CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-273

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	N022-273 / N 000
Drug Name:	fludarabine phosphate oral tablets
Indication(s):	Treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating agent containing regimen
Applicant:	Xanthus Pharmaceutical, Inc.
Date(s):	Submission date: November 15, 2007 PDUFA due date: September 19, 2008 Review completion date: June 9, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
Concurring Reviewers:	Rajeshwari Sridhara, Ph.D., Team Leader Aloka Chakravarty, Ph.D., Division Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Martin Cohen, M.D. & Bhupinder Mann, M.D.
Project Manager:	James Saunders

Keywords: single-arm studies, new formulation, response rate, duration of response, historical data

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1. EXECUTIVE SUMMARY

This is a New Drug Application (NDA) submission seeking indication for fludarabine phosphate oral tablets (oral Fludara) as treatment of adult patients with B-cell chronic lymphocytic leukemia (B-CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating agent containing regimen.

b(4)

b(4)

1.1 Conclusions and Recommendations

In this reviewer's opinion, the efficacy results from the pivotal study ME96029 have not provided a substantial evidence from a statistical point of view to support oral Fludara for the proposed indication. Although the observed overall response rate of 51% based on the National Cancer Institute Criteria for B-CLL may seem to be comparable to the ones seen with the IV Fludara (48% in the study by M. D. Anderson Cancer Center, and 32% in the study by Southwestern Oncology Group), cross-study comparisons may not be adequate considering the differences in dose, treatment duration, and use of supportive therapy between the studies. In addition, there was no follow-up of patients after completion of study and information about duration of response or survival could not be obtained.

Furthermore, data from supportive studies B820 and CLL4 in previously untreated B-CLL patients are not adequate to support an approval for the oral Fludara in 2nd line CLL. Duration of response and time to progression collected in the single-arm study B820 are difficult to quantify in the absence of a control group, and any comparison between IV and oral Fludara in Study CLL4 can only be viewed as exploratory because the Fludara treated patients did not receive IV or oral Fludara according to randomization.

A study in the targeted patient population with patients randomized to either an oral or an IV formulation will be necessary if oral Fludara is to be considered for approval based on efficacy comparability between the two formulations.

1.2 Brief Overview of Clinical Studies

This NDA contains data from one pivotal study ME96029 and additional data from supportive studies B820 and CLL4.

Study ME96029, which was conducted in Europe and Canada, was a single-arm study in 81 B-CLL patients who had failed to respond or who showed signs of disease progression during or after previous treatment with at least one standard alkylating agent containing regimen. Patients were to receive oral fludarabine phosphate 40 mg/m^2 daily, 5 days every 4 weeks, for six four-week cycles or up to eight cycles if they responded to treatment but had not achieved a complete response after the sixth treatment cycle. Patients who did not respond or showed clinical signs of disease progression after two cycles of treatment were withdrawn from the study. The study was planned to recruit 80 patients to detect an unfavorable efficacy profile with a point estimate of the overall response rate (CR+PR) that was statistically significant lower than 45%. Among 81 recruited patients, 78 received oral Fludara treatment and were used for assessment of treatment efficacy and safety.

Study B820 was a single-arm European study with oral Fludara administrated to 81 previously-untreated B-CLL patients. Patients were to receive oral fludarabine phosphate 40 mg/m^2 daily for 5 days every 4 weeks up to six cycles or up to eight cycles of treatment if they responded to treatment but had not achieved a complete response after the sixth treatment cycle. Patients who did not respond or showed clinical signs of disease progression after two cycles of treatment were withdrawn from the study and considered treatment failures. The sample size was calculated to determine whether the response rate equaled a pre-specified value, 70%, which was the overall response rate of patients receiving IV fludarabine as first-line treatment for B-CLL in the European _____ 101 study. The study protocol was amended on 22 Feb 2002, after the original NDA withdrawal, to have patients followed up for measurements on duration of response and time to progression. b(4)

Study CLL4 was an open-label study conducted by the UK Leukemia Research Foundation. Previously-untreated B-CLL patients were randomly assigned at a 1:1:2 ratio to fludarabine phosphate alone, fludarabine phosphate plus cycleophosphamide, or chlorambucil. Oral fludarabine was allowed after it became available part way through the study in 2001. The study was powered for difference in 5-year survival rate between chlorambucil group and the groups containing fludarabine phosphate combined.

1.3 Statistical Issues and Findings

Statistical Issues:

1. Response rate form a single-arm pivotal study without measurement on duration of response is not adequate for providing conclusive evidence for clinical activity.
2. Additional data from supportive studies B820 and CLL4 in previously untreated B-CLL patients are not adequate to support an approval for the oral Fludara in 2nd line CLL. Duration of response and time to progression measured in Study B820 are difficult to interpret in the absence of randomization. Any comparison between IV and oral Fludara in Study CLL4 can only be viewed as exploratory because the patients were not randomly assigned with respect to route of formulation.

Primary Findings:

Table 1 displays the observed response rates from the pivotal study ME96029 by the International Working Group for Chronic Lymphocytic Leukemia (IWCLL) and the National Cancer Institute (NCI) response criteria for B-CLL. Two scenarios were considered by the sponsor while documenting the response rates: the best case scenario considered responders to be patients who were classified as complete or partial remissions at the end of treatment visit (after 6 months of treatment or after the patient withdrew from the study); the worst case scenario considered responders to be patients who were classified as complete or partial remissions at the end of treatment visit AND did not withdraw from the study prior to treatment completion.

The best case scenario gives an overall response rate (CR+PR) of 46.2% with a 95% confidence interval 34.8% to 57.8% based on the IWCLL criteria, and an overall response rate of 51.3% with a 95% confidence interval 39.7% to 62.8% based on the NCI criteria.

The worst case scenario gives an overall response rate of 34.6% (95% CI: 24.2% to 46.2%) and 41.0% (95% CI: 30.0% to 52.8%) based on the IWCLL criteria and the NCI criteria respectively.

There was no follow-up of patients after completion of study and information about duration of response or survival could not be obtained.

Table 1: Response Rates – Study ME96029

	Response Rates ITT population (N = 78)	95% CI	p-value[1]
IWCLL criteria – best case, n (%)			
CR+PR	36 (46.2)	34.8% - 57.8%	p=0.91
CR	16 (20.5)		
PR	20 (25.6)		
SD	24 (30.8)		
PD	11 (14.1)		
NCI criteria – best case, n (%)			
CR+PR	40 (51.3)	39.7% - 62.8%	p=0.31
CR	14 (17.9)		
PR	26 (33.3)		
SD	19 (24.4)		
PD	12 (15.4)		
IWCLL criteria – worst case[2], n (%)			
Treatment success (CR+PR)	27 (34.6)	24.2% - 46.2%	p=0.07
CR	15 (19.2)		
PR	12 (15.4)		
Treatment failure	51 (65.4)		
NCI criteria – worst case[2], n (%)			
Treatment success	32 (41.0)	30.0% - 52.8%	p=0.50
CR	14 (17.9)		
PR	18 (23.1)		
Treatment failure	46 (59.0)		

ITT = intent-to-treat; CI = confidence interval; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; NCI = National Cancer Institute; CR = complete remission; PR = partial remission; SD = stable disease; PD = progressive disease.

[1] p-value using the Fisher's exact test for test of null hypothesis that the response rates are equal to 45% (historical control)

[2] All patients achieving CR or PR who did not withdraw prematurely from the study were classified as treatment successes, and all other patients including those who withdrew prematurely from the study (regardless of their response) were classified as treatment failures.

2. INTRODUCTION

2.1 Overview

B-cell chronic lymphocytic leukemia (B-CLL) is an incurable chronic lymphoproliferative malignancy, and is the most common leukemia in adults in the Western world (North America, Europe, and Australasia). It affects twice as many men as women, with the peak incidence between 60 and 70 years of age. Clinical stage as defined by Rai or Binet is the most important prognostic factor. In the end stages of the disease, the disease progresses rapidly and patients will require immediate treatment. Efficacy evaluation of response to B-CLL treatment is usually based on both the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) and the National Cancer Institute (NCI) response criteria, with the NCI criteria differs from the IWCLL criteria by not allowing focal infiltrates or nodules in the bone marrow for a complete response (CR) and by recommending validation of the relevance of stage shift for a partial response (PR).

Prior to discovery of purine analogues including fludarabine phosphate in 1980s, initial therapy for B-CLL patients consisted of low-dose chlorambucil with or without prednisone, and therapies for patients who did not respond or who relapsed after initial response to chlorambucil were combination regimens containing alkalating agents and often anthracyclines.

2.1.1 Background

The primary action of fludarabine phosphate is inhibition of DNA synthesis and replication, which results in an irreversible inhibition of cell division, manifested in a time-dependent reduction of clonogenic potential, resulting in programmed cell death of cancer cell lines.

IV fludarabine phosphate (Fludara) was approved in 1991 under NDA # 20-038 for the indication as a treatment of patients with B-CLL who have not responded or have progressed during treatment with at least one standard alkylating agent containing regimen. Such approval was based on results from two single-arm studies in previously treated CLL patients showing an overall response rate of 48% (23/48 patients) with median response duration of 91 weeks in a study by the M. D. Anderson Cancer Center (the MDAH study), and an overall response rate of 32% (10/31 patients) with median response duration of 65 weeks in a study by Southwestern Oncology Group (the SWOG study).

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Reviewer Comment: IV Fludara had an advisory committee meeting on September 11 of 1990. The committee members voted 8 to 0 for recommendation of approval. This recommendation was based on the impressive CR rate of 13% for an overall response rate of 41%, and a very impressive duration of these responses for the heavily pretreated patients enrolled in the MDAH and SWOG studies. The observed hematologic changes in participated patients who were anemic or thrombocytopenic prior to therapy were also thought to be clinically significant. In addition, it was agreed that appropriate historical controls were difficult to come up, and each patient could represent his own control in the refractory setting.

2.1.2 Clinical Studies

This NDA contains data from one pivotal study ME96029 and additional data from supportive studies B820 and CLL4.

Study ME96029, which was conducted in Europe and Canada, was a single-arm study in 81 B-CLL patients who had failed to respond or who showed signs of disease progression during or after previous treatment with at least one standard alkylating agent containing regimen. Patients were to receive oral fludarabine phosphate 40 mg/m^2 daily, 5 days every 4 weeks, for six four-week cycles or up to eight cycles if they responded to treatment but had not achieved a complete response after the sixth treatment cycle. Patients who did not respond or showed clinical signs of disease progression after two cycles of treatment were withdrawn from the study. The study was planned to recruit 80 patients to detect an unfavorable efficacy profile with a point estimate of the response rate (CR+PR) that was statistically significant lower than 45%. Among 81 recruited patients, 78 received oral Fludara treatment and were used for assessment of treatment efficacy and safety.

Study B820 was a single-arm European study with oral Fludara administrated to 81 previously-untreated B-CLL patients. Patients were to receive oral fludarabine phosphate 40 mg/m^2 daily for 5 days every 4 weeks up to six cycles or up to eight cycles of treatment if they responded to treatment but had not achieved a complete response after the sixth treatment cycle. Patients who did not respond or showed clinical signs of disease progression after two cycles of treatment were withdrawn from the study and considered treatment failures. The sample size was calculated to determine whether the response rate equaled a pre-specified value, 70%, which was the overall response rate of patients receiving IV fludarabine as first-line treatment for B-CLL in the European [redacted] 101 study. The study protocol was amended on 22 Feb 2002, [redacted] to have patients followed up for measurements on duration of response and time to progression. b(4)

Study CLL4 was an open-label study conducted by the UK Leukemia Research Foundation. Previously-untreated B-CLL patients were randomly assigned at a 1:1:2 ratio to fludarabine phosphate alone, fludarabine phosphate plus cycleophosphamide, or chlorambucil. Oral fludarabine was allowed after it became available part way through the study in 2001. The study was powered for difference in 5-year survival rate between chlorambucil group and the groups containing fludarabine phosphate combined.

2.1.3 Major Statistical Issues

1. Response rate form a single-arm pivotal study without measurement on duration of response is not adequate for providing conclusive evidence for clinical activity.
2. Additional data from supportive studies B820 and CLL4 in previously untreated B-CLL patients are not adequate to support an approval for the oral Fludara in 2nd line CLL. Duration of response and time to progression measured in Study B820 are difficult to interpret in the absence of randomization. Any comparison between IV and oral Fludara in Study CLL4 can only be viewed as exploratory because the patients were not randomly assigned with respect to route of formulation.

2.2 Data Sources

Data used for this review are located on network with path
\\FDSWA150\NONECTD\N22273\N_000\2007-12-20

Data on Study CLL4 were received via email on March 10, 2008

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The NDA is comprised of one pivotal study in previously treated B-CLL patients, with additional data from supportive studies in previously untreated B-CLL patients.

3.1.1 Pivotal Study ME96029

3.1.1.1 Study Objectives

To assess the overall response rate (complete remission and partial remission) and the toxicity profile of orally administrated fludarabine phosphate in previously treated B-CLL patients.

3.1.1.2 Study Design

This trial was designed as a prospective, multi-center, single-arm study with fludarabine phosphate tablets given orally to previously treated B-CLL patients. B-CLL patients must be age 18 years or older, have WHO performance status grade ≤ 2 and a life expectance of greater than 6 months, and have failed to respond to or showed signs of disease progression during or after treatment with at least one standard alkylating agent containing regiment which did not contain either anthracycline or mitozantrone in order to participate in this study.

Each patient was to receive up to 6 cycles of treatment each consisting of five days with 40 mg/m^2 of fludarabine phosphate daily. Each treatment cycle was given at 4-week intervals. Patients who did not respond after 2 cycles of treatment, or who showed signs of disease progression after this time were withdrawn from the study (two cycles of treatment were considered as the minimum time required before an evaluation of treatment failure could be made). The treatment could be stopped early if a patient had achieved a complete remission after fewer than 6 cycles. Patients who responded to treatment but had not achieved a complete remission after the 6^{th} treatment cycle were allowed to continue treatment for up to 8 cycles after consulting with the study manager. Supportive therapy was allowed with the treating physician's clinical judgement.

Extent of disease (based on Binet and Rai staging systems as described in APPENDIX I) was assessed at baseline, at the end of 2^{nd} to 6^{th} treatment cycle, and after the end of treatment. Evaluation of response to treatment was assessed 3 to 5 weeks after the end of treatment based on the International Working Group for Chronic Lymphocytic Leukemia and the National Cancer Institute response criteria for B-CLL (the IWCLL and the NCI response criteria as described in APPENDIX II). Safety data were collected during the entire treatment period.

3.1.1.3 Efficacy Endpoints

The main efficacy variable in this study was overall response rate to treatment, defined as the percentage of treated patients with either a complete remission (CR) or a partial remission (PR).

In order to assess response to treatment, each patient's disease stage at baseline was compared with the disease stage determined at the end of treatment (EOT) visit after 6 months of treatment or after the patient withdrew from the study. Patients' responses were then evaluated by each investigator based on both the IWCLL and NCI criteria for B-CLL patients (see APPENDIX II). The IWCLL criteria are based on the Binet staging system whereas the NCI response criteria are based on specific values of clinical parameters. Both systems use the same terminology to describe response (complete remission, partial remission, stable disease, and progressive disease).

Two scenarios were used for classifying responders. The best case scenario had patients who were classified as complete or partial remissions at EOT visit regarded as responders. The worst case scenario had patients who were classified as complete or partial remissions at EOT visit and did not withdraw before treatment completion regarded as responders.

Reviewer Comments:

1. In 1988, the National Cancer Institute-sponsored Working Group (NCI-WG) on CLL published guidelines on diagnosis and response criteria in CLL primarily designed for the conduct of clinical trials. A year later, the International Working Group on CLL (IWCLL) published general practice recommendations for CLL. In 1996, the original NCI guidelines were revised by Cheson et al.[1] to require ≥ 2 months of duration of CR or PR as part of response criteria. The NCI criteria used for this study are the 1988 guidelines, which do not require a response confirmation as the revised guidelines do.
2. There was no follow-up once the patients achieved response. Duration of response in responders could not be determined in this study.
3. Responders by the worst case scenario are a subset of the responders by the best case scenario. A patient could withdraw from the study before treatment completion for reasons including non-responsive after 2 cycles of treatment, disease progression, unacceptable toxicity, and refusal to continue treatment. The worst case was used by the sponsor as a sensitivity analysis for missing data.
4. The IV Fludara label presented results based on the 1988 NCI response criteria.

[1] Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, Rai KR "National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment" Blood. 1996 Jun 15;87(12):4990-7.

3.1.1.4 Statistical Methods and Sample Size Justification

Per Protocol:
'The only endpoint to be analyzed is response. Since this is a binary endpoint, a simple chi square test will be used.'

'The testing problem is:
Ho: Response rate under oral fludarbine equals 45%
Versus
H1: Response rate under oral Fludarabine phosphate differs from 45%.
The level of significance was α= 0.05'

'The primary analysis will be done on an intent to treat basis. '

'Sample size calculation:
With 60 patients, one is able to detect a decrease in response rates (in comparison to the historical control of 45%) under oral Fludarabine to 25% with a probability of 90%. To increase the power of the study it was decided to enroll 80 patients. With this number of patients, one is able to detect a decrease in response rates under oral fludarabine phosphate to 25% with a probability of 96%.'

'Historical Control: 45% response was the rate that was observed in th[redacted]101 study comparing the response to treatment with CAP versus fludarabine phosphate in previously treated patients with B-CLL. ' b(4)

Reviewer Comment: The study was designed to compare the response rate under oral Fludara to the response rate previously observed under IV Fludara in study [redacted]101. With 78 oral Fludara treated patients in this study, an overall response rate lower than 34% will be declared as statistically significantly worse than the pre-specified rate of 45%. b(4)

3.1.1.5 Analysis Populations

The Intent-to-Treat (ITT) population is consisted of the treated patients, and is the analysis population for efficacy and safety evaluations.

3.1.1.6 Efficacy Results and Conclusions

3.1.1.6.1 Disposition of Efficacy Analysis Populations

A total of 81 patients were enrolled in Study ME96029. Three patients did not receive study medication due to withdrawal of consent (n=2) and protocol violation (no B-CLL, n=1). Therefore, the ITT population has 78 patients.

Thirty-five (35) patients discontinued their treatment due to adverse events (n=25), lack of efficacy (n=8), or withdrawal of consent (n=2).

3.1.1.6.2 Demographics and Other Baseline Characteristics

Of the 78 B-CLL patients in the ITT population, 77 were Caucasian and 1 was Asian. The patient population consisted of 56 males and 22 females with a mean age of 63.4 years (range: 55.0 to 71.8 years). The patients were recruited from 29 centers in Europe and Canada.

Staging at baseline according to the Binet system showed that 23, 24, and 31 patients were stages A, B, and C respectively. According to the Rai disease staging system, there were 3, 16, 25, 9, and 25 patients in stages 0, I, II, III, and IV respectively at baseline. The assessment of WHO performance status at baseline revealed that 54 patients had status 0, 21 patients had status 1, and 3 patients had status 2.

All patients were previously treated for the underlying hematological illness with cytotoxic drugs. Each patient had a mean of 2 prior treatment regimens.

Fifty-two patients underwent bone marrow aspirate analysis at baseline, 6 showed hypocellularity, and 23 showed hypercellularity. Bone marrow biopsies were performed at baseline for 37 of these 52 patients, all except 2 patients showed abnormal cellular architecture whereas 19 patients showed hypercelluarity and 7 patients showed hypocellularity.

3.1.1.6.3 Efficacy Results

Response rates

Response to treatment (achievement of a complete or partial remission after treatment) was determined after comparing the results of restaging at the "end of treatment' examination to the disease stage determined at baseline according to either the IWCLL or the NCI criteria. In one scenario, the responders included all patients who responded (called the "best case" scenario by the sponsor). In the other scenario, all responders who withdrew early were considered as treatment failures like the non-responders.

Table 2 displays the response rates for all 78 intent-to-treat patients by IWCLL and NCI criteria, and by the best and the worst case scenarios. The best case scenario gave the overall response rate and complete remission rate of 46.2% and 20.5% based on the IWCLL criteria, and 51.3% and 17.9% based on the NCI criteria. The worst case scenario removed 9 responders to an overall response rate of 34.6%, and removed 8 responders to an overall response rate of 41.0% according to the IWCLL and NCI criteria, respectively. The majority of the responders removed in the worst case scenario had a partial remission. The worst case scenario was considered by the sponsor as a sensitivity analysis for missing data.

The p-values for test of null hypothesis that the response rates are equal to 45% were greater than 0.05.

Table 2: Response Rates – Study ME96029

	Response Rates ITT population (N = 78)	95% CI	p-value[1]
IWCLL criteria – best case, n (%)			
CR+PR	36 (46.2)	34.8% - 57.8%	p=0.91
CR	16 (20.5)		
PR	20 (25.6)		
SD	24 (30.8)		
PD	11 (14.1)		
NCI criteria – best case, n (%)			
CR+PR	40 (51.3)	39.7% - 62.8%	p=0.31
CR	14 (17.9)		
PR	26 (33.3)		
SD	19 (24.4)		
PD	12 (15.4)		
IWCLL criteria – worst case[2], n (%)			
Treatment success (CR+PR)	27 (34.6)	24.2% - 46.2%	p=0.07
CR	15 (19.2)		
PR	12 (15.4)		
Treatment failure	51 (65.4)		
NCI criteria – worst case[2], n (%)			
Treatment success	32 (41.0)	30.0% - 52.8%	p=0.50
CR	14 (17.9)		
PR	18 (23.1)		
Treatment failure	46 (59.0)		

ITT = intent-to-treat; CI = confidence interval; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; NCI = National Cancer Institute; CR = complete remission; PR = partial remission; SD = stable disease; PD = progressive disease.

[1] p-value using the Fisher's exact test for test of null hypothesis that the response rates are equal to 45% (historical control)

[2] All patients achieving CR or PR who did not withdraw prematurely from the study were classified as treatment successes, and all other patients including those who withdrew prematurely from the study (regardless of their response) were classified as treatment failures.

Reviewer Comments:

1. In the review to the original NDA, the clinical reviewer Dr. Amna Ibrahim found that responses for 10 patients should be downgraded from CR to PR because the response criteria were not exactly matched for these patients.
2. The objective response rate was compared to the one observed under IV Fludara in study ——— I01, instead of being compared to the MDAH and SWOG studies which the IV Fludara were approved upon. b(4)
3. Cross-study comparisons between oral and IV Fludara for efficacy may not be adequate because of differences in dose, treatment duration, and use of supportive therapy between the studies.

4. The study report had provided in-correct p-values for test of null hypothesis that the response rates are equal to 45%. A query was sent to the sponsor on May 23 of 2008. The sponsor made corrections to the p-values in their response. All p-values remained to be > 0.05.

Follow-up Duration

This reviewer calculated the individual follow-up duration as time from baseline to the follow-up visit (see APPENDIX III for listing of calculated follow-up duration). The summary statistics on follow-up duration are listed below for the ITT population, and for the responders only. The average follow-up duration was similar between the all treated patients and patients who responded, with the patients who achieved a complete remission had a longer follow-up time on average.

Table 3: Summary Statistics on Follow-up Duration – Study ME96029

Group	Follow-up Duration (week)					
	N	Median	Mean	Std Dev	Min	Max
ITT pop.	78	27.1	26.1	9.2	5.9	43.6
IWCLL – CR+PR	36	28.2	29.4	7.6	11.6	43.6
IWCLL – CR	16	29.1	30.1	5.4	21.1	39.1
IWCLL – PR	20	27.6	28.8	9.0	11.6	43.6
NCI – CR+PR	40	29.1	30.2	6.8	12.3	43.6
NCI – CR	14	29.3	31.2	4.8	24.1	39.1
NCI – PR	26	28.1	29.7	7.7	12.3	43.6

ITT = intent-to-treat; IWCLL = International Working Group for Chronic Lymphocytic Leukemia; NCI = National Cancer Institute; CR = complete remission; PR = partial remission ; Std Dev = standard deviation ; Min = minimum ; Max = maximum.

Reviewer Comment: The prolonged duration of response served as a basis of approval for IV Fludara (median response duration: 91 weeks seen in the MDAH study, and 65 weeks observed in the SWOG study). The amount of follow-up in study ME96029 is not sufficient for comparing oral and IV Fludara in terms of durability of responses.

Changes in hemoglobin and platelet count

IV Fludara was approved on the basis of an impressive response rate and response duration, and also the improvement in hemoglobin and platelet count. The IV Fludara label stated that mean hemoglobin concentration improved from 9.0 g/dL at baseline to 11.8 g/dL at the time of response for the subgroup of responders (NCI criteria) who were anemic at baseline (hemoglobin < 10.5 g/dL, n=14). It also stated that average platelet count improved from 63,500/mm^3 to 103,300/mm^3 at the time of response for the subgroup of responders who were thrombocytopenic

at baseline (platelet count < 100,000/mm^3, n=12). These statements were mentioned in the label as added clinical benefits.

To evaluate oral Fludara in a manner comparable to IV Fludara, mean hemoglobin concentrations at baseline and end of treatment assessments are calculated in the NCI responders with baseline hemoglobin < 10.5 g/dL, and average platelet counts at baseline and end of treatment visits are calculated in the NCI responders with baseline platelets less than 100,000/ mm^3.

Results of changes in hemoglobin and platelet count for the selected groups are displayed in Table 4. The improvements in hemoglobin and platelet count are similar to those seen with the IV Fludara.

Table 4: Change in Hemoglobin and Platelet Count for Selected Groups – Study ME96029

Parameter	Group	N	Baseline[2] mean	EOT[3] mean	Change since baseline[4]	
					Mean	SD
Hemoglobin (g/dL)	NCI responders[1] with hemoglobin <10.5 g/dL	7	9.5	11.6	2.1	1.9
Platelet count (1000/mm^3)	NCI responders[1] with platelets < 100,000/mm^3	7	67.4	107.0	39.6	27.9

[1] NCI responders = Patients achieved a CR or PR response according to NCI criteria
[2] Baseline for assessment at the baseline visit
[3] EOT for assessment at the end of treatment visit
[4] Change since baseline calculated for each patient in the group

Reviewer Comment: Study ME96029 was not designed to examine efficacy with respect to improvements in hemoglobin and platelet counts. The post hoc analyses of hemoglobin and platelet counts should be viewed as exploratory.

3.1.2 Supportive Studies

3.1.2.1 Overview

Study B820

Study B820 was a single-arm European study with oral Fludara administrated to 81 previously-untreated B-CLL patients. Patients were to receive oral fludarabine phosphate 40 mg/m^2 daily for 5 days every 4 weeks up to six cycles or up to eight cycles of treatment if they responded to treatment but had not achieved a complete response after the sixth treatment cycle. Patients who did not respond or showed clinical signs of disease progression after two cycles of treatment

were withdrawn from the study and considered treatment failures. The sample size was calculated to determine whether the response rate equaled a pre-specified value, 70%, which was the overall response rate of patients receiving IV fludarabine as first-line treatment for B-CLL in the Europear ——— 101 study. The study protocol was amended on 22 Feb 2002. ——— ——————— , to have patients followed up for measurements on duration of response and time to progression.

b(4)

Study CLL4

Study CLL4 was an open-label study conducted by the UK Leukemia Research Foundation. Previously-untreated B-CLL patients were randomly assigned at a 1:1:2 ratio to fludarabine phosphate alone, fludarabine phosphate plus cycleophosphamide, or chlorambucil. Oral fludarabine was allowed after it became available part way through the study in 2001. The study was powered for difference in 5-year survival rate between chlorambucil group and the groups containing fludarabine phosphate combined.

3.1.2.2 Efficacy Results

Study B820

Study B820 efficacy results of response rate, duration of response (DOR), and time to progression (TTP) according to the NCI response criteria as of data cut-off date 23 November 2004 are presented below.

The observed overall response rate in the 81 treated patients was 80.2% (95% CI: 69.9% - 88.3%), with 12.3% of complete remission rate.

Duration of response data were collected in the follow-up period and were available from 61 of the 65 responders. Forty or 65.6% of the 61 patients had a documented progressive disease (PD) and did not receive subsequent therapy prior to their documented PD. Median response duration was 643 days (92 weeks).

Time to progression data were also collected in the follow-up period and were available from 74 patients. Fifty-one or 68.9% of the 74 patients had a documented progressive disease (PD) and did not receive subsequent therapy prior to their documented PD. Median time to progression was 739 days (106 weeks).

Table 5: Efficacy Results* of Response Rates, Duration of Response, and TTP – Study B820

Endpoint	Type of event	# Event: n / N (%)	Summary Statistics for Time to Event Endpoint				
			Median	Mean	Std Dev	Min	Max
Response Rate	CR+PR	65 / 81 (80.2%)					
	CR	10 / 81 (12.3%)					
	PR	55 /81 (67.9%)					
DOR (day)	PD	40 / 61 (65.6%)	643	626	330	1	1394
TTP (day)	PD	51 / 74 (68.9%)	739	729	393	28	1562

NCI = National Cancer Institute; CR = complete remission; PR = partial remission; DOR = duration of response; TTP = time to progression; PD = progressive disease; Std Dev = standard deviation; Min = minimum; Max = maximum

*Response to treatment classified according to the NCI criteria; Data cut-off date: 23 Nov. 2004

Study CLL4

Table 6 presents the results of overall response and duration of response for IV and oral Fludara. This study used modified NCI criteria for response classification, with partial response further divided into nodular partial response and regular partial response. Higher overall response rates were observed for IV Fludara, but longer median response durations were documented for oral Fludara.

Table 6: Overall Response and Duration of Response for IV and oral Fludara – Study CLL4

Study Population	N	Overall Response[1] n (%)	Duration of response[2] (days)					
			# of event[3]	Median	Mean	Std. Dev.	Min	Max
F_{IV}	57	51 (89.5%)	40	701	724	542	16	2580
F_{oral}	124	88 (70.9%)	58	779	644	352	126	1505
$F_{IV}C$	58	55 (94.8%)	32	1266	990	553	97	2066
$F_{oral}C$	129	108 (83.7%)	39	1810	827	424	152	1926
All F_{IV}	115	106 (92.2%)	72	980	842	559	16	2580
All F_{oral}	253	196 (77.5%)	97	1187	718	391	126	1926

F_{IV}: patients treated with IV Fludara monotherapy; F_{oral}: patients treated with oral Fludara monotherapy; $F_{IV}C$: patients treated with IV Fludara and cyclophosphamide; $F_{oral}C$: patients treated with oral Fludara and cyclophosphamide; All F_{IV}: all patients treated with IV Fludara; All F_{oral}: all patients treated with oral Fludara.

[1] Overall response = complete response (CR) + nodular partial response (nPR) + partial response (PR)

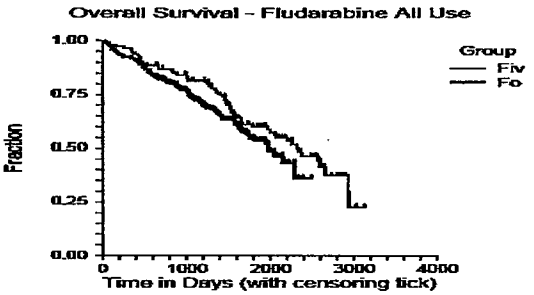
[2] Duration of response calculated in patients who achieved CR, nPR, or PR as duration from the date of best response to the date of disease progression. Responders without progression prior to death or further treatment had their duration of response censored at the last date know alive without progression, the date of death, or the date of further treatment.

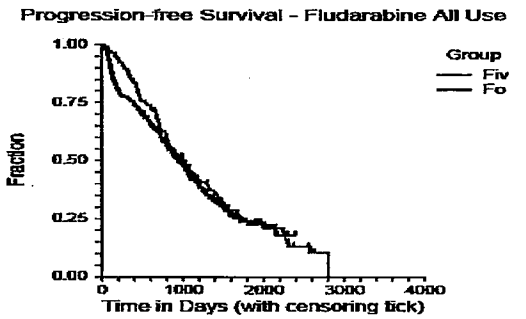
[3] Event = disease progression

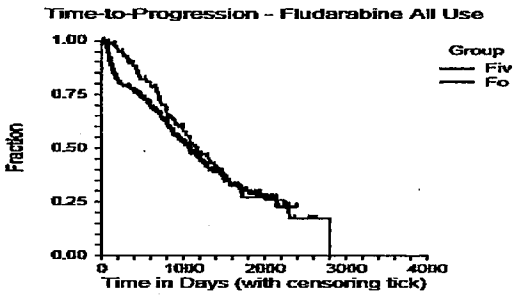
Table 7 shows median and overall distribution by route of Fludara administration (IV or oral) for time to event endpoints including overall survival, progression-free survival, and time to progression. IV Fludara had longer median times, with similar time to event distribution to oral Fludara in general.

Table 7: Time to Event Analyses for IV and Oral Fludara – Study CLL4

OVERALL SURVIVAL			
Study Population	**N**	**# of events**	**Median (days)**
F_{IV}	57	28 (49.1%)	2569
F_{oral}	124	52 (41.9%)	1937
$F_{IV}C$	58	29 (50.0%)	2061
$F_{oral}C$	129	47 (36.4%)	2140
All F_{IV}	115	57 (49.6%)	2324
All F_{oral}	253	99 (39.1%)	1976
PROGRESSION-FREE SURVIVAL			
Study Population	**N**	**# of events**	**Median (days)**
F_{IV}	57	51 (89.5%)	786
F_{oral}	124	100 (80.6%)	657
$F_{IV}C$	58	43 (74.1%)	1320
$F_{oral}C$	129	75 (58.1%)	1196
All F_{IV}	115	94 (81.7%)	990
All F_{oral}	253	175 (69.2%)	928
TIME TO PROGRESSION			
Study Population	**N**	**# of events**	**Median (days)**
F_{IV}	57	45 (78.9%)	797
F_{oral}	124	93 (75.0%)	708
$F_{IV}C$	58	33 (56.9%)	1454
$F_{oral}C$	129	56 (43.4%)	1548
All F_{IV}	115	78 (67.8%)	1169
All F_{oral}	253	149 (58.9%)	1060







Reviewer Comments:

1. Time to event endpoints from the single-arm study B820 cannot be interpreted.
2. Comparisons between IV and oral Fludara in Study CLL4 cannot be interpreted in the absence of randomization.

3.1.3 Conclusions for Efficacy

In this reviewer's opinion, the design and efficacy results from the pivotal study ME96029 are not sufficient for demonstrating clinical benefit of oral Fludara as a therapy to previously-treated B-CLL patients. Although good response rates were observed, data on duration of response or survival were not obtained.

Furthermore, data from supportive studies B820 and CLL4 in previously untreated B-CLL patients are not adequate to support an approval for the oral Fludara in 2nd line CLL. Duration of response and time to progression collected in the single-arm study B820 are difficult to quantify in the absence of a control group, and any comparison between IV and oral Fludara in Study CLL4 can only be viewed as exploratory because the Fludara treated patients did not receive IV or oral Fludara according to randomization.

3.2 Evaluation of Safety

Please refer to Clinical Evaluations of this application for safety results and conclusions.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 6 displays results of response rates based on NCI criteria-best case by sex and age. Males had a higher overall response rate, a higher complete remission rate, and a lower partial remission rate compared to female patients. Younger patients had a better response to treatment compared with patients older than 65 years of age.

Response rates are not tabulated by race because 77 of the 78 treated patients have the same race (Caucasian).

Table 8: Response to Treatment by Sex and Age – Study ME96029

Factor	Group	N	Response to Treatment, n (%)		
			CR+PR	CR	PR
Sex	Male	56	31 (55.4%)	13 (23.2%)	18 (32.1%)
	Female	22	9 (40.9%)	1 (4.5%)	8 (36.4%)
Age	≤ 65 years	42	24 (57.1%)	8 (19.0%)	16 (38.1%)
	> 65 years	36	16 (44.4%)	6 (16.7%)	10 (27.8%)

CR = complete remission; PR = partial remission

4.2 Other Special/Subgroup Populations

Table 7 displays results of response rates based on NCI criteria-best case by region and disease stage at baseline. Patients treated in Europe had a comparable overall response rate with patients treated in Canada. Patients who had an aggressive disease at baseline (Binet Stage C, or Rai Stage III/IV) did not respond to treatment as well as patients who entered the study with a better disease status.

Table 9: Response to Treatment by Region, and Disease Stage Systems – Study ME96029

Factor	Group	N	Response to Treatment, n (%)		
			CR+PR	CR	PR
Region	Europe	69	27 (39.1%)	14 (20.3%)	23 (33.3%)
	Canada	9	3 (33.3%)	0 (0.0%)	3 (33.3%)
Binet Stage	A	23	15 (65.2%)	7 (30.4%)	8 (34.8%)
	B	24	15 (62.5%)	6 (25.0%)	9 (37.5%)
	C	31	10 (32.3%)	1 (3.2%)	9 (29.0%)
Rai Stage	0	3	2 (66.7%)	2 (66.7%)	0 (0.0%)
	I	16	12 (75.0%)	4 (25.0%)	8 (50.0%)
	II	25	16 (64.0%)	7 (28.0%)	9 (36.0%)
	III	9	3 (33.3%)	1 (11.1%)	2 (22.2%)
	IV	25	7 (28.0%)	0 (0.0%)	7 (28.0%)

CR = complete remission; PR = partial remission

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

1. Response rate form a single-arm pivotal study without measurement on duration of response is not adequate for providing conclusive evidence for clinical activity.
2. Additional data from supportive studies B820 and CLL4 in previously untreated B-CLL patients are not adequate to support an approval for the oral Fludara in 2nd line CLL. Duration of response and time to progression measured in Study B820 are difficult to interpret in the absence of randomization. Any comparison between IV and oral Fludara in Study CLL4 can only be viewed as exploratory because the patients were not randomly assigned with respect to route of formulation.

5.2 Conclusions and Recommendations

In this reviewer's opinion, the efficacy results from the pivotal study ME96029 have not provided a substantial evidence from a statistical perspective to support oral Fludara for the proposed indication. Although the observed overall response rate of 51% based on the National Cancer Institute Criteria for B-CLL may seem to be comparable to the ones seen with the IV Fludara (48% in the study by M. D. Anderson Cancer Center, and 32% in the study by Southwestern Oncology Group), cross-study comparisons may not be adequate considering the differences in dose, treatment duration, and use of supportive therapy between the studies. In addition, there was no follow-up of patients after completion of study and information about duration of response or survival could not be obtained.

Furthermore, data from supportive studies B820 and CLL4 in previously untreated B-CLL patients are not adequate to support an approval for the oral Fludara in 2nd line CLL. Duration of response and time to progression collected in the single-arm study B820 are difficult to quantify in the absence of a control group, and any comparison between IV and oral Fludara in Study CLL4 can only be viewed as exploratory because the Fludara treated patients did not receive IV or oral Fludara according to randomization.

A study in the targeted patient population with patients randomized to either an oral or an IV formulation will be necessary if oral Fludara is to be considered for approval based on efficacy comparability between the two formulations.

APPENDIX I: Disease Staging Systems for CLL

Table 10: Binet Staging System for CLL

Stage	Clinical Features
A	Hemoglobin ≥ 10 g/dL, platelets ≥ 100 x 10^9/L, and < three areas of lymph nodes involved*
B	Hemoglobin ≥ 10 g/dL, platelets ≥ 100 x 10^9/L, and ≥ three areas of lymph nodes involved
C	Hemoglobin < 10 g/dL, platelets < 100 x 10^9/L, or both (independently of the areas of lymph nodes involved)

*The three areas include the cervical, axillary and inguinal lymph nodes (whether unilateral or bilateral), the spleen and the liver.

Table 11: Rai Staging System for CLL

Stage	Clinical Features
0	Lymphocytosis in blood and bone marrow only
I	Lymphocytosis and enlarged lymph nodes
II	Lymphocytosis plus hepatomegaly or splenomegaly or both
III	Lymphocytosis and anemia (hemoglobin < 11 g/dL)
IV	Lymphocytosis and thrombocytopenia (platelets < 100 x 10^9/L)

APPENDIX II: Response Criteria for B-CLL

Table 12: IWCLL Criteria for Response in B-CLL

Response	Criteria
Complete remission	No evidence of disease*
Partial remission	Change from stage** C disease to stage A or B, or from stage B to A
Stable disease	No change in stage of disease
Progressive disease	Change from stage A disease to B or C, or from B to C

*Absence of lymph nodes/hepato-splenomegaly and bone marrow aspirate < 30% lymphocytes
** Stage refers to Binet staging system (see APPENDIX I)

Table 13: NCI Criteria for Response in B-CLL

Response	Criteria
Complete remission	Absence of lymphadenopathy, hepatomegaly, splenomegaly or constitutional symptoms. Normal blood count: neutrophils > 1.5 x 10^9/L, platelets > 100 x 10^9/L, Hb > 11 g/dL, lymphocytes < 4.0 x 10^9/L. BM biopsy normal cellularity, lymphocytosis < 30%.
Partial remission	50% reduction in blood lymphocytes and 50% reduction in lymphadenopathy and/or 50% reduction in hepatomegaly and/or splenomegaly. Neutrophils > 1.5 x 10^9/L or 50% improvement over baseline, platelets > 1 00 x 10^9/L or 50% improvement over baseline, Hb > 11 g/dL (not supported by transfusion) or 50% improvement over baseline.
Stable disease	No change in stage of disease
Progressive disease	At least one of the following: > 50% increase in the size of at least two lymph nodes or new palpable lymph nodes; > 50% increase of splenomegaly or hepatomegaly or appearance if there were not present; transformation to a more aggressive histology (Richter or prolymphocytic leukemia), > 50% increase in the absolute number of circulating lymphocytes.

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