" letter and should be submitted in the complete response.

It was agreed that a telecon did not appear to be necessary. Dr. Schechter will contact Kelly Tate if any telecon is needed. The sponsor was advised that analyses for adverse events and infections will need to be done by stage and response, however before she can discuss this further she needs to review the data further. With regard to safety information, adverse events, which occur greater than 5% of the time, must be included in tabular form. The sponsor is aware of this and will correct the information. Dr. Schechter will provide the table numbers in which she thought there were errors.

With regard to the "request for information letter" signed by Dr. Weiss, the sponsor inquired if the omission of 006-0019 was an error? Dr. Schechter advised that she would check and advise the sponsor. The telecon was ended as there were no additional issues to be discussed.

**Appears This Way
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our Reference Number 99-0786

MAY 03 2000

Kelly D. Tate
 L&I Partners, LP
 11550 IH-10 West, Suite 300
 San Antonio, TX 78230-1064

Dear Mr. Tate:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has reviewed the clinical section of your application dated December 22, 1999, for Alemtuzumab for the treatment of chronic lymphocytic leukemia, and as discussed during the April 6, 2000, telephone conversation between you and Dr. Genevieve Schechter of this office, has determined that a response to the questions and requests for clarification as listed in the attached documents regarding studies 005, 009, and 211 is necessary to take a complete action on your application.

It is requested that you promptly submit a complete response to the attached information requests. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the preclinical, human pk/pd, CMC, and facility sections of your application is continuing.

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FILE
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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP	Sickofuse	5-2-00						
DARP	W. Jones	5-2-00	DARP	DIXON	5/3/00			
2000A	W. Jones	5-2						

Page 2 – Mr. Tate

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

Sincerely yours,

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

Enclosures (3): Request for Information: Study 005
Request for Information: Study 009
Request for Information: Study 211

Page 3 - Mr. Tate

cc: DARP file
HFM-588/S. Sickafuse
HFM-570/K. Weiss
HFM-570/P. Keegan
HFM-573/G. Schechter (Comments received 4-12-00)
HFM-500/S. Risso
HFM-500/J. Siegel
HFM-585/G. Jones
HFM-110/RIMS
HFM-515/P. Harris
HFM-555/K. Webber
HFM-555/K. Stein
HFM-579/M. Green
HFM-556/M. Brunswick
HFM-215/C. Gnecco
HFM-650/L. Johnson
HFM-675/W. Lange

OTRR:DARP:Sickafuse:4-14-00:4-17-00:amw:4-18-00:sks:4-25-00:dixon:4-25-00:4/28/00
(S:/Sickafuse/Campath/IRletter.doc)

CORR: INFORMATION REQUEST

TELECON MINUTES

DATE: April 19, 2000
TIME: 10:30 AM
BLA: 99-0786
PRODUCT: Campath (Alemtuzumab)
ATTENDEES:

L&I Partners: L. Brettman, M.D., Millennium
J. Cinicola, Millennium
J. Badgers, Millennium
B. Wacker, ILEX
P. Santabarbara, M.D., ILEX
G. Cooke, ILEX
K. Tate, ILEX
FDA: G. Schechter, M.D. *BRS 4/19/00*
P. Lincoln-Smith, Administrative Asst., DCTDA
J. Minor, Office of Special Health Issues

SUMMARY:

The definition of progression was discussed. The sponsor was advised that the definition was taken from the statistical section of the protocol, Volume 3.31, pg. 222. The sponsor was advised that the Agency would research the definition of progression, but that for the present the definition would remain as in their algorithm in the statistical plan. The Agency is using the sponsor's definition of time to progression, although technically this measurement is considered as disease-free survival (patients are dead from any cause or have evidence of progression)

The definition of time to treatment failure is usually defined as the time from initiation of treatment to discontinuation treatment due to death, adverse event, refusal to participate, or progression. The sponsor will add this analysis. The Agency could find only one patient considered a treatment failure who had not progressed in their preliminary analysis for Study 211.

To document response the sponsor was asked to submit the bone marrow reports from the study sites. The reviewer must be able to state that the source document was reviewed for all responders and she is in agreement with the independent panel's assessment. Any disagreements will be discussed with the sponsor (Note: For about half of the PRs and for all CRs the bone marrow report is need to confirm the PR status.)

For response assessments, the sponsor will use completion of 10 treatments (detailed in the statistical plan instead of one four week treatment cycle (12-14 treatments) generally used in oncology.

The following items with regard to specific patients on Study 211 were discussed (issues raised in the sponsor's fax of 4/14/00):

- 001-005 Considered PR by Agency; ALCs verified by sponsor
- 006-024 No follow-up after 8/18/98 is a problem. Sponsor states that patient considered as PD by the investigator so the CRFs were not completed. PR assessed by independent review panel. The sponsor was able to obtain information with regard to follow-up, but this information was not included in the safety update. The sponsor will obtain all physician notes in follow-up for this patient through March, 2000, provide information with regard to post-study infections or other possible AEs related to study drug and submit this to the IND.
- 006-027 Sponsor to provide physician notes for all visits after enrollment on study. Reviewed noted that the lymph node measurements are crossed out or written over making assessment difficult and raising a red flag to the reviewer. Will revisit response category assessment.
- 006-033 Sponsor will provide physician notes for review. The sponsor will provide bone marrows. The sponsor will also provide a narrative that will discuss in detail the development of a plasma cell disorder and type of drug therapy used to treat plasma cell disorder. This is a serious adverse event that should have been discussed more fully within the 211 study report in the safety section.
- 006-044 Lymph node measurements were crossed out at baseline, week 4, and week 8. Sponsor will provide the physician notes from time of study enrollment to ensure correct measurement of nodes.
- 007-007 Will consider this patient evaluable as the patient had twelve treatments. Sponsor will provide physician notes for all visits.
- 007-029 Persistence of hepatomegaly is problematic. The sponsor will provide all physician notes on this patient and the case will be re-reviewed.
- 007-091 Sponsor agrees with agency assessment.
- 011-014 Sponsor will provide physician notes to review assessment.
- 019-065 On day assigned for PR response patient's hemoglobin was 5.8gm%, Plt. = 49,000/ul and ANC was 400/ul. The independent review panel assigned response based on platelet count > 100,000 /ul. The sponsor will revisit this CRF and provide notes but it is unlike that PR status was attained.
- 027-067 The sponsor was advised that the hematological data does not support a PR. The sponsor was advised to review this patient's CRF, transfusion history and CBC values. The sponsor will provide physician notes to the Agency for on-study and follow-up and response assessment will be revisited.

Additional items that were discussed:

005-039 Sponsor advised that this patient is not considered a PR due to a 50% increase in lymph node size a week 4. The sponsor will review this CRF and provide a discussion if they disagree.

The eligibility criteria have not been addressed in the fax.

- The sponsor is addressing the eligibility with regard for \leq Stage II. Has one patient who is a stage III (down from Stage I). Information about RAI stage will be exchanged.
- Using the sponsor's definition the agency found ~ 10 - 12 patients who are not refractory to fludarabine using the protocol definition. Dr. Schechter's list will be provided to the sponsor.
- With regard to disease, reviewer has identified three patients who do not have B-CLL, the sponsor states they have identified four patients. Case numbers will be exchanged.

The sponsor was advised that besides an intent-to-treat analysis, that an evaluable analysis will need to be done using patients with B-CLL, with need for therapy, proven fludarabine refractory, with previous exposure to alkylators

The sponsor was advised to review the database for Study 005 as the Agency had identified ~ eight patients who did not appear to have B-CLL. The sponsor was asked to:

- 1) verify the numbers sent to Dr. Schechter to make sure the correct patient numbers were included in the database sent to her;
- 2) review the data to determine if N=40 is the number that they wish to use as the data base for efficacy;
- 3) look at the CRFs to determine if some B-CLL patients were excluded accidentally; and consider amending the study.

Once a group of responders has been identified and response categories have been assigned, then the issues of safety and clinical benefit can be addressed. Since these are single arm studies with a high rate of adverse events demonstration of clinical benefit is necessary for licensing. The sponsor was advised that telecons will be occurring regularly to resolve issues.

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Table 211-2: Listing of Patients Not Refractory to Fludarabine

Patient No.	Reason Patient Not Fludarabine Refractory
001-0041	PR response with relapse after ten months; no further fludarabine therapy
003-0049	PR response with relapse twelve months after completion of therapy. No retreatment
006-0022	PR response with relapse after seven months; no further fludarabine exposure
006-0027	PR response of "unknown duration" with date of relapse crossed out twice in the chart and final date for relapse is given as six months. Patient did not start new treatment until almost 12 months after last dose of fludarabine
006-0094	PR response lasting 25 months; no retreatment:
007-0008	PR response with a duration of 25 months; No retreatment
011-0009	PR after fludarabine therapy lasting twenty-four months; No retreatment with fludarabine
011-0053	PR of 14 months duration by dates provided for various therapies
016-0080	PR after fludarabine therapy. Duration of "8" months crossed out and "5 ". By treatment dates patient did not start new therapy until 10 months after fludarabine therapy ended.; No further therapy with fludarabine
023-0064	PR after fludarabine therapy lasting eight months; No retreatment with fludarabine

DISEASE OTHER THAN B-CLL:

- 005-0057 Lymphoma
- 016-0081 Lymphoma
- 018-0082 Lymphoma
- 026-0073 Lymphoma
- 023-0070 PLL

Appears This Way
On Original

TELECON MINUTES

DATE: April 19, 2000 TIME: 10:00 - 10:25 AM
BLA: 99-0786
PRODUCT: Campath (Alemtuzumab)
ATTENDEES:

L&I Partners: L. Brettman, M.D., Millennium
J. Cinicola, Millennium
J. Badgers, Millennium
B. Wacker, ILEX Oncology
P. Santabarbara, M.D., ILEX Oncology
G. Cooke, ILEX Oncology
K. Tate, ILEX Oncology

FDA: Patricia Keegan, M.D. Deputy Director, DCTDA
Richard Steffen, M.D., Branch Chief, Oncology, DCTDA
Genevieve A. Schechter, M.D., Medical Reviewer, DCTDA
Joann Minor, Office of Special Health Issues

*bms
4/19/00*

SUMMARY:

ILEX was advised that a midcycle meeting for Campath was held on Friday, April 14, 2000. After presentation of the clinical data, a consensus was reached by the attendees including the office director, Dr. Jay Siegel, that the BLA review should be completed and a letter issued to the sponsor with regard to outstanding issues from each discipline. The Agency explained to the sponsor that too many questions remain regarding the clinical data including questions of eligibility, response rate, response duration, demonstration of safety, and the demonstration of clinical benefit response to allow for a complete, well-balanced presentation at an ODAC meeting in June. The Agency thinks that it would be of little benefit and may even be detrimental with regard to approval of this product for the sponsor or for the Agency to publicly present major disagreements with regard to the data and/or analyses. The Agency feels that many of these disagreements can be resolved by discussion between the reviewer and the sponsor with further examination of the data. Every attempt should be made to resolve differences prior to any public presentation of the data.

The sponsor suggested that the BLA be presented to a BRM advisory panel. Dr. Keegan explained that at the present time, all new oncologic therapies are presented only at the ODAC in keeping with agency policy.

The sponsor expressed disappointment about the Agency's decision but agreed that any outstanding issues and any areas of disagreement should be resolved or the differences well defined prior to presentation at any advisory committee meeting.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: ^{SKS} March 31, 2000
From: Sharon Sickafuse, OTRR/DARP, HFM-588
Subject: Vial and Carton Labeling for CAMPATH; BLA 99-0786
To: Kelly Tate

Vial Label

1. There seems to be a lot of empty space above where the wording starts. Can this be reduced and the font size consequently increased?

2.

3.

4.

5.

6.

7.

8.

9.

10.)

Campath 3 Ampule Carton

All of the comments regarding the vial label also apply, except for the first comment. In addition:

1.

2.

3. 1

4. L

Campath 12 Ampule Carton

All of the comments regarding the Campath 3 Ampule carton also apply.

L

L

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FEB 09 2000

Our Reference Number 99-0786

Kelly D. Tate
 L and I Partners, LP
 11550 IH-10 West, Suite 300
 San Antonio, TX 78230-1064

Dear Mr. Tate:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act and the determination of the acceptability for filing this supplement.

The Center for Biologics Evaluation and Research has completed an initial review of your application dated December 23, 1999, for Alemtuzumab for the treatment of chronic lymphocytic leukemia. In accordance with 21 CFR 601.2(a), the application is considered to be filed effective today's date.

This acknowledgment of filing does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
 Director
 Division of Application Review and Policy
 Office of Therapeutics
 Research and Review
 Center for Biologics
 Evaluation and Research

FILE
 COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP	Sickafuse	2-9-00						
DARP	G. Jones	2-8-00						
DARP	O'Ryan	2-9-00						

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cc DARP file
HFM-588/S. Sickafuse
HFM-555/K. Webber
HFM-570/K. Weiss
HFM-570/P. Keegan
HFM-110/RIMS
HFM-573/G. Schechter
HFM-579/M. Green
HFM-556/M. Brunswick
HFM-675/W. Lange
HFM-215/C. Gnecco
HFM-207/L. Johnson
HFM-515/P. Harris (Bld. 29 Division Coordinator)

OTRR:DARP:Sickafuse:2-3-00:amw:2-4-00:dixon:2-8-00
(S:/Sickafuse/Campath/filinglet.doc

MILESTONE FILING LETTER - (FA)

MEMORANDUM

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

Date: February 4, 2000

To: Sharon Sickafuse, CSO, HFM-588

From: Catherine Miller, Regulatory Reviewer, HFM-602 *cm*

Through: William Purvis, Director, APLS, HFM-602 *WP*

Subject: Review of brand name CAMPATH upon BLA submission:
ACCEPTABLE with concerns

APLS was asked to review the proposed brand name "CAMPATH" since some time has passed since it was found "acceptable with concerns" in March 1999. We have completed our evaluation and found one additional product, recently approved by CDER, that is similar to CAMPATH.

COMTAN (entacapone) is a tablet which should always be administered in association with levodopa/carbidopa to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing off." COMTAN is an adjunct to levodopa/carbidopa and has no antiparkinsonian effect of its own.

The unique dosage schedule and use is regarded to be significantly and materially different from that of CAMPATH. There is a remote possibility that the two products may be confused.

Our conclusion, regarding the proposed tradename of CAMPATH, is that it is acceptable with concerns, primarily based on name recognition by oncologists (see item B.1. of March 31, 1999 review). However, a potential does still exist for medication errors with other prescription drugs (see above and items A.1., B.2., & B.3. in March 31, 1999 review). Therefore, to further minimize this potential, we recommend that the proprietary name be graphically distinguished from other products by using various sizes of letters (e.g., CamPath), fonts, or colors, etc. on all carton, container, approved package inserts, and advertising and promotional labeling. This step would further assure that the similar products would be sufficiently distinguishable and preclude misadministration.

Kelly D. Tate
L and I Partners, LP
11550 IH-10 West, Suite 300
San Antonio, TX 78230-1064

July 1, 1999

Dear Mr. Tate:

REFERENCE NUMBER 99-0786 has been assigned to your recent submission for your biologics license application for CAMPATH® for the treatment of chronic lymphocytic leukemia, received on June 21, 1999.

This application was submitted under provision (c) of Section 506 of the Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 356) for review of an incomplete application for a Fast Track Product. We acknowledge your submitted schedule for submission of the remaining portions of this application. In accordance with provision (c) of the Act, our review clock will not start until the date on which you submit the final portion and inform us that your application is complete.

All future correspondence, supportive data, or labeling relating to this application should be submitted in triplicate and should bear the above REFERENCE NUMBER and be addressed to the Director, Center for Biologics Evaluation and Research, HFM-585, HHS/PHS, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

This acknowledgement does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application, we shall advise you in writing as to what action has been taken and request additional information if needed.

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Should you have the need to discuss any technical aspects of the application, you may obtain the name of the chairperson of the licensing review committee by contacting this office, 301-827-5101. Any questions concerning administrative or procedural matters should also be directed to this office.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CC: Sharon Sickafuse
Margaret Naecker
Red Folder
Annette Williams

OTRR:DARP:srf:7/1/98
99-0786.apl