CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-273

MEDICAL REVIEW

Application Type	NDA 22-273
Submission Number	001
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Reviewer Name	Martin H. Cohen, M.D.
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Established Name	Oral Fludarabine Phosphate
Trade Name	Fludara
Therapeutic Class	Antimetabolite
Sponsor	Xanthus Pharmaceuticals
Priority Designation	S

Formulation

10 mg tablets - Film-coated tablets that are capsule shaped and salmon pink in color, marked on one side with 'LN' in a regular hexagon, 10

Dosing Regimen

The recommended adult dose of fludarabine is 40 mg/m2 administered daily for five days. Each 5-day course of treatment should commence every 28 days, Dosage may be decreased or delayed based on evidence of hematologic or nonhematologic toxicity, Physicians should consider delaying or discontinuing the drug if neurotoxicity occurs, Fludarabine tablets can be taken either on an empty stomach or with food, The tablets have to be swallowed whole with water; they should not be chewed or broken,

With renal impairment reduce dose by 20% in adult patients with moderate renal mpairment (creatinine clearance 30 to 70 mL/min/1.73 m2). Fludarabine should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m2).

Indication

Fludarabine is indicated for the 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.

Intended Population

See indication.

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1.0 EXECUTIVE SUMMARY

The purpose of this review is to evaluate fludarabine phosphate tablets for oral use for the proposed indication: "Fludarabine is indicated for the 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".

One phase 2 study was performed in patients with CLL **refractory to at least one prior standard alkylating-agent containing regimen.** Study ME96029 enrolled 78 patients who received oral fludarabine at a dose of 40 mg/m^2 daily for 5 days every 28 days. The overall objective response, according to NCI criteria, was 51%, including 18% complete responses (CR) and 33% partial responses (PR). The overall response rate, according to IWCLL criteria, was 46%, including 21% CRs, best case analysis (all patients who responded to treatment were deemed a responder, regardless of when they discontinued treatment) and 41% NCI criteria (18% CR) and 35% IWCLL criteria (19% CR), worst case analysis (patients who were withdrawn from study were regarded as treatment failures unless the reason for withdrawal was achievement of CR. Duration of response and time to progression were not assessed in study ME96029. However, the mean number of treatment cycles for patients in study ME96029 was 5.1, with a mean daily dose of fludarabine of 38 mg/m^2/day which was slightly below the target dose of 40 mg/m^2/day. Since cycles were repeated at a minimum of every 28 days and since remissions often occurred after 1 cycle of treatment a minimum estimated remission duration is >16 weeks.

Two other studies, conducted in **previously-untreated B-CLL patients**, support the activity of oral fludarabine with respect to time dependent efficacy endpoints. Study 303080 included 81 patients treated with fludarabine 40 mg/m^2 PO daily for five days every four weeks. The remission rate was 80%, NCI criteria (12% CR) and 72% IWCLL criteria (37% CR), best case analysis and 69% NCI criteria and 61% IWCLL criteria, worst case analysis. Median duration of remission was 22.6 months and median time to treatment progression was 29.2 months.

Study LRF CLL4 (sponsor analysis after initial data submission) included 124 assessable non-randomized patients who received fludarabine 40 mg/m^2 PO daily for five days every four weeks and 57 non-randomized patients who received IV fludarabine. The overall response rate (CR +nPR + PR) was 90% for IV fludarabine and 71% for oral fludarabine. Median response duration was 779 days for oral fludarabine and 701 days for IV fludarabine. It is emphasized that these are non-randomized comparisons. Patients receiving oral fludarabine were enrolled when that drug became available and were older, with poorer performance status, more advanced disease, and lower platelet and hemoglobin levels.

These results were compared with efficacy data from three studies of IV fludarabine, 20+ mg/m^2 daily for five days every 28 days in previously treated CLL patients and two studies

of IV fludarabine in previously-untreated B-CLL patients, CALGB 9011, (175 patients) and CLL 101 ——— study (53 patients). b(4)

Efficacy data from two of the former studies, the subset of 48 refractory B-CLL patients from MDAH (T83-1275) and 32 refractory or relapsed B-CLL patients from SWOG [83-78]) were the basis of approval of the IV fludarabine formulation. The third study (CLL 101 ——— ,tudy) included 53 previously-treated B-CLL patients who received fludarabine 25 mg/m^2 IV daily for five days every four weeks. b(4)

The overall response rates in the pivotal study of oral fludarabine in relapsed or refractory patients with B-CLL (ME96029) were slightly better than the rates observed following treatment with IV fludarabine in the MDAH (T83-1275) study (48%, 13% CRs using NCI criteria, best case analysis and 23% (8% CR) using NCI criteria, worst case analysis) and in refractory or relapsed patients with B-CLL from the SWOG (83-78) study (32% using NCI criteria 13% CR), best case analysis and 19% using NCI criteria (13% CR), worst case analysis). When response was assessed using IWCLL response criteria and compared with results from the subset of previously-treated patients with B-CLL in Study CLL 101 ——— Study) using IWCLL criteria, the overall response rate in the pivotal study of oral fludarabine (ME96029) was lower than that observed with IV fludarabine (35% in ME96029), versus 45% in CLL 101 ——— Study. b(4)

The median duration of response in relapsed or refractory patients with B-CLL treated with IV fludarabine ranged from > 37 weeks(SWOG, 83-78) to > 41 weeks (MDAH, T83-1275), and median survival time ranged from 45 weeks (MDAH, T83-1275) to 54 weeks (SWOG, 83-78).

For studies in previously-untreated patients, the criteria used to assess response varied among the studies. The overall response rate seen in the study of oral fludarabine (303080) was as good as or better than the overall response rates seen in the studies of IV fludarabine, which ranged from 61% (CALGB criteria) to 70% (IWCLL criteria).

The median duration of response for previously-untreated patients ranged from 19 months following IV fludarabine (CALGB 9011) to 22.6 months following oral fludarabine (303080). Median time to progression ranged from 17.4 months following IV fludarabine (CALGB 9011) to 29.2 months following oral fludarabine (303080).

AE's associated with fludarabine treatment have been well described. The safety database of oral fludarabine phosphate provides data on 502 patients including 474 patients treated with oral fludarabine phosphate tablets. In addition to the 78 patients in the pivotal trial (Study ME96029) and 81 patients in Study 303080. 92 B-CLL, NHL and low grade NHL patients were treated with oral fludarabine phosphate monotherapy in pharmacokinetic studies, Additionally, limited safety data are available from Study LRF CLL4, where 122 B-CLL patients received oral fludarabine phosphate monotherapy Finally, post-marketing safety

surveillance data are available from over [redacted] patients treated with oral fludarabine phosphate in regions of the world where this formulation is approved. b(4)

Across all of these studies oral fludarabine phosphate therapy was generally well tolerated. The most commonly reported adverse events reported across all studies included myelosuppression, fever, cough, nausea, vomiting, diarrhea, asthenia, anorexia, and infections. These events were usually mild or moderate in severity with non-hematological Grade 3-4 events occurring in up to 8% of patients and hematological grade 3-4 toxicities occurring in up to 25% of patients. Adverse events and toxicities observed with oral fludarabine did not significantly differ from the adverse event profile of the IV formulation, with the exception of mild/moderate nausea, vomiting and diarrhea which seemed to occur at slightly higher rates in patients treated with oral formulation. Post-marketing experience in clinical practice with oral fludarabine over the past 6 years shows that, based on voluntary reported adverse drug reactions during the marketed period, the safety profile of oral fludarabine has not significantly changed from when oral fludarabine was initially approved in 2000 in the UK.

1.1 Recommendation On Regulatory Action

The clinical reviewer recommends that oral fludarabine phosphate tablets receive accelerated approval for the 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. Accelerated approval is based on the absence of remission duration data for the indicated patient population. Accelerated approval is supported by similar clinical outcomes including response rates, response duration, and progression free survival of intravenous and oral fludarabine treatment as well as a reasonable complete response (CR) rate of adequate duration in previously untreated CLL patients.

1.2 Recommendation On Post-marketing Actions

Not applicable

1.21 Risk Management Activity

Not applicable.

1.22 Required Phase 4 Commitments

A randomized trial comparing oral and intravenous fludara, with or without other agents, in the first-line CLL setting. The sponsor has proposed a study randomizing patients with progressive CLL to oral fludara or chlorambucil. This is acceptable.

1.23 Other Phase 4 Requests

None

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Overview of Clinical Program

One phase 2 study was performed in patients with CLL **refractory to at least one prior standard alkylating-agent containing regimen.** Study ME96029 enrolled 78 patients who received oral fludarabine at a dose of 40 mg/m^2 daily for 5 days every 28 days. The overall objective response (NCI criteria) was 51%, including 18% complete responses (CR) and 33% partial responses (PR). The overall response rate, according to IWCLL criteria, was 46%, including 21% CRs, best case analysis (all patients who responded to treatment were deemed a responder, regardless of when they discontinued treatment) and 41% NCI criteria (18% CR) and 35% IWCLL criteria (19% CR), worst case analysis (patients who were withdrawn from study were regarded as treatment failures unless the reason for withdrawal was achievement of CR. Duration of response and time to progression were not assessed. However, the mean number of treatment cycles for patients in study ME96029 was 5.1. Since cycles were repeated at a minimum of every 28 days and since remissions often occurred after 1 cycle of treatment a minimum estimated remission duration is >16 weeks.

Two other studies, conducted in **previously-untreated B-CLL patients,** support the activity of oral fludarabine with respect to time dependent efficacy endpoints. Study 303080 included 81 patients treated with fludarabine 40 mg/m^2 PO daily for five days every four weeks. The remission rate was 80%, NCI criteria (12% CR) and 72% IWCLL criteria (37% CR), best case analysis and 69% NCI criteria and 61% IWCLL criteria, worst case analysis. Median duration of remission was 22.6 months and median time to treatment progression was 29.2 months.

Study LRF CLL4 included 124 assessable non-randomized patients who received fludarabine 40 mg/m^2 PO daily for five days every four weeks and 57 non-randomized patients who, early in the study, received IV fludarabine . The overall response rate (CR +nPR + PR) was 90% for IV fludarabine and 71% for oral fludarabine. Median response duration was 779 days for oral fludarabine and 701 days for IV fludarabine. Again, it should be emphasized that these are non-randomized comparisons. Patients receiving oral fludarabine were enrolled when that drug became available and were older, with poorer performance status, more advanced disease, and lower platelet and hemoglobin levels.

These results were compared with efficacy data from three studies of IV fludarabine, 20+ mg/m^2 daily for five days every 28 days in previously treated CLL patients and two studies of IV fludarabine in previously-untreated B-CLL patients, CALGB 9011, (175 patients) and CLL 101 ——— study (53 patients). b(4)

The overall response rates in the pivotal study of oral fludarabine in relapsed or refractory patients with B-CLL (ME96029) were slightly better than the rates observed following treatment with IV fludarabine in the MDAH (T83-1275) study (48%, 13% CRs using NCI

criteria, best case analysis and 23% (8% CR) using NCI criteria, worst case analysis) and in refractory or relapsed patients with B-CLL from the SWOG (83-78) study (32% using NCI criteria 13% CR), best case analysis and 19% using NCI criteria (13% CR), worst case analysis). When response was assessed using IWCLL response criteria and compared with results from the subset of previously-treated patients with B-CLL in Study CLL 101 ——— Study) using IWCLL criteria, the overall response rate in the pivotal study of oral fludarabine (ME96029) was lower than that observed with IV fludarabine (35% in ME96029), versus 45% in CLL 101 ——— Study. b(4)

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The median duration of response for previously-untreated patients ranged from 19 months following IV fludarabine (CALGB 9011) to 22.6 months following oral fludarabine (303080). Median time to progression ranged from 17.4 months following IV fludarabine (CALGB 9011) to 29.2 months following oral fludarabine (303080).

Background

Fludarabine has been extensively studied in patients with CLL and the intravenous (IV) formulation was the first agent approved by the Food and Drug Administration for the treatment of the disease when there is failure to respond to an alkylating agent.

Intravenous fludarabine administration requires regular visits to hospitals or physician offices. Because of inconvenience associated with intravenous administration an oral formulation of the drug as an immediate-release tablet containing 10 mg of fludarabine was developed. The oral formulation of fludarabine was first approved for marketing in the United Kingdom in 2000. Currently the oral tablet is approved in approximately 75 countries. Oral fludarabine is administered at a dose of 40 mg/m^2 given for 5 days every 4 weeks. Pharmacokinetic (PK) analysis has confirmed that administration of 25 mg/m^2 IV or 40 mg/m^2 PO result in comparable systemic exposure (AUC) of fludarabine.

1.3.2 Efficacy

1.3.3 Dosing Regimen and Administration

For the treatment of CLL the recommended adult dose of fludarabine is 40 mg/m^2 administered daily for five consecutive days. Each 5-day course of treatment should

commence every 28 days, Dosage may be decreased or delayed based on evidence of hematologic or nonhematologic toxicity, Physicians should consider delaying or discontinuing the drug if neurotoxicity occurs. Fludarabine tablets can be taken either on an empty stomach or with food. The tablets have to be swallowed whole with water; they should not be chewed or broken,

1.3.4 Drug-Drug Interactions

The use of fludarabine in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity.

1.3.5 Special Populations

Pediatric patients

No studies of oral fludarabine have been conducted in pediatric CLL patients. Data on intravenous fludarabine were insufficient to establish efficacy in any childhood malignancy, Limited pharmacokinetic data for fludarabine are available from a published study of children (ages 1 to 21 years) with refractory acute leukemias or solid tumors (Children's Cancer Group Study 097).
Hepatic Insufficiency: No clinical studies were conducted with fludarabine in patients with hepatic insufficiency.

Renal Insufficiency The total body clearance of the principle metabolite 2-fluoro-ara-A correlated with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the drug. Renal clearance represents approximately 40% of the total body clearance. Patients with moderate renal impairment (17 to 41 mL/min/m2) receiving 20% reduced fludarabine dose had a similar exposure (AUC; 21 versus 20 nM•h/mL) compared to patients with normal renal function receiving the recommended dose. The mean total body clearance was 172 mL/min for normal and 124 mL/min for patients with moderately impaired renal function.

Geriatric Use: In Study ME96029 the patient population mean age was 63.4 (43-75). In Study 303080 the patient population median age was 64.0 (30-75).

2.0 INTRODUCTION AND BACKGROUND

2.1 Product Information

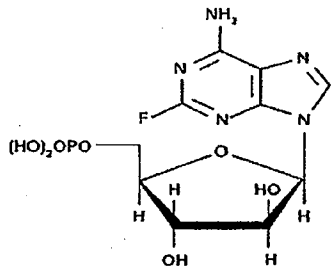
Fludarabine (2F-ara-AMP; 2-fluoro-9-(5-O-phosphono-β-Darabinofuranosyl)- 9H-purin-6-amine) is a water-soluble form of fludarabine, a fluorinated nucleoside analogue of adenine which is relatively resistant to deamination by adenosine deaminase. Fludarabine is derived from the anti-leukemic agent 9- β-D-arabinofuranosyl adenine (ara-A). Upon reaching the systemic circulation, the compound is rapidly dephosphorylated to yield its primary metabolite, 2F-ara-A, which undergoes carrier-mediated transport into cells and is converted

intracellularly to the pharmacologically active 5'-tri , 2F-ara-ATP. In vitro and in vivo studies have demonstrated that the cytotoxicity and hence efficacy of fludarabine is highly dependent upon the generation of 2F-ara-ATP. This intracellular metabolite elicits the cytotoxic activity of the drug through inhibition of DNA, RNA and protein synthesis. The primary action of 2F-ara-ATP is on DNA synthesis and replication, resulting in an irreversible inhibition of cell division, manifested in time-dependent reduction of clonogenic potential and programmed cell death.

Each tablet contains 10 mg of the active ingredient fludarabine , The tablet core consists of microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silicon dioxide, croscarmellose sodium and magnesium stearate, The film-coat contains hypromellose, talc, titanium dioxide (EI71) and ferric oxide pigment (red/E172, yellow/EI72).

The chemical name for fludarabine is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-ß-D-arabinofuranosyl)(2-fluoro-ara-AMp),7o The molecular formula of fludarabine is $C_{10}H_{13}FN_5O_7P$ (MW 365.2) and the structure is provided in Figure 1.

Figure 1: Chemical Structure of Fludarabine



2.2 Currently Available Treatment For Proposed Indication

Intravenous fludarabine, alkylating agents such as cyclophosphamide and chlorambucil, adriamycin, corticosteroids as single agents or in combination. **Table 1** lists common treatment regimens.

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Table 1: CLL Treatment Regimens

Regimen	Dosing Schedules
Chlorambucil (Chl)	0.4 mg/kg PO Day 1 with dose escalation of 0.1 mg/kg until toxicity or disease control, every 2 weeks
Cyclophosphamide	500-700 mg/m2 PO every 2-4 weeks
Prednisone	0.8 mg/kg for 14 days; halving of the daily dose on Days 15 and 29 for a total of 6-week course
Chl+P Chlorambucil Prednisone	 0.4 mg/kg PO Day 1 with dose escalation of 0.1 mg/kg until toxicity or disease control, every 2 weeks 75 mg PO Day 1, 50 mg PO Day 2, 25 mg PO Day 3 every 2 weeks
COP (CVP) Cyclophosphamide Vincristine (V) Prednisone	 300 mg/m2 PO Day 1-5 1.4 mg/m2 IV Day 1 100 mg/m2 PO Day 1-5 every 3 weeks
CAP Cyclophosphamide Adriamycin Prednisone	 750 mg/m2 IV Day 1 50 mg/m2 IV Day 1 100 mg/m2 orally Day 1-5 every 3 weeks
CHOP Cyclophosphamide Doxorubicin Vincristine Prednisolone	 300 mg/m2 PO Day 1-5 25 mg/m2 IV Day 1 1 mg/m2 IV Day 1 40 mg/m2 PO Day 1-5 monthly

Fludarabine alone was shown to be more effective for the treatment of previously-untreated patients with B-CLL than chlorambucil. Combinations of fludarabine with conventional chemotherapy for the treatment of previously-treated and untreated B-CLL patients have been extensively studied and are commonly used in the clinic. The combination of fludarabine plus cyclophosphamide resulted in higher response rates in previously treated patients than fludarabine alone.

Many studies have evaluated the combination of fludarabine and other conventional chemotherapeutics with the combination of targeted monoclonal antibody therapy in both untreated and previously-treated B-CLL patients. Combinations of fludarabine with rituximab have shown to be highly effective and associated with superior response rates and survival. Another study showed improved rates of CR and overall response (OR) and overall survival with fludarabine + cyclophosphamide + rituximab compared with fludarabine + cyclophosphamide or fludarabine alone, as initial therapy for B-CLL patients. The CR rate with FCR is about 70%. Effectiveness of fludarabine in combinations with other antibody therapeutics including alemtuzumab or the combination of alemtuzumab and rituximab in B-CLL patients has also been evaluated. While the increased number of treatment options has lead to more effective therapy for B-CLL patients, currently no curative therapy for B-CLL is available. Patients with B-CLL experience multiple relapses and require repeated treatment with a wide range of therapies during the course of their disease.

A number of other combinations, single agents, or novel therapies are undergoing clinical

investigation. These include:

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2.3 Availability Of Proposed Active Ingredient In The United States

Fludarabine is approved for use in the United States. See current indication.

2.4 Important Issues With Pharmacologically Related Products

See warning regarding pentostatin

2.5 Presubmission Regulatory Activity

New Drug Application (NDA) # 20-038 (1990) was submitted by Triton Biosciences for the IV formulation of fludarabine based on retrospective analysis of data from single-arm studies performed by the MD Anderson Hospital (MDAH; T83-1275) and Southwest Oncology Group (SWOG; 83-78) studies. Both studies determined the effectiveness of IV fludarabine based on response rate, duration of response and overall survival following treatment of B-CLL patients refractory to at least one alkylating agent-containing regimen studies. Approval for IV fludarabine phosphate (Fludara®) in 1991 for the treatment of adult patients with B-CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-containing regimen was granted to Berlex Laboratories Inc. who acquired Triton Biosciences, the US Division of Schering AG, now called Bayer Schering Pharma AG in the US.

In the European Union (EU) the IV formulation of fludarabine was approved in 1994. Efficacy and safety were demonstrated in a trial comparing IV fludarabine treatment to cyclophosphamide, adriamycin and prednisone (CAP) in both previously-treated and untreated B-CLL patients (———Study CLL 101). Data collected in this study on fludarabine treatment in the untreated B-CLL patient population were supported with three additional studies of IV fludarabine. These were the study conducted in B-CLL patients comparing fludarabine and chlorambucil treatment, conducted by the Cancer and Leukemia Group B (CALGB 9011), the study comparing IV fludarabine and chlorambucil plus methylprednisolone (Spriano study, A00545) and a study comparing fludarabine with CAP (cyclophosphamide, Adriamycin and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) by the French Cooperative Study Group on CLL ([FCGCLL] study). The analysis of these studies led to the approval of IV fludarabine for the treatment of previously-untreated (i.e., first-line) B-CLL patients in several countries.

b(4)

Since the introduction of IV fludarabine, more than ——— patients with B-CLL have been treated worldwide. b(4)

Development Strategy for Oral Fludarabine

An oral formulation of fludarabine containing 10 mg of fludarabine phosphate was developed by Bayer Schering Pharma AG. The development program was directed towards achieving an immediate-release oral dosage form which would provide, after dose adjustment, a similar drug exposure (area under the curve, AUC) and clinical profile to the IV formulation, based on the hypothesis that the same AUC following oral dosing would achieve similar efficacy and safety results as observed after IV dosing. It had been previously shown that the AUC of 2F-ara-A, the main systemic metabolite of fludarabine (2F-ara-AMP) is the pharmacokinetic parameter most relevant to the biological effect of fludarabine. It has shown that there is a linear relationship between the exposure of 2F-ara-A (arithmetic product of extracellular concentration and duration of exposure) and intracellular concentrations of cytotoxic metabolite, 2F-ara-ATP.

The clinical development program was focused on the bioavailability of the oral formulation and the pharmacokinetic comparability of IV and PO fludarabine, and demonstration of safety and efficacy of oral fludarabine. Several pharmacokinetic studies, including a food-effect study, were undertaken with oral fludarabine. To determine the efficacy of oral fludarabine in previously-treated B-CLL patients, a single efficacy study was undertaken (Study ME96029) in 1996 with adult patients with 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. The endpoint for the study was response to treatment measured as CR + PR. This study is the only efficacy study with oral fludarabine as monotherapy conducted in this specific patient population to date and has formed the basis for approval of oral fludarabine for second-line B-CLL patients in the United Kingdom in 2000 and subsequently in 75 countries in Europe and the rest of the world. An estimated ——— patients have received oral fludarabine treatment since its approval in 2000. b(4)

2.6 Other Relevant Background Information

None

3.0 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (And Product Microbiology. If Applicable)

See CMC review.

3.2 Animal Pharmacology/Toxicology

See pharmacology review.

4.0 Data Sources, Review Strategy And Data Integrity

4.1 Sources of Clinical Data

The paper fludarabine submission consists of 5 modules. The clinical modules are 2 and 5.

4.2 Table of Clinical Studies

Clinical studies submitted are listed below.

To determine the efficacy of oral fludarabine in previously-treated B-CLL patients, a single efficacy study was undertaken (Study ME96029). Seventy-eight (78) adult patients with B-CLL who had not responded to, or whose disease had progressed during or after treatment with at least one standard alkylating agent-containing regimen were treated. The endpoint for the study was response rate.

Data from the above study (ME96029) was compared with available efficacy data from three studies conducted with IV fludarabine , 20 mg/m2 IV daily for five days every 28 days, in previously-treated B-CLL. Efficacy data from two of these studies, the subset of 48 refractory B-CLL patients from MDAH (T83-1275) and 32 refractory or relapsed B-CLL patients from SWOG [83-78]) were the basis of approval of the IV formulation in the US and the rest of the world. A third study (CLL 10[illegible] ——— study) included 53 previously-treated and 53 previously-untreated B-CLL patients who received fludarabine 25 mg/m2 IV daily for five days every four weeks. b(4)

In addition, two oral fludarabine efficacy studies were conducted in previously-untreated B-CLL patients. Study 303080 included 81 patients and Study LRF CLL4 included 122 fludarabine treated patients. Endpoints of the former study included response rate, response duration, progression free survival and overall survival while the primary efficacy endpoints of the latter study were response rate and overall survival.

Two studies conducted with IV fludarabine 25 mg/m2 IV daily for five days every four weeks in previously-untreated (first-line) B-CLL patients have also been included in the analysis of efficacy. The CALGB 9011 study included 175 fludarabine treated patients and study (CLL 10[illegible] ——— included 53 previously-untreated patients. b(4)

4.3 Review Strategy

Efficacy data pertaining to response rates and durations, as appropriate, were reviewed. All safety data was reviewed.

4.4 Data Quality And Integrity

Because this submission primarily relied on published data no DSI inspections are planned.

4.5 Compliance With Good Clinical Practices

All studies were conducted, as could best be determined, in full compliance with Good Clinical Practice.

4.6 Financial Disclosures

The clinical studies included in NDA 22-273 for oral fludarabine were sponsored by Schering AG (now known as Bayer Schering Pharma). The sponsor (Xanthus) has requested certification of financial interests for the clinical investigators who participated in the oral fludarabine clinical trials from Bayer Schering Pharma. To date Xanthus has not been provided this certification. They have no reason to believe, however, that the clinical investigators were the recipient of significant payments or compensation, as defined in 21 CFR Part 54, that would have affected the outcome of the clinical study. Xanthus confirms that they have no financial relationship with any study investigators; have made no payments directly to any of these individuals and no listed investigator owns Xanthus stock.

5.0 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

2F-ara-AMP is rapidly and completely dephosphorylated to 2F-ara-A in the systemic circulation by ubiquitous phosphatases, 2F-ara-A is the primary circulating metabolite after oral and IV doses of 2F-ara-AMP and hence clinical pharmacology studies have focused on 2F-ara-A pharmacokinetics,

The pharmacokinetics of 2F-ara-A have been determined in studies of approximately 98 Caucasian and Japanese patients given single or multiple oral doses of fludarabine.

Systemic plasma clearance of 2F-ara-A is modest, approximately 117-145 mL/min. After the five daily 30 minute intravenous infusions of 25 mg 2F-ara-AMP/m2 to cancer patients, trough concentrations of 2F-ara-A increased by a factor of about 277. The terminal half-life of 2F-ara-A is approximately 20 hours. Plasma protein binding of 2F-ara-A is modest, ranging from 19% to 29%.

2F-ara-A exhibits dose proportional increases in AUC and Cmax after single oral doses of 50, 70 or 90 mg of2F-ara-AMp77. Maximum plasma concentrations of 2F -ara-A are produced 1 -2 hours after single or multiple oral doses and are approximately 20 to 30 % of the maximum plasma concentrations produced at the end of a 30 minute intravenous infusion of the same dose. The absolute oral bioavailability of 2F-ara-A is 50 - 65% following single and repeated doses of the immediate release tablet formulation. The Cmax, AUC and terminal half-life of 2F-ara-A are unaffected when administered with a high fat meal, although Tmax is slightly delayed from 1.3 to 2.2 hours.

Renal clearance represents approximately 40% of the total body clearance of fludarabine , and total body clearance is inversely correlated with creatinine clearance. Dosage adjustment based on creatinine clearance is recommended as follows:

- Reduce dose by 20% in adult patients with moderate renal impairment (creatinine clearance 30 to 70 mL/min/1.73 m2),
- Not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m2)80,

5.2 Pharmacodynamics

No data are available.

5.3 Exposure-Response Relationships

No new data are available and therefore no changes of the label are required.

6.0 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Fludarabine phosphate is indicated for the 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.

6.1.1 Background

B-cell chronic lymphocytic leukemia (B-CLL) is an incurable chronic lymphoproliferative malignancy. With an incidence of 3 in 100,000 adults per year in North America, Europe, and Australasia, it is the most common leukemia in adults in the Western world, accounting for one-third of all leukemia cases. It affects twice as many men as women, with the peak incidence between 60 and 70 years of age. In individuals older than 70 years, the incidence is 50 per 100,000.

The disease is characterized by the accumulation of non-proliferating mature-appearing, immunologically-incompetent B-lymphocytes in the blood, bone marrow, lymph nodes, and spleen. The diagnosis is established by three features:
1. absolute morphologically mature-appearing lymphocytosis in the peripheral blood with a count of > 5.0 x 109/L unexplained by other causes;
2. at least 30% lymphocytes in a normocellular or hypercellular bone marrow;
3. a monoclonal B-cell population of lymphocytes that express low levels of surface immunoglobulin and CD5, CD23, CD19, and CD20.

Approximately 40% of B-CLL patients are asymptomatic when the disease is first detected. If present, common symptoms are fatigue, lymphadenopathy, or splenomegaly. In the end stages of the disease, the progressive accumulation of leukemia cells disturbs normal hematopoiesis causing fatigue and weakness (due to anemia), infections (due to granulocytopenia and hypogammaglobulinemia), as well as bleeding (due to thrombocytopenia).

The decision as to whether a patient should be treated or whether a "wait and see" strategy should be adopted is dependent on disease stage, clinical symptoms, and prognosis. The clinical course and prognosis for patients with B-CLL is extremely variable. Clinical stage as defined by Rai or Binet is the most important prognostic factor **(Tables 2 and 3)**.

Table 2: Chronic Lymphocytic Leukemia: Binet Staging System and Survival

Stage	Criteria		Median Survival (years)
Stage A	Haemoglobin ≥ 10 g/dL and Platelets ≥ 100 x 109/L	< 3 areas of lymph nodes involved (1)	14
Stage B		≥3 areas of lymph nodes involved	5
Stage C	Haemoglobin < 10 g/dL and/or Platelets < 100 x 109/L	Any number of enlarged areas	2.5
1. Lymphoid areas considered are: cervical, axillary, and inguinal lymphadenopathy (whether unilateral or bilateral), spleen, and liver.			

Table 3: Chronic Lymphocytic Leukemia: Rai Staging System and Survival

Rai Stages	Risk Group	Clinical Features	Median Survival (years)
0	Low risk	Lymphocytosis in blood (≥ 5.0x109/L) and marrow (>30% only)	>13
I	Intermediate risk	Lymphocytosis in blood (≥ 5.0x109/L) and enlarged lymph nodes	8
II	Intermediate risk	Lymphocytosis in blood (≥ 5.0x109/L) and spleen and/or liver (nodes + or -)	5-6
III	High risk	Lymphocytosis in blood (≥ 5.0x109/L) and anemia (hemoglobin < 11 g/dL)	4
IV	High risk	Lymphocytosis in blood (≥ 5.0x109/L) and thrombocytopenia (platelets < 100x109/L)	2

Most patients present at diagnosis with Binet stage A or Rai stages I/II. Their life expectancy is comparable to an age-matched population. These patients do not require immediate treatment. Binet A patients with evidence of progressive disease (Binet stage A-progressive) will, however, progress rapidly and are candidates for immediate treatment. Patients presenting with stages B or C are generally treated immediately. Similarly, patients with progressive Rai stage I and Rai stages II-IV should also be treated at presentation. Only 10% of patients present with Binet stage C or Rai stages III/IV. The Rai staging system has been condensed to three major risk groups (low [0], intermediate [I-II], and high [III-IV]) to correspond with Binet stages A, B, and C, respectively.

Generally, indications for therapy include disease-related symptoms (e.g., fever, chills, night sweats, weight loss), bone marrow involvement with progressive anemia and thrombocytopenia, progressive or massive splenomegaly, progressive or bulky lymphadenopathy, autoimmune hemolytic anemia (AIHA), or autoimmune thrombocytopenia (AIT), recurrent bacterial infections, and rapidly increasing lymphocytosis with doubling time of less than six months.

Clinical and biological markers of poor prognosis in B-CLL are:
- Advanced Rai or Binet stage
- Peripheral lymphocyte doubling time of less than six months
- Diffuse involvement of the bone marrow
- Increased number of prolymphocytic or cleaved cells
- Poor response to chemotherapy
- High β2-microglobulin levels
- High serum thymidine kinase levels
- Raised level of lactate dehydrogenase
- Presence of distinct chromosomal aberrations (11q-, 17p-)[35]
- Naïve or unmutated immunoglobulin variable domains (VH)
- Presence of the p53 mutation
- Increased expression of ZAP-70 (>30%)
- Increased expression of CD38 (>30%)

The latter biomarkers (ZAP-70 and CD38) are still considered investigational but their evaluation is being incorporated into many current clinical research trials. The presence of a p53 mutation or deletion, found in 12% of B-CLL patients, may predict response (or lack thereof) to certain anti-leukemia agents, and thus influence the choice of therapy. In a small study[15], 56% of patients with wild p53 responded whereas 0% with p53 mutation/deletion responded to fludarabine or pentostatin.

6.1.2 Methods

Phase 2 studies submitted by the sponsor were reviewed. See section 6.1.3.

6.1.3 General Discussion of Endpoints

Efficacy endpoints have been discussed with, and approved by, the FDA. Definitions of endpoints are summarized below.

Response Definitions

There are 2 response classification systems the International Workshop on CLL (IWCLL) **(Table 4)** and the United States (US) National Cancer Institute system **(Table 5)**.There are differences between the two; the NCI criteria specify for a CR presence of less than 30% lymphocytes without residual nodules in the bone marrow, the IWCLL criteria allow focal infiltrates or nodules in the bone marrow. Patients with this diagnosis at the end of treatment are often designated "nodular partial response (nPR). Furthermore, while the IWCLL uses a shift in clinical stage as the sole index of PR, the NCI criteria provide more specific characteristics of PR and recommends validation of the relevance of stage shift. In most studies, efficacy is evaluated with both NCI and IWCLL criteria.

Table 4: Response Criteria for CLL According to the International Workshop.

Outcome	IWCLL Criteria
CR	No evidence of disease Absence of constitutional symptoms Resolution of lymphadenopathy No hepatomegaly or splenomegaly Lymphocyte counts < 4 x 109/L Granulocyte counts > 1.5 x 109/L Platelet counts > 100 x 109/L Normal findings from bone marrow aspirate and biopsy, possibly with nodular or focal lymphoid infiltrates
PR	Change from Stage C disease to Stage A or B, or from Stage B to A
SD	No change in stage of disease
PD	Change from Stage A disease to Stage B or C, or from Stage B to C

Table 5: Response Criteria for CLL According to NCI Criteria

Outcome	NCI Criteria
CR	Absence of lymphadenopathy, hepatomegaly, splenomegaly or constitutional symptoms. Normal blood count: neutrophils > 1.5x109/L, platelets > 100x109/L, Hb > 11 g/dL, lymphocytes < 4.0x109/L, bone marrow biopsy normal cellularity, lymphocytosis < 30%.
PR	50% reduction in blood lymphocytes and 50% reduction in lymphadenopathy and/or 50% reduction in hepatomegaly and/or splenomegaly. Neutrophils > 1.5x109/L or 50% improvement over baseline, platelets > 100x109/L or 50% improvement over baseline, Hb > 11 g/dL (not supported by transfusion) or 50% improvement over baseline.
SD	No change in stage of disease
PD	At least one of the following: > 50% increase in the size of at least two lymph nodes or new palpable lymph nodes; > 50% increase in splenomegaly or hepatomegaly or appearance if they were not present; transformation to a more aggressive histology (Richter or prolymphocytic leukemia), > 50% increase in the absolute number of circulating lymphocytes.

6.1.4 Study Design

Phase 2 and 3 Studies

To determine the efficacy of oral fludarabine in previously-treated B-CLL patients, a single efficacy study was undertaken by Bayer Schering Pharma AG (Study ME96029) in 1996. Patients with 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 were enrolled. The endpoint for the study was response rate.

Two other studies conducted in previously-untreated B-CLL patients support the activity of oral fludarabine with respect to duration of response. Study 303080 included 81 B-CLL

patients and Study LRF CLL4 included 122 patients who received fludarabine 40 mg/m^2 PO daily for five days every four weeks.

Results from the pivotal oral fludarabine study were compared with efficacy data from three studies of IV fludarabine, 20 mg/m^2 daily for five days every 28 days. Two of these studies, the subset of 48 refractory B-CLL patients from MDAH (T83-1275) and 32 refractory or relapsed B-CLL patients from SWOG [83-78]) were the basis of approval of the IV formulation by the FDA and by many other countries. The third study (CLL 101, ——— study) included 53 previously-treated B-CLL patients who received fludarabine 25 mg/m^2 IV daily for five days every four weeks.

b(4)

Two studies of IV fludarabine in previously-untreated B-CLL patients are also included. The CALGB 9011 study included 175 patients randomized to receive fludarabine 25 mg/m^2 IV daily for five days every four weeks. The second study (CLL 101, ——— study, mentioned above) included a subset of 53 previously-untreated B-CLL patients.

Finally, published literature treatment of oral fludarabine has been reviewed and compared with the major clinical studies conducted with IV fludarabine treated patients.

Pivotal study ME96029 provides evidence of clinically meaningful remission rate with oral fludarabine similar to that observed following IV fludarabine therapy. Supportive study 303080 provides evidence of both clinically meaningful overall remission rate (72-80%) and duration of remission (22.6 months) and time to treatment progression (29.2 months) following oral fludarabine therapy of previously untreated B-CLL, similar to that observed following IV fludarabine therapy. Taken together, these data provide evidence reasonably likely to predict benefit of oral fludarabine in the treatment of previously-treated B-CLL.

6.1.5 Study reports

Pivotal Study ME96029: Oral Fludarabine in Relapsed and Refractory B-CLL

Study MD96029 was a multicenter, open-label, multinational (Belgium, Canada, France, Germany, Great Britain, Italy, the Netherlands, Spain, and Sweden), Phase 2, single-arm study reported by Boogaerts et al. (2001). Patients with B-CLL 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 (which did not include anthracycline or mitoxantrone) and who had a World Health Organization (WHO) performance status of 0-2 and life expectancy of more than six months were eligible for enrollment.

Patients received oral fludarabine 40 mg/m^2 daily for five days every four weeks. Each patient was to receive six cycles of treatment. Criteria for adjustment of fludarabine dosing, postponement of study drug, and withdrawal from the study because of toxicity were stipulated in the protocol.

Patients who responded to treatment but who had not achieved a complete remission

(CR) after the sixth treatment cycle were allowed to continue treatment for up to eight cycles after consulting with the Core Clinician/Study Manager.

Patients who did not respond after two cycles of treatment, or who showed clinical signs of disease progression after this time were withdrawn from the study. Two cycles of treatment were considered the minimum time required before an evaluation of treatment failure could be made. Additionally, any patient who was experiencing severe toxicity was to have been withdrawn.

The study protocol planned for the recruitment of 80 patients. Given the reported response rate of 45% in the historical control group (Study CLL 101) at least 60 patients were required to detect an unfavorable efficacy profile with a point estimate of the response rate (CR+PR) that was statistically significantly lower than 45%. Eighty-one patients were recruited and 78 patients were assessed for efficacy and safety. Three patients did not receive study treatment.

Table 6 summarizes the demographics of patients included in Study ME96029.

Table 6: Demographics

	ITT Group (n=78)
Gender, N (%)	
Males	56 (71.8)
Females	22 (28.2)
Mean age in years (range)	63.4 (43-75)
Race, N (%)	
Caucasian	77 (98.7)
Asian	1 (1.3)
Binet stage, N (%)	
Stage A-progressive	23 (29.5)
Stage B	24 (30.8)
Stage C	31 (39.7)
Rai stage (n, %)	
Stage 0	3 (3.9)
Stage I	16 (20.5)
Stage II	25 (32.1)
Stage III	9 (11.5)
Stage IV	25 (32.1)
WHO Performance Status, N (%)	
0	54 (69)
1	21 (27)
2	3 (4)
3	0
4	0
Previous therapy, N (%)	78 (100)
Mean number of prior treatment regimens	2.0

Response Rates

Response was defined by achieving a CR or PR based on the NCI (**Table 7**) or IWCLL criteria (**Table 8**) for B-CLL. Determination of response duration was not included as an efficacy endpoint in this study.

Table 7: National Cancer Institute Response Criteria for CLL

CR	Absence of lymphadenopathy, hepatomegaly, splenomegaly or constitutional symptoms. Normal blood count: neutrophils > 1.5x109/L, platelets > 100x109/L, Hb > 11 g/dL, lymphocytes < 4.0x109/L, bone marrow biopsy normal cellularity, lymphocytosis < 30%.
PR	50% reduction in blood lymphocytes and 50% reduction in lymphadenopathy and/or 50% reduction in hepatomegaly and/or splenomegaly. Neutrophils >1.5x109/L or 50% improvement over baseline, platelets > 100x109/L or 50% improvement over baseline, Hb > 11 g/dL (not supported by transfusion) or 50% improvement over baseline.
SD	No change in stage of disease
PD	At least one of the following: > 50% increase in the size of at least two lymph nodes or new palpable lymph nodes; > 50% increase in splenomegaly or hepatomegaly or appearance if they were not present; transformation to a more aggressive histology (Richter or prolymphocytic leukemia), > 50% increase in the absolute number of circulating lymphocytes.

Table 8: International Workshop on CLL Response Criteria

Treatment Outcome	**Criteria**
CR	No evidence of disease Absence of constitutional symptoms Resolution of lymphadenopathy No hepatomegaly or splenomegaly Lymphocyte counts < 4 x 109/L Granulocyte counts > 1.5 x 109/L Platelet counts > 100 x 109/L Normal findings from bone marrow aspirate and biopsy, possibly with nodular or focal lymphoid infiltrates
PR	Change from Stage1 C disease to Stage A or B, or from Stage B to A
SD	No change in stage of disease
PD	Change from Stage A disease to Stage B or C, or from Stage B to C

Response to treatment was defined as a binary variable. A one-sample chi-squared test was used to determine whether the response rate equaled a pre-specified value. The null hypothesis was H_0: response rate after oral fludarabine was 45% versus the alternate hypothesis, H_1: response rate after oral fludarabine was different than 45%. The level of significance was α=0.05.

Two analyses of responders were performed. In the protocol-specified analysis (termed by the Sponsor the "worst case" analysis), patients who were withdrawn from study were regarded as treatment failures unless the reason for withdrawal was achievement of CR.

In a second analysis performed by the Sponsor (termed the "best case" analysis), all patients who responded to treatment was deemed a responder, regardless of when they discontinued treatment.

A summary of the response rates is presented in **Table 9**. The null hypothesis that the response rate in patients receiving oral fludarabine is equal to 45% was not rejected. The confidence intervals (CIs) of the response rates ranged from 35% to 63% for the best case analysis and from 24% to 53% for the worst case analysis.

Table 9:Response Rates (ME96029)

	Response Rates ITT Group (n=78)	**95% CI**	**p-value1**
IWCLL response rates – 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 response rates – 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)		
NCI response rates – best case, with FDA reclassification of response, N (%)2			
CR+PR	40 (51.3)		
CR	4 (5.1)		
PR	36 (46.2)		
SD	19 (24.4)		
PD	12 (15.4)		
IWCLL response rates – best case, with FDA reclassification of response, N (%)2			
CR+PR	36 (46.2)		
CR	6 (7.7)		
PR	30 (38.5)		
SD	24 (30.8)		
PD	11 (14.1)		
IWCLL response – worst case3, 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 response – worst case3, N (%)			
Treatment success (CR+PR)	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; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; NCI = National Cancer Institute; PD = progressive disease; PR = partial remission; SD = stable disease.
1. p-value for test of null hypothesis that the response rates are equal to 45%.
2. An FDA review of data found that the NCI and/or IWCLL criteria were not exactly matched for 10 patients. The responses for these 10 patients were downgraded from CR to PR.
3. "Worst case" analysis - Patients who were withdrawn from study were regarded as treatment failures unless the reason for withdrawal was achievement of CR. 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.
"Best case" analysis - All patients who responded to treatment was deemed a responder, regardless of when they discontinued treatment.

The best case responses using the NCI and IWCLL criteria exhibited good concordance. Of the 40 NCI best case responders, four patients (all with PR by NCI criteria) were judged to have stable disease by IWCLL criteria, and two patients (both with PR by NCI criteria) were judged to have CR by IWCLL criteria. Two patients (both with SD by NCI criteria) were judged to have PR by IWCLL criteria.

An FDA review of data found that the NCI and/or IWCLL criteria for response were not exactly matched for 10 patients (**Table 10**). As a consequence, the responses for these patients were downgraded from CR to PR. The reclassification of the responses of these 10 patients did not change the primary efficacy endpoint of overall response rate (CR + PR), 51% under the best case analysis (NCI criteria) and 46% under the best case analysis (IWCLL criteria; **Table 9**).

Table 10: Patients with CR Downgraded to PR – Study ME96029

Patient ID	Reason for Downgrading	Response in Study Report AZ84		Response per FDA
		NCI	IWCLL	
38	Peripheral blood counts did not meet CR criteria	CR	CR	PR
73	Hemoglobin did not meet CR criteria	CR	CR	PR
75	Platelet count did not meet CR criteria	CR	CR	PR
83	ANC 1.3x109/L on CR date (14 Oct 1997)	CR	CR	PR
88	Lymphocytes 4.9x109/L on CR date (23 Sep 1997)	CR	CR	PR
130	Lymphocytes % not reported in the bone marrow	CR	CR	PR
131	Hypocellular biopsy specimen	CR	CR	PR
132	Hypocellular biopsy specimen	CR	CR	PR
135	Lymphocytes % not reported in the bone marrow	CR	CR	PR
159	Lymphocytes 49% in the bone marrow	CR	CR	PR

The disease stage of patients had an impact on response rate. In general, the more advanced the stage of disease at baseline, the less likely that a response could be

achieved. Overall, the highest percentage of response (CR + PR) occurred among patients in the Rai low-risk group at baseline (67% according to both NCI and IWCLL criteria), and the Rai intermediate-risk group (68% and 61% according to NCI and IWCLL, respectively), and was lowest for Rai high-risk patients (29% and 26% according to NCI and IWCLL, respectively; **Table 11**).

Table 11: Response (NCI and IWCLL) by Baseline Rai Stage –Study ME96029

Rai Risk Groups1 at Baseline	NCI Criteria		IWCLL Criteria	
	CR N (%)	PR N (%)	CR N (%)	PR N (%)
Low (n=3)	2 (67)	0	2 (67)	0
Intermediate (n=41)	11 (27)	17 (41)	13 (32)	12 (29)
High (n=34)	1 (3)	9 (26)	1 (3)	8 (24)
Total (n=78)	14 (18)	26 (33)	16 (21)	20 (26)

Rai stage improved in more patients who responded to fludarabine than in those who did not (**Table 12**). In responders, Rai stage improved in 63% (25/40) of patients, remained stable in 30% (12/40) of patients, and worsened in 8% (3/40) patients. Ten of the 40 responders (NCI criteria) were Rai stage III or IV at baseline. In five of these 10 patients (50%), Rai stage improved to stage II or better. Two of the patients with Rai 0 at the end of treatment visit were stage III or IV at baseline. One of those patients was categorized as a CR and the other was categorized as a PR.

In non-responders, Rai stage at the end of treatment improved in 13% (5/38) of patients, remained stable in 47% (18/38) of patients, worsened in 26% (10/38) of patients, and was unknown in 13% (5/38) of patients.

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Table 12: Change in Rai Stage – Study ME96029

Baseline Rai Stage	Baseline (n)	End of Treatment					
		Rai 0 or No Disease	Rai I	Rai II	Rai III	Rai IV	Unknown
All Patients (n=78)							
Rai IV	25	1	1	2	4	16	1
Rai III	9	1	0	2	2	2	2
Rai II	25	9	3	5	4	2	2
Rai I	16	7	5	1	1	2	0
Rai 0	3	2	0	0	0	1	0
Responders (NCI Criteria, Best Case Analysis, n=40)							
Rai IV	7	1	1	1	1	3	0
Rai III	3	1	0	1	1	0	0
Rai II	16	9	3	3	1	0	0
Rai I	12	7	3	0	1	1	0
Rai 0	2	2	0	0	0	0	0
Non-Responders (NCI Criteria, Best Case Analysis, n=38)							
Rai IV	18	0	0	1	3	13	1
Rai III	6	0	0	1	1	2	2
Rai II	9	0	0	2	3	2	2
Rai I	4	0	2	1	0	1	0
Rai 0	1	0	0	0	0	1	0

Almost half of the patients (38 patients) had WHO performance status 0 upon inclusion in Study ME96029. WHO performance status showed an improvement for 15% (12/78) of patients in Study ME96029, no change for 55% (43/78 patients) and a worsening for 30% (23/78 patients).

Of the 12 patients showing an improvement in WHO performance status compared with baseline, three achieved a CR, one achieved a PR, five had SD, and three developed PD. Of the 23 patients showing a worsening in WHO performance status compared with baseline, four achieved a PR, seven had SD, and 10 developed PD.

For most of the patients, six cycles was the optimal duration of treatment; approximately 10% of patients had a documented response by cycle 5 (9% by NCI criteria and 10% by IWCLL criteria), an additional 22% (IWCLL criteria) to 27% (NCI criteria) had a response by cycle 6, and about 14% of patients required 7–8 cycles before a response was noted. These data replicate the experience with the use of IV fludarabine therapy in second-line B-CLL patients.

Analysis of peripheral blood normalization was not specified in the protocol for Study ME96029. However, hemoglobin improved in six of seven responders (NCI criteria) who had anemia at baseline. Additionally, platelet counts improved in seven of eight patients who had thrombocytopenia at baseline.

The numbers of patients in Study ME96029 requiring red blood cell transfusions are provided in **Table 13.** Five responding patients required red blood cell transfusions. The transfusion requirement for two patients was not quantitated; the remaining three patients required a mean of four units (range 2-5 units) of red blood cells. Eight patients who did not respond to fludarabine required red blood cell transfusions. The transfusion requirement for two patients was not quantitated, and the remaining six patients required a mean of 7.5 units (range 4-14 units) of red blood cells.

Table 13: Red Blood Cell Transfusion Requirements – Study ME96029

Responders			Non-Responders		
Patient Number	**Cycle of Treatment**	**Units Transfused**	**Patient Number**	**Cycle of Treatment**	**Units Transfused**
38	6 & 7	5	33	1 & 2	9
42	1	5	37	2 & 4	4
44	1	2	40	1 & 2	4
58	2	NQ	45	1	4
158	2 & 3	NQ	67	1 & 3	14
			93	2	NQ
NQ = non-quantitated			97	1, 2, & 3	10
			113	7	NQ

Two patients who had a response by NCI criteria (Patients 36 and 58) and one non-responder (Patient 157) required G-CSF for neutropenia. One responder (Patient 42) required platelet transfusions for thrombocytopenia.

Supportive Study 303080: Oral Fludarabine in Untreated B-CLL
Study 303080 was a prospective, multicenter, open-label, European (Belgium, France, Italy, the Netherlands, and the UK) Phase 2 uncontrolled study to assess the efficacy and safety of oral fludarabine , as well as its effects on quality of life in previously-untreated B-CLL patients. The study was reported by Rossi et al. (2004).

Patients with B-CLL (Binet stage A-progressive, stage B, or stage C) who had not received treatment for the disease and who had a WHO performance status of 0-2 and life expectancy of more than six months were eligible for enrollment. Patients received oral fludarabine 40 mg/m2 daily for five days every four weeks. Each patient was to receive up to six cycles of treatment. Patients who responded to treatment but who had not achieved a CR after the sixth treatment cycle were allowed to continue treatment for up to a total of eight cycles after consulting with the Core Clinician/Study Manager. Patients who did not

respond after two cycles of treatment, or who showed clinical signs of disease progression after this time were withdrawn from the study and considered treatment failures. Two cycles of treatment were considered the minimum time required before an evaluation of treatment failure could be made. Additionally, any patient who was experiencing severe toxicity (WHO toxicity grade 4 non-hematological toxicity) was to have been withdrawn.

The study protocol originally planned for the recruitment of 80 patients. With 60 patients, a change in response rate of 20% could be detected (in comparison to a historical control response rate of 70% with IV fludarabine with a power (probability) of 90%. To increase the power of the study it was decided to recruit 80 patients. With 80 patients, a change in response rate with oral fludarabine of 20% with a power (probability) of 96% could be detected.

Eighty-two patients were recruited and 81 patients were assessed for efficacy and safety. One patient did not receive study drug because he was found to be ineligible according to the inclusion/exclusion criteria.

Table 14 summarizes demographics and baseline characteristics of patients included in

Table 14: Demographics and Baseline Characteristics – Study 303080

	ITT Group (n=81)
Gender, N (%) Male/ Female	 51 (63.0)/30 (37.0)
Median age in years (range)	64.0 (30-75)
Race, N (%) Caucasian Other	 80 (98.8) 1 (1.2)
Binet stage, N (%) Stage A-progressive Stage B Stage C	 15 (18.5) 51 (63.0) 15 (18.5)
Rai stage, N (%) Stage 0 Stage I Stage II Stage III Stage IV	 3 (3.7) 30 (37.0) 30 (37.0) 8 (9.9) 10 (12.3)
WHO Performance Status, N (%) 0/1	 58 (71.6)/23 (28.4)
Previous therapy	0

The primary measure of efficacy was response to treatment at the final study assessment. In case of a CR or PR, a bone marrow investigation and computed tomography/ultrasound examination of abdomen/chest/pelvis (if abnormal at baseline) were performed to confirm the response classification.

As part of the assessment of response according to NCI criteria, patients who fulfilled all

criteria for CR but had persistent anemia or thrombocytopenia apparently unrelated to disease activity and more likely the consequence of persistent drug toxicity were assessed as PR marrow failure. Patients who fulfilled all criteria for CR but had evidence of nodules of residual B-CLL in the BM trephine biopsy were assessed as nPR. Patients in these two sub-categories of PR were classified as responders.

For patients withdrawn before receiving six cycles of treatment, response was assessed when the patient discontinued.

Response to treatment (CR+PR) was defined as a binary variable. An exact one-sample test was used 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 multicenter study CLL 101. The null hypothesis was H_0: response rate after oral fludarabine was 70% versus the alternative hypothesis, H_1: response rate after oral fludarabine was different than 70%. The level of significance was α=0.05. Two analyses of responders were performed. In the worst case analysis, patients who were withdrawn from study were regarded as treatment failures unless the reason for withdrawal was achievement of CR. In the best case analysis, all patients were evaluated within 3 to 5 weeks after withdrawal from treatment when possible, and any patient who responded to treatment was deemed a responder, regardless of when they discontinued treatment. A two-sided exact 95% CI for the observed response rate was constructed.

A summary of the response rates is presented in **Table 15**. The null hypothesis that the response rate in patients receiving fludarabine tablets is equal to 70% was not rejected. The CIs of the response rates ranged from 60.5% to 88.3% for the best case analysis and from 49.0% to 78.9% for the worst case analysis.

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Table 15: Response rates-Study 303080

	ITT Group (n=81)	95% CI	p-value 2
IWCLL response rates – best case, N (%)			
CR+PR	58 (71.6)	60.5% - 81.1%	0.86
CR	30 (37.0)		
PR	28 (34.6)		
SD	17 (21.0)		
PD	5 (6.2)		
Not assessable	1 (1.2)		
NCI response rates – best case, N (%)			
CR+PR	65 (80.2)	69.9% - 88.3%	0.052
CR	10 (12.3)		
PR	55 (67.9)		
SD	9 (11.1)		
PD	6 (7.4)		
Not assessable	1 (1.2)		
IWCLL response – worst case1, N (%)			
Responder (CR+PR)	49 (60.5)	49.0% - 71.2%	0.086
Non-responder	32 (39.5)		
NCI response – worst case1, N (%)			
Responder (CR+PR)	56 (69.1)	57.9% - 78.9%	0.95
Non-responder	25 (30.9)		

1. 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. p-value for test of null hypothesis that the response rates are equal to 70%.

In both the best case and worst case analyses, the overall response rate according to the NCI criteria was higher than the response rate according to the IWCLL criteria due to the larger number of PRs. In the best case analysis, PR was achieved by 28 patients (35%) according to IWCLL criteria compared to 55 patients (68%) according to NCI criteria. Of these 55 patients, 14 were nPRs, four were PR marrow failures, and one was nPR/marrow failure. In the worst case analysis, 22 patients (27%) achieved PR according to IWCLL, versus 46 patients (57%) according to NCI criteria. Of these 46 patients, 13 were nPRs, three were PR marrow failures, and one was nPR/marrow failure.

The disease stage of patients had an impact on response rate. In general, the more advanced the stage of disease at baseline, the less likely that a response could be achieved; this was true for both the Rai and Binet staging systems. Overall, the highest percentage of response (including CRs and PRs) occurred among patients in the Rai low-risk group at baseline (100% according to both NCI and IWCLL criteria), and the Rai intermediate-risk group (85% and 75% according to NCI and IWCLL, respectively), and was lowest for Rai high-risk patients (61% and 56% according to NCI and IWCLL, respectively.

The analysis of duration of response and time to progression was not planned in the original protocol, but was added by protocol amendment. After completing study treatment, patients were followed up regularly according to local practice. Additional information on date and evidence of disease progression, date and cause of death, and subsequent treatments received for B-CLL were collected to enable analysis of duration of response and time to progression. Follow-up was continued until sufficient data were available to determine median for analysis of survival, after which collection of followup data was stopped.

A total of 81 patients were considered for follow-up. Seven patients were excluded from the follow-up analysis due to lack of informed consent to participate in the follow-up study.

At the completion of the three-year-follow-up period, 22 (30%) of the 74 patients included in the follow-up analysis had not progressed). Median time to progression was 29.2 months. Median duration of response was 22.6 months responding according to both IWCLL and NCI criteria (**Table 16**).

Table 16: Duration of Response and Time to Progression -Study 303080

Criteria	Overall Response Rate (CR+PR) at End of Treatment	Patients with Progression-Free Survival	Median Duration of Response	Median Time to Progression
NCI	61/74 (82.4%)	22/74 (29.7%)	22.6 months	29.2 months
IWCLL	54/74 (73.0%)	Not assessed	22.6 months	Not assessed

Of the 74 patients analyzed in the follow-up period, 51 (69%) showed progression of disease according to the NCI progression criteria (**Table 17**). In 41 (80%) of these cases, an increase in circulating lymphocytes was given as at least one reason for the evidence of progression. An increase in the sum of the products of at least two lymph nodes and/or appearance of new palpable nodes was given as at least one reason for the evidence of progression in 23 cases (45%). For each patient it was possible to record more than one reason for evidence of progression. Response was assessed by both NCI and IWCLL criteria; progression during follow-up was assessed according to NCI progression criteria only.

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Table 17: Evidence of Progression (NCI Criteria) - Study 303080

Number of Patients in Follow-up Period	74
Progression, N (%)	
No	22 (29.7)
Yes	51 (68.9)
Not available	1 (1.4)
Evidence of Progression	
1) ≥ 50% increase in the sum of the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one node must have been ≥ 2 cm); appearance of new palpable nodes	23 (45.1%)
2) ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.	5 (9.5%)
3) ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5.0x109/L	41 (80.4%)
4) Transformation to a more aggressive histology (e.g., Richter's syndrome or prolymphocytic leukemia with > 55% prolymphocytes)	3 (5.9%)

The median time to progression was 890 days (29.2 months; Table 2.7.3.27). Sixteen patients were censored for time to progression at the date they were last observed to be progression free. Ten patients received subsequent treatment for B-CLL prior to progression and were censored at the date of the first day of treatment.

Supportive Study LRF CLL4: Fludarabine (Oral and IV, Single-Agent and in Combination with Cyclophosphamide) in Untreated B-CLL

The Leukemia Research Foundation (LRF) study CLL4 was a multicenter, randomized, open-label, multinational (Argentina, Croatia, Greece, Ireland, Italy, New Zealand, Russia, and the UK), controlled study and was conducted in compliance with UK medical research council guidelines for GCP. The study was reported by Catovsky et al., and results presented in this section are based on those publications.

Previously untreated patients with B-CLL of all ages with Binet stages A-progressive, B, or C were eligible for enrollment.

Patients were randomly assigned in a 1:1:2 ratio to fludarabine alone, fludarabine plus cyclophosphamide, or chlorambucil. Oral fludarabine became available part way through the study in 2001, and the protocol was modified to allow its use. Doses of single-agent fludarabine were 25 mg/m^2/day given IV or 40 mg/m^2/day given PO for five days. Patients randomized to fludarabine plus cyclophosphamide received fludarabine 25 mg/m^2/day IV plus cyclophosphamide 250 mg/m^2/day IV for three days every four weeks, or fludarabine 24 mg/m^2/day PO plus cyclophosphamide 150 mg/m^2/day PO for five days every four weeks. Patients randomized to chlorambucil received chlorambucil 10 mg/m^2/day PO for seven days every four weeks. Each cycle was given every four weeks. Single-agent

fludarabine and fludarabine plus cyclophosphamide were given for up to six cycles, and chlorambucil was given until maximum response or up to 12 courses. After patients progressed or did not respond to treatment on this study, they received second-line treatment.

Patients with stage C disease (hemoglobin concentration < 10 g/dL or platelet count < 100 x 109/L that was not due to AIT occurrence) received prednisolone 30 mg/m^2 orally for three weeks plus a one-week taper before starting the study treatment to reduce the initial myelotoxicity of chlorambucil.

The dose of study drug was reduced if there was a two-week delay in treatment due to neutropenia or thrombocytopenia and the fludarabine dose was reduced if the creatinine clearance was between 30 and 60 mL/min.

The primary endpoint was overall survival, with secondary endpoints of response rates (CR, nPR, PR, no response [stable disease], and PD), progression-free survival, toxic effects, and quality of life (as measured by the European Organization for Research and Treatment of Cancer Quality of Life [EORTC QLQ-C30] questionnaire).

Patient Population – Study LRF CLL4

The initial sample size was 500, to provide 90% power to detect a 15% absolute difference at five years between the chlorambucil group and the groups containing fludarabine combined, assuming a survival of 40% with chlorambucil, based on historical data. This analysis also provided only 65% power to detect a 15% difference between fludarabine and fludarabine plus cyclophosphamide. The sample size was later increased to 750, without knowledge of study results, since good recruitment showed that this number was feasible.

Seven hundred eighty-three patients were recruited, 764 patients were randomized and received study drug, and 720 patients were assessable for efficacy and safety. **Table 18** summarizes the disposition of patients included in Study LRF CLL4.

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Table 18: Patient Disposition- Study LRF CLL4

	Fludarabine	Fludarabine + Cyclophosphamide	Chlorambucil
Enrolled and randomized	194	196	387
Not treated (clinical decision)	0	0	1
Unknown	2	0	1
Other cancer	1	0	0
Raised creatinine	1	0	0
Never returned to hospital	1	0	0
Received prednisone (clinical decision)	0	1	0
Received randomized study drug	187	193	384
Route of administration, N (%)			
Oral	122 (65)	129 (67)	384 (100)
IV	58 (31)	59 (31)	0
Unknown	7 (4)	5 (3)	0

Table 19 summarizes demographics and baseline characteristics of patients included in Study LRF CLL4.

Table 19: Demographics and Baseline Characteristics – Study LRF CLL4

	Fludarabine (n=194)	Fludarabine + Cyclophosphamide (n=196)	Chlorambucil (n=387)
Gender, N (%)			
Males	142 (73)	145 (74)	286 (74)
Females	52 (27)	51 (26)	101 (26)
Median age in years (range)	64 (38-85)	65 (40-86)	65 (35-85)
Binet stage, N (%)			
Stage A-progressive	46 (24)	49 (25)	96 (25)
Stage B	91 (47)	89 (45)	172 (44)
Stage C	57 (29)	58 (30)	119 (31)
Risk group1			
Good	35 (29)	36 (26)	73 (30)
Standard	76 (63)	91 (67)	156 (64)
Poor	10 (8)	9 (7)	14 (6)
Unknown	73	60	144

1. Risk groups: Good = not 17p del, VH mutated (< 98% homology), and no VH3 usage; Standard = not 17p del, VH unmutated (> 98% homology) or VH3-21 usage or 11q del; Poor = 17p del.

Overall response rates are shown in **Table 20.**

Table 20: Response Rates (Modified NCI Criteria)– Study LRF CLL4

	Fludarabine (n=181) N (%)	Fludarabine + Cyclophosphamide (n=182) N (%)	Chlorambucil (n=366) N (%)
CR	27 (15)	69 (38)	26 (7)
nPR	49 (27)	41 (23)	71 (19)
PR	69 (38)	61 (34)	167 (46)
No response/PD	36 (20)	11 (6)	102 (28)
Good response (CR+nPR)	76 (42)	110 (60)	97 (27)
Overall response (CR+nPR+PR)	145 (80)	171 (94)	264 (72)

Ccomparison of response rates by route of fludarabine administration is shown in **Table 21.** It must be remembered that this is not a randomized comparison. Oral fludarabine therapy only became available later in the study.

Table 21: Comparison of IV and PO Fludarabine Response Rates-LRF CLL4

Parameter	Fludarabine		Fludarabine + Cyclophosphamide	
	IV (n=51)	Oral (n=107)	IV (n=55)	Oral (n=116)
CR/nPR	54%	41%	73%	59%
No response	8%	26%	2%	10%

Survival

The primary endpoint was overall survival. Five-year survival was 52% (95% CI 42-61%) in the single-agent fludarabine group. Overall survival was confounded by second-line and subsequent therapy received by the patients.

Studies of IV Fludarabine Phosphate

MD Anderson Hospital (MDAH; T83-1275): IV Fludarabine in Refractory B-CLL

Study MDAH (T83-1275) was a single center, open-label, Phase 1-2, uncontrolled study to determine the antitumor effect of fludarabine phosphate in hematologic malignancies and to determine the toxicity and maximum tolerated dose of fludarabine phosphate. Patients with acute myelogenous, lymphoblastic, or undifferentiated leukemia, B-CLL, refractory anemia with excess blasts, hairy cell leukemia, non-Hodgkin lymphoma, Hodgkin disease, or multiple myeloma were considered for entry; only data from patients with B-CLL are included in this summary.

Patients were required to have a Zubrod performance status of 0-3, and a life expectancy of at least six weeks. Dosing began with fludarabine phosphate 20 mg/m^2 IV over 30 minutes daily for five days every 28 days. If necessary, dose changes to achieve additional effect or

to reduce hematologic toxicity were made. If bone marrow lymphocytosis decreased by 50% at some time during a treatment cycle, the same dose was to be given for the next cycle. If the lymphocytic infiltrate decreased by less than 50%, the dose was to have been increased by one level provided toxicity to organs other than the marrow was not dose-limiting. Chemotherapy was to have been continued for a total period of one year after achieving complete remission. Patients were to be withdrawn if there was progressive disease or lack of antileukemic effect after two cycles of treatment associated with moderate toxicity to organ other than the bone marrow, or unacceptable toxicity, or unacceptable status quo.

Demographics and baseline characteristics of the MDAH study population are summarized in **Table 22.**

Table 22: Demographics and baseline characteristics - MDAH Study (T83-1275)

	Patients with Refractory B-CLL (n=48)
Gender, N (%)	
Males/Females	35 (73)/13 (27)
Age, years	
Mean	60.1
Median	59.5
Range	33 - 82
Race, N (%)	
Caucasian	42 (88)
Black	4 (8)
Other	1 (2)
Unknown	1 (2)
Rai stage, N (%)	
Stage 0	1 (2)
Stage I	6 (12)
Stage II	9 (19)
Stage III	12 (25)
Stage IV	20 (42)
Zubrod performance status, N (%)	
0	17 (35)
1	24 (50)
2	4 (8)
3	0
4	0
Unknown	3 (6)
Previous therapy for B-CLL1, N (%)	
1 Agent/Therapy	7 (26)
2 Agents/Therapies	3 (11)
3 Agents/Therapies	9 (33)
>3 Agents/Therapies	8 (30)
Number of prior agents/therapies	
Mean (SD)	3.0 (1.8)
Median	3
Range	1-8

Response was defined as achieving a CR or PR based on the NCI criteria for B-CLL. The overall response rate in the MDAH (T83-1275) study was 48% (95% CI 33%-63%). Under a worst case analysis, where patients who withdrew from the study prior to completion for any reason other than CR were considered treatment failures, the overall response rate was 23% (95% CI 12%-37%).

Southwest Oncology Group (SWOG; 83-78): IV Fludarabine in Relapsed or Refractory B-CLL

Study SWOG (83-78) was a nine-center, open-label, Phase 1-2, single-arm study to determine the response rate and remission duration of relapsing or refractory B-CLL after treatment with fludarabine phosphate and to determine the qualitative and quantitative toxicities of fludarabine phosphate. Patients with relapsing or refractory B-CLL with lymphocytosis of greater than $1.5x10^9/L$ and bone marrow infiltration with greater than 40% of the nucleated cells classified as lymphocytes were eligible for enrollment. Patients were also eligible if they had progressive measurable bulk disease attributed to B-CLL. Patients were required to be Rai stage III or IV, and have a WHO performance status of 0-3. Patients who had received more than two prior treatment regimens with chemotherapy and/or radiation therapy, patients who had received previous therapy with ara-C (cytarabine), and patients with hepatic or renal dysfunction were excluded.

Dosing began with fludarabine phosphate 20 mg/m^2 IV daily for five days, as a rapid IV bolus. Courses were administered every 28 days. Patients were to have received three cycles initially. If there was evidence of response, patients were to have received three additional cycles for a total of six cycles of therapy. Patients achieving a PR after six cycles of therapy were to have received six additional cycles. If necessary, dose changes were made for hematologic toxicity. If significant deterioration in the peripheral blood counts occurred, study drug was to have been stopped and a bone marrow aspirate and biopsy was to have been obtained.

Patients were to be withdrawn if there was no reduction in bone marrow leukemic infiltrate after three cycles, if potentially fatal non-myelosuppressive toxicity occurred, if relapse occurred after attainment of remission, or if the patient elected to discontinue treatment.

The SWOG study included 32 patients who received study drug. Of these patients, 31 were considered to be refractory to at least one prior standard alkylating agent-containing regimen and were assessed for efficacy.

Demographics and Baseline Characteristics – SWOG Study (83-78) are summarized in **Table 23.**

Table 23: Demographics and Baseline Characteristics – SWOG Study (83-78)

	Patients with Refractory/Relapsed B-CLL (n=31)
Gender, N (%)	
Males	21 (68)
Females	10 (32)
Age, years	
Mean	61.9
Median	62
Range	40 - 79
Race, N (%)	
Caucasian	28 (90)
Black	3 (10)
Rai stage, N (%)	
Stages 0-III	7 (23)
Stage III	9 (29)
Stage IV	14 (45)
Unknown	1 (3)
WHO Performance Status, N (%)	
0	7 (23)
1	15 (48)
2	7 (23)
3	1 (3)
Unknown	1 (3)
Previous therapy for B-CLL, N (%)	**n=32**
1 Agent/Therapy	3 (9)
2 Agents/Therapies	19 (59)
3 Agents/Therapies	7 (22)
>3 Agents/Therapies	3 (9)
Number of prior agents/therapies	
Mean (SD)	2.3 (0.8)
Median	2
Range	1-4

Response was defined by achieving a CR or PR based on the NCI criteria for B-CLL. The overall response rate in the SWOG study was 32% (95% CI 17%-51%). Under a worst case analysis, where patients who withdrew from the study prior to completion for any reason other than CR were considered treatment failures, the overall response rate was 19% (95% CI 7%-37%).

Median time to maximum clinical response to treatment was 19 weeks (range: 1-53 weeks). Median duration of response was more than 37 weeks (range: 7->81 weeks), and median survival time was 54 weeks.

CLL 101 ——— Study): IV Fludarabine Phosphate in Refractory or Relapsed or Untreated B-CLL b(4)

Study CLL 101 ——— Study) was a multicenter, open-label, multinational (France, Germany, Sweden, and the UK), Phase 3, randomized, controlled study. Patients older than

18 years of age with B-CLL who had failed to respond to or who had progressed following standard therapy for a minimum of six months and a maximum of three years of standard therapy. Patients had to have received a regimen that did not contain either anthracycline or mitoxantrone or had to have previously untreated B-CLL of Binet stage B or C. Patients had to have a WHO performance status of 0-2 and life expectancy of more than six months to be eligible for enrollment. Patients randomized to fludarabine phosphate received study drug 25 mg/m2 IV daily for five days every four weeks.

Patient Population – Study CLL 101 ——— Study) b(4)

Fifty three previously-treated patients and 53 previously-untreated patients received IV fludarabine phosphate. **Table 24** summarizes demographics and baseline characteristics of patients included in Study CLL 101.

Table 24: Demographics and Baseline Characteristics – Study CLL 101 ———

	Previously Treated (n=53)	**Previously Untreated** (n=53)
Gender, N (%)		
Male	40 (75.5)	39 (73.6)
Female	13 (24.5)	14 (26.4)
Mean age in years (range)	60.9 (29-79)	61.8 (39-77)
Binet stage, N (%)		
Stage A	1 (1.9)	0
Stage B	27 (50.9)	31 (58.5)
Stage C	25 (47.2)	22 (41.5)
Rai stage, N (%)		
Stage 0	0	0
Stage I	5 (9.4)	9 (17.0)
Stage II	19 (35.8)	16 (30.2)
Stage III	7 (13.2)	14 (26.4)
Stage IV	22 (41.5)	13 (24.5)
Not recorded	0	1 (1.9)
WHO Performance Status, N (%)		
0	19 (35.8)	29 (54.7)
1	20 (37.7)	21 (39.6)
2	12 (22.6)	3 (5.7)
3	1 (1.9)	0
4	1 (1.9)	0
Number of prior treatment regimens, N (%)		
1	45 (84.9)	
2	7 (13.2)	--
3	1 (1.9)	
Mean (range)	1.2 (1-3)	

Response was defined by achieving a CR or PR based on the IWCLL criteria for B-CLL. The overall response rate was 45% in previously treated patients and 70% in previously untreated patients.

The median survival for the two fludarabine treatment groups was 42.6 months. Previously-untreated patients had a prolonged survival compared with those who had received previous treatment (data not available).

Cancer and Leukemia Group B (CALGB) 9011: IV Fludarabine in Previously Untreated B-CLL

The CALGB 9011 study was a multicenter (CALGB, SWOG, National Cancer Institute Canada [NCIC], and Eastern Cooperative Oncology Group [ECOG] centers), open-label, randomized, Phase 3 study of fludarabine phosphate versus chlorambucil and was reported by Rai et al. (2000). Patients 18 years of age or older with previously untreated B-CLL of Rai stage I or II with evidence of active disease or of Rai stage III or IV were eligible for enrollment.

Fludarabine patients received 25 mg/m2 IV daily for five days every four weeks. Patients with clinical CR were to be treated for two months beyond the diagnosis of a clinical CR. If the clinical CR was sustained at the end of these two months, bone marrow examinations, blood lymphocyte phenotyping, as well as computed tomography scans of areas abnormal prior to therapy were to be performed. If these examinations confirmed a CR, the treatment was to continue for one additional month and then stopped. If the bone marrow sample submitted to confirm a CR was hypocellular, the patient was to be taken off treatment and a repeat sample was to be taken four weeks after the initial sample. Patients who did not achieve clinical CR but who did show evidence of a beneficial response (PR or SD) were to be treated for a maximum of one year.

A total of 175 patients received fludarabine phosphate during the induction phase, **Table 25** summarizes demographics and baseline characteristics of patients included in Study CALGB 9011.

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Table 25: Demographics and Baseline Characteristics – Study CALGB 9011

	Fludarabine Phosphate ITT Group (n=175)
Gender, N (%)	
Males	125 (71.4)
Females	50 (28.6)
Age in years	
Mean (SD)	62.2 (10.74)
Median	64
Range	37-85
Race, N (%)	
Caucasian	152 (86.9)
Hispanic	2 (1.1)
Black	20 (11.4)
Other	1 (0.6)
Rai stage, N (%)	
Stage 0 (low risk)	1 (0.6)
Stage I, II (intermediate risk)	99 (56.6)
Stage III, IV (high risk)	69 (39.4)
Missing	6 (3.4)
CALGB Performance Status, N (%)1	
0	112 (64.0)
1	51 (29.1)
2	10 (5.7)
3	0
missing	2 (1.1)

Response rates for fludarabine treated patients (CALGB criteria, similar to NCI criteria) were 15% CRs (95% CI 10%-21%), and 46% PRs (95% CI 39%-54%). The median duration of response was 19 months.

Progression-free survival was the primary efficacy The median duration of PFS for patients treated with fludarabine phosphate was 17.4 months. During the induction phase, 47.4% of patients in the fludarabine phosphate group had progressive disease.

The median duration of survival was 56 months.

Literature Review Summary – Second-Line Treatment

There is an extensive amount of published literature regarding the use of IV fludarabine as second-line therapy in B-CLL patients. Only studies of 25 patients or more are included in (**Table 26**).

Across the studies noted in **Table 26**, 1668 B-CLL patients were enrolled; these patients were predominantly male (range: 63 to 78%) with a median age ranging from 53.5 to 66 years. As is expected in trials of second-line treatments, the enrolled population tended to have more advanced disease than those enrolled in the first-line

treatment studies, with 37.5 to 100% of enrolled patients in Rai stage III or IV among the eight studies reporting these data. Across the 18 published reports using IV fludarabine as second-line treatment for B-CLL that included 25 or more patients, 17 contained an efficacy evaluation including CR, PR, and OR rates. The most common dosage administered intravenously was 25 mg/m2/day for 5 days, once a month. The OR rate ranged from 12% to 73% (excluding the subgroup of patients not refractory to alkylating agents from Keating et al. (1993); these patients had an OR rate of 93%. Reports of CR rates ranged from 0 to 28% excluding the non-refractory patients from Keating et al. (1993[39]; CR rate was 57% for these patients) and PR rates ranged from 9 to 71%. This range most likely reflects the extent of prior therapy and other prognostic factors relevant at the time of the study. The median duration of response was reported in two studies and ranged from 6 to 16 months. Median time to progression was reported in only six of these studies and ranged from 8 to 20 months. Nine studies reported median survival time, which ranged from 9 to 24.3 months, excluding the non-refractory patients from Keating et al. (1993); median survival of 29 months).

In contrast, only one study has been published to date using oral fludarabine alone as second-line therapy in this population (Boogaerts et al., 2001); this was a publication based on Study ME96029. This study noted a 51% OR rate (CR 18%, PR 33%). The reported SD rate was 24%. Duration of response, time to progression, and median survival time were not reported in this published paper.

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Table 26: Literature Review Summary – Second-Line Treatment

First Author and Year*	Number of Evaluable Patients	Fludarabine Regimen	Study Phase	Response Criteria	CR	nPR	PR	SD	ORR	DOR -M	TTP-M	Med Surv-M
Grever MR, 1988.	32	20 mg/m2 IV daily for 5 days every 4 weeks	Phase 2 SWOG study***	Described but not specified	3.1		9.3		12.4			
Keating MJ, 1989.	68	25-30 mg/m2 IV daily for 5 days every 4 weeks	Phase 1-2 MDACC study***	Described but not specified	13	16	28		57			16
Puccio CA, 1991.	42	20 mg/m2 IV bolus + 30 mg/m2 IV infusion daily for 48 hours	Phase 2 NYUMC study***	Described but not specified			31	33	31	6		10
**Keating M.J, 1993.	78 (refractory 50, non-refractory 28)†	25-30 mg/m2 IV daily for 5 days every 4 weeks	Not mentioned	NCIWG	14R (28) 16NR (57)		5R (10) 10NR (36)		19R (38) 26NR (93)		18 R, 17 NR	9R, 29 NR

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First Author and Year*	Number of Evaluable Patients	Fludarabine Regimen	Study Phase	Response Criteria	Response Rate (%)					DOR -M	TTP-M	Med Surv-M
					CR	nPR	PR	SD	ORR			
Zinzani PL, 1993.	29	25 mg/m2 IV daily for 5 days every 4 weeks	Not mentioned	Described but not specified	0		37		37	16		15
Kemena A, 1993.	46	25-30 mg/m2 IV daily for 5 days every 3 to 4 weeks	Not mentioned	Described but not specified	15		9		24			
Hensel M, 1994.	45	25 mg/m2 iv daily for 5 consecutive days every 4 weeks	Not mentioned	Not specified	4		30		34		12	
Johnson S, 1994.	126	25 mg/m2 IV daily for 5 consecutive days every 4 weeks	Phase 2	Not specified	6 (4.8)		26 (20.6)		32 (25.3)			
O'Brien ME, 1994.	26‡	25 mg/m2 IV daily on 5 consecutive days every 4 weeks; 5 cycles given	Not mentioned	IWCLL	15		37		52			
Fenchel K, 1995.	59	25 mg/m2 IV daily for 5 days as a 30 minute infusion every 5 weeks	Not mentioned	NCI	5		68		73			
Robertson LE, 1995.	80	30 mg/m2 IV daily for 3 days every 4 weeks	Not mentioned	NCIWG	10	15	21		46			18††
Johnson S, 1996.	48	25 mg/m2 IV daily for 5 days	Prospective randomized fludarabine vs. CAP	NCIWG	13		35		48		10.8	24.3

First Author and Year*	Number of Evaluable Patients	Fludarabine Regimen	Study Phase	Response Criteria	Response Rate (%)					DOR -M	TTP-M	Med Surv-M
					CR	nPR	PR	SD	ORR			
Montserrat E, 1996.	68	20-30 mg/m2 IV daily for 3-5 days every 4 weeks; most commonly used regimen fludarabine 25 mg/m2 IV daily for 5 days	Not mentioned	Described but not specified	4		24		28			
Sorensen JM, 1997.	703	25 mg/m2 IV daily for 5 consecutive days every 4 weeks	Phase 2	NCIWG	3		29		32		13.1	12.6‡‡
Zinzani PL, 1997.	77	25 mg/m2 IV daily for 5 consecutive days every 4 weeks.	Not mentioned	NCIWG	4		41		45		20	24
Foran JM, 1999.	27 7 CLL	Cycles 1-3: 50, 70, or 90 mg PO on day 1, 25 mg/m2 IV daily for days 2-5. Cycle 4: 50 mg PO on day 1, 25 mg/m2 IV daily for days 2-5 Cycle 5+: 25 mg/m2 IV daily for 5 days		IWCLL			71		71			
Bezares FR, 1998.	63	25 mg/m2 IV daily for 5 days every 28 days; 6 cycles given	Not mentioned	Not specified	18		43		61		8	20

First Author and Year*	Number of Evaluable Patients	Fludarabine Regimen	Study Phase	Response Criteria	Response Rate (%)					DOR -M	TTP-M	Med Surv-M
					CR	nPR	PR	SD	ORR			
Stelitano C, 1999.◊	30	25 mg/m2 IV daily for 4 days every 3 weeks in 29 cases, or for 5 days every 4 weeks in 18 cases		TTM Scores								
Boogaerts AM, 2001.◘	78	40 mg/m2 PO daily for 5 days every 4 weeks.		NCIWG & IWCLL	17.9	-	33.3	24.4	51.3			

BM = bone marrow; CAP = cyclophosphamide, doxorubicin and prednisone; CR = complete remission; DOR = duration of response; IV = intravenous; nPR = nodular

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6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

The proposed indication is; Fludarabine is indicated for the 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 regimen.

Submitted pivotal study ME96029 included 78 *previously treated* B-CLL patients treated with fludarabine 40 mg/m^2 orally daily for 5 days every 28 days. Remission rates were 51%, (NCI criteria, 5% CR) and 46% IWCLL (International Workshop on CLL criteria, 21% CR), best case analysis (all patients who responded to treatment were deemed a responder, regardless of when they discontinued treatment) and 41% NCI criteria (18% CR) and 35% IWCLL criteria (19% CR), worst case analysis (patients who were withdrawn from study were regarded as treatment failures unless the reason for withdrawal was achievement of CR. Duration of response and time to progression were not assessed in study ME96029. However, the mean number of treatment cycles for patients in study ME96029 was 5.1, with a mean daily dose of fludarabine of 38 mg/m^2. which was slightly below the target dose of 40 mg/m^2/day. Since cycles were repeated at a minimum of every 28 days and since remissions often occurred after 1 cycle of treatment a minimum estimated remission duration is >16 weeks.

Two other studies, conducted in *previously-untreated* B-CLL patients, support the activity of oral fludarabine with respect to time dependent efficacy endpoints. Study 303080 included 81 patients treated with fludarabine 40 mg/m^2 PO daily for five days every four weeks. The remission rate was 80%, NCI criteria (12% CR) and 72% IWCLL (37% CR), best case analysis and 69% NCI criteria and 61% IWCLL criteria, worst case analysis. Median duration of remission was 22.6 months and median time to treatment progression was 29.2 months.

Study LRF CLL4 included 124 assessable non-randomized patients who received fludarabine 40 mg/m^2 PO daily for five days every four weeks and 57 non-randomized patients who, early in the study, received IV fludarabine . The overall response rate (CR +nPR + PR) was 90% for IV fludarabine and 71% for oral fludarabine. Median response duration was 779 days for oral fludarabine and 701 days for IV fludarabine. Again, it should be emphasized that these are non-randomized comparisons. Patients receiving oral fludarabine were enrolled when that drug became available and were older, with poorer performance status, more advanced disease, and lower platelet and hemoglobin levels.

These results were compared with efficacy data from three studies of IV fludarabine, 20+ mg/m^2 daily for five days every 28 days in previously treated CLL patients and two studies of IV fludarabine in previously-untreated B-CLL patients, CALGB 9011, (175 patients) and CLL 101 [redacted] study (53 patients). b(4)

The overall response rates in the pivotal study of oral fludarabine in relapsed or refractory patients with B-CLL (ME96029) were slightly better than the rates observed following treatment with IV fludarabine in the MDAH (T83-1275) study (48%, 13% CRs using NCI criteria, best case analysis and 23% (8% CR) using NCI criteria, worst case analysis) and in refractory or relapsed patients with B-CLL from the SWOG (83-78) study (32% using NCI criteria 13% CR), best case analysis and 19% using NCI criteria (13% CR), worst case analysis). When response was assessed using IWCLL response criteria and compared with results from the subset of previously-treated patients with B-CLL in Study CLL 101 (———— Study) using IWCLL criteria, the overall response rate in the pivotal study of oral fludarabine (ME96029) was lower than that observed with IV fludarabine (35% in ME96029), versus 45% in CLL 101 ———— Study. b(4)

The median duration of response in relapsed or refractory patients with B-CLL treated with IV fludarabine ranged from > 37 weeks(SWOG, 83-78) to > 41 weeks (MDAH, T83-1275), and median survival time ranged from 45 weeks (MDAH, T83-1275) to 54 weeks (SWOG, 83-78). Duration of response and time to progression were not assessed in study ME96029.

For studies in previously-untreated patients, the criteria used to assess response varied among the studies. The overall response rate seen in the study of oral fludarabine (303080) was as good as or better than the overall response rates seen in the studies of IV fludarabine, which ranged from 61% (CALGB criteria) to 70% (IWCLL criteria).

The median duration of response for previously-untreated patients ranged from 19 months following IV fludarabine (CALGB 9011) to 22.6 months following oral fludarabine (303080). Median time to progression ranged from 17.4 months following IV fludarabine (CALGB 9011) to 29.2 months following oral fludarabine (303080).

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

Safety assessments consisted of reviewing the submitted data and manuscripts. These are summarized below as AEs and SAEs.

In the pivotal study ME96029 Hematologic examinations (hematology and differential count, and chemistries) were performed at baseline, within 48 hours before the start of each treatment cycle, and at the end of treatment visit. Immunologic evaluations of peripheral blood, including CD4 and CD8 counts and Coombs test were performed at baseline and at the end of treatment examination. At each evaluation, patients were asked if they had experienced any health-related problems or if they had any symptoms of concurrent disease or comorbid medical conditions.

Exposure to Study Drug – Study ME96029

The mean number of treatment cycles for patients in this study was 5.1, with a mean daily dose of fludarabine of 38 mg/m^2, which was slightly below the target dose of 40 mg/m^2/day. A summary of exposure to oral fludarabine is presented in **Table 27.**

Patients who responded to treatment but who had not achieved a complete remission (CR) after the sixth treatment cycle were allowed to continue treatment for up to eight cycles after consulting with the Core Clinician/Study Manager.

Patients who did not respond after two cycles of treatment, or who showed clinical signs of disease progression after two cycles were withdrawn from the study. Two cycles of treatment were considered the minimum time required before an evaluation of treatment failure could be made. Additionally, any patient who was experiencing severe toxicity (according to WHO toxicity scale) was to have been withdrawn.

Table 27: Exposure to Oral Fludarabine – Study ME96029 (AZ84)

	ITT Group (n=78)
Number of cycles, N (%)	
1	3 (4)
2	12 (15)
3	8 (10)
4	3 (4)
5	5 (6)
6	30 (38)
7	3 (4)
8	14 (18)
Total number of courses	401
Daily dose (mg/m2/day) Mean (range)	38 (18-43)
Dose/cycle (mg/m2) Mean (range)	187 (27-214)
Cumulative dose (mg/m2/patient) Mean (range)	968 (191-1647)
Cycles/patient (range) Mean (range)	5.1 (1-8)

A summary of dose adjustments during this study is presented in **Table 28.** Fifty-three (68%) of the 78 patients had no dose reduction during the study, and 25 (32%) patients had dose reductions. Dose reductions due to hematological toxicity occurred 49 times for 20 patients, three times due to non-hematological toxicity for three patients, and three times due to both hematological and non-hematological toxicity for two patients.

Table 28: Dose Adjustments – Study ME96029

	ITT Group (n=78)
No adjustment	31 (40%)
Study discontinuation before end of cycle 6 without dose adjustment	21 (27%)
Dose increase	1 (1%)
Dose increase with subsequent dose reduction	0
Dose reduction	9 (12%)
Dose reduction with subsequent dose increase	6 (8%)
Dose reduction then discontinuation before end of cycle 6	10 (13%)

A summary of treatment postponements by treatment cycle are presented in **Table 29**. A total of 45 treatment postponements were required in 26 patients because of hematological toxicities. In 14 patients, there were 15 postponements of study drug treatment because of non-hematological toxicities. There were four postponements due to both hematological and non-hematological toxicities for four patients and 70 postponements for other reasons for 33 patients.

Table 29: Treatment Postponements – Study ME96029

Treatment Cycle	Number of Patients Receiving Oral Fludarabine During the Cycle	Number of Patients with Treatment Postponements for Any Reason
2	75	28/75 (37%)
3	63	28/63 (44%)
4	55	21/55 (38%)
5	52	20/52 (39%)
6	47	19/47 (40%)
7	17	12/17 (71%)
8	14	6/14 (43%)

Adverse events were reported for 82.1% of patients (64/78) in study ME96029. The most common adverse events (those reported for at least 5% of patients) in study ME96029 are shown in **Table 30** while **Table 31** shows moderate adverse events that were reported at an incidence of at least 2% in patients receiving oral fludarabine phosphate.

Table 30: Adverse Events Reported in ≥5% of Patients – Study ME96029

Adverse event (HARTS Code Version 2.3)	Study 96029 (N=78)	
	n	%
At least 1 adverse event	64	82.1
Fever	20	25.6
Cough increase	16	20.5
Anorexia	15	19.2
Asthenia	10	12.8
Infection	9	11.5
Headache	7	9.0
Upper respiratory infection	7	9.0
Flu syndrome	6	7.7
Herpes simplex	6	7.7
Pain abdomen	6	7.7
Pneumonia	6	7.7
Sweating	6	7.7
Bronchitis	5	6.4
Diarrhea	5	6.4
Nausea	4	5.1
Pain	4	5.1
Rash	4	5.1

Table 31: Moderate AEs Reported with an Incidence of ≥2%, Study ME96029

Adverse event (HARTS Code Version 2.3)	Study ME96029 (N=78)	
	n	%
Fever	13	17
Infection	5	6
Upper respiratory infection	5	6
Abdominal pain	3	4
Anorexia	3	4
Bronchitis	3	4
Cough	3	4
Pneumonia	3	4
Asthenia	2	3
Headache	2	3
Herpes simplex	2	3
Pain	2	3
Rash	2	3

A summary of severe (grade 3-4) adverse events that occurred at an incidence of ≥2% for study ME96029 is shown in **Table.32**. The predominant severe toxicity reported with oral fludarabine phosphate was related to myelotoxicity.

Table 32: Severe AEs Reported with an Incidence of ≥2%, Study ME96029

Adverse event (HARTS Code Version 2.3)	Study ME96029 (N=78)	
	n	%
Autoimmune hemolytic anemia	4	5.2
Pneumonia	3	3.8
Anemia	2	2.6
Anorexia	2	2.6
Fever	2	2.6
Leukopenia	2	2.6
Taste perversion	2	2.6
Thrombocytopenia	2	2.6

Study 303080

Exposure to Study Drug – Study 303080 (B820)

The mean number of treatment cycles in this study was 5.9. Most patients (48.1%) received six cycles of fludarabine. A summary of exposure to oral fludarabine during this study is presented in **Table 33.**

Table 33: Exposure to Oral Fludarabine – Study 303080 (B820)

	ITT Group (n=81)
Number of cycles, N (%)	
1	5 (6.2)
2	1 (1.2)
3	3 (3.7)
4	3 (3.7)
5	7 (8.6)
6	39 (48.1)
7	2 (2.5)
8	21 (25.9)
Cycles/patient (cycles) Mean (range)	5.9 (1 – 8)

Dose reductions due to hematological toxicity were necessary 11 times for seven patients, 10 times due to non-hematological toxicity for three patients, and seven times due to other reasons for four patients.

Study drug postponements because of hematological toxicities were necessary 20 times for 12 patients. In eight patients, there were nine postponements of study drug treatment because of non-hematological toxicities. There was one postponement due to both hematological and non-hematological toxicities for one patient, and there were

31 postponements for other reasons for 21 patients.

In clinical study 303080, adverse events were reported for 88.9% of patients (72/81). The most common adverse events (those reported for at least 5% of patients) in study 303080 are shown in **Table 34**. Severe adverse events reported in ≥2% of patients are shown in **Table 35**.

Table 34: Adverse Events Reported in ≥5% of Patients - Study 303080

Adverse event (HARTS Code Version 2.3)	Study 303080 (N=81)	
	n	%
At least 1 adverse event	72	88.9
Asthenia	25	30.9
Pain	15	18.5
Infection	14	17.3
Sweating increased	11	13.6
Upper respiratory infection	11	13.6
Fever	9	11.1
Rhinitis	9	11.1
Abdominal pain	8	9.9
Back pain	7	8.6
Headache	7	8.6
Bronchitis	7	8.6
Peripheral edema	6	7.4
Herpes simplex	6	7.4
Anemia	5	6.2
LDH increased	5	6.2
Weight loss	5	6.2
Cough increased	5	6.2

Table 35: Severe AEs Reported with an Incidence of ≥2%, Study 303080

Adverse event (HARTS Code Version 2.3)	Study 303080 (N=81)	
	n	%
Anemia	3	3.7
Asthenia	3	3.7
Infection	3	3.7
Sweating increased	3	3.7
Pneumonia	2	2.5

In Study LRF-CLL4 (publication by Catovsky et al. 2007), the most common adverse events reported for patients receiving fludarabine phosphate are shown in **Table 36.** In the reporting of AEs no distinction was made between the fludarabine phosphate groups treated with PO and IV fludarabine phosphate. According to the authors, diarrhea and nausea increased with oral administration of fludarabine phosphate (data were not provided).

Table 36: Most Common Adverse Events - Study LRF-CLL4

Adverse event	Fludarabine phosphate a (N=187)	
	n	%
Neutropenia (neutrophils <1x109/L)	78	41
Hospitalization (≥1 day)	69	36
Nausea and vomiting	53	28
Febrile episodes (≥1)	52	27
Diarrhea	46	24
Mucositis	22	12
Thrombocytopenia (platelets <100x109/L)	21	11
Hemolytic anemia	21	11
Alopecia	17	9

a Includes both PO and IV fludarabine phosphate.

In Study ME95101, the most frequently reported adverse events were cough 30% [8/27]), fever 22% [6/29]), dizziness (15% [4/29]), and chills and fever (11% [3/29]). The most frequent WHO non-laboratory toxicities consisted of infection (74% [20/29]), consciousness toxicity (56% [15/29]), pulmonary (37%. [10/29]), nausea/vomiting (33% [9/29]), oral, diarrhea and drug-fever (all in 30% [8/29]), constipation and cutaneous (22% [6/29]), peripheral neurotoxicity (19% [5/29), and hair, cardiac rhythm and cardiac function (all 11% [3/29]).

In Study ME94204, the most common adverse events were fever (16% [3/19]), nausea/vomiting, diarrhea, lymphadenopathy and urticaria (all reported in 11% [2/19] of

patients). All three patients with fever and the two patients with nausea/vomiting and diarrhea had the adverse events during oral therapy.
In Study ME96079 adverse events occurred in 83% (15/18) of patients. The most frequently reported adverse events were infection (22% [4/18]) and fever, pain, illdefined experience, dizziness, eye, pneumonia, and nausea/vomiting (each occurring in 11% [2/18] of patients). The incidence of adverse events in the fed and fasting states was similar and indicates that the drug may be administered with or without food.
In Study BL03-1109, the overall adverse experiences reported were consistent with those associated with IV fludarabine phosphate treatment. One exception was a report of a mild seizure that occurred 12 days after the last IV dose of fludarabine phosphate and was considered not related to study drug. Regardless of the route of administration, the most common events were hematologic, and those relating to the digestive tract and body as a whole. Two patients experienced gastrointestinal adverse events after oral treatment and six patients experienced gastrointestinal adverse events after intravenous treatment.

For Study TB03-1103, safety results were not reported to the Sponsor.

7.1.1 Deaths

Most deaths in the oral studies were due to progression of disease. Two deaths (Patient 139 and Patient 150) in Study ME96029 were reported to be probably related to study drug. One patient died two months after completing cycle 3 due to respiratory failure and pneumonia. The patient had pneumonia and thrombocytopenia. A second patient died more than two months after completing cycle 2 due to pulmonary aspergillosis. One patient in Study 303080 (Patient 2006) died approximately 3 weeks after completion of Cycle 1; the investigator judged the death possibly related to study treatment. Post-mortem examination cited the cause of death as septicemia with disease progression.

The cause of death and incidence in all fludarabine phosphate oral studies is presented in **Table 37**. No death in the oral pharmacokinetic studies was judged to have been related to study drug. One patient in Study BL03-1109 died of metastatic laryngeal carcinoma; the investigator did not indicate whether or not the death was related to study drug.

Table 37: Deaths - Oral Fludarabine Studies

Primary Cause of Death	Study ME96029 (N=78)				Study 303080 (N=81)				Phase 1/2 Studies (N=80)			
	Any Death		Drug Related Death		Any Death		Drug Related Death		Any Death		Drug Related Death	
	n	%	n	%	n	%	n	%	n	%	n	%
Death due to any cause	4	5	2	3	1	1	1	1	5	6	0	0
Progression of disease	2	3	0	0	0	0	0	0	3	4	1*	1
Respiratory failure	1	1	1	1	0	0	0	0	1	1	0	0
Cardiac arrest	0	0	0	0	0	0	0	0	1	1	0	0
Infection	1	1	1	1	1	1	1	1	0	0	0	0

7.1.2 Other Serious Adverse Events

Serious adverse events occurred in 37% (29/78) of patients in Study ME96029, of which 26% were determined to be drug-related (**Table 38**). A total of 49 serious adverse events were reported in these 29 patients. Most serious adverse events were related to infection or myelosuppression. The serious adverse events most frequently reported consisted of fever (10% [8/78]), pneumonia (8% [6/78]), infection (6% [5/78]), hemolysis (4% [3/78]), leukopenia (4% [3/78]), and anemia (3% [2/78]).A total of 33 serious adverse events was determined to be study drug related.

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Table 38: Drug Related SAEs – Study ME96029

	Study ME96029 (N=78)			
	Serious Adverse Events		Serious Adverse Events considered drug-related	
HARTS Term	n	%	n	%
Total	29	37	20	26
Fever	8	10	6	8
Pneumonia	6	8	3	4
Infection	5	6	5	6
Hemolytic anemia	3	4	3	4
Cough	3	4	3	4
Anemia#	2	3	2	3
Leukopenia	3	4	2	3
Thrombophlebitis	2	3	0	0
Sepsis	1	1	1	1
Angina pectoris	1	1	1	1
Vasculitis	1	1	1	1
Urinary tract infection	1	1	1	1
Pancytopenia or myelosuppression	1	1	1	1
Thrombocytopenia	1	1	1	1
Headache	1	1	1	1
Dyspnea	1	1	1	1
Upper respiratory infection	1	1	1	1
Abdominal pain	1	1	NR	NR
Cellulitis	1	1	NR	NR
Surgery	1	1	NR	NR
Carcinoma GI	1	1	NR	NR
Hemoptysis	1	1	NR	NR
Pleural Effusion	1	1	NR	NR

Abbreviations; NR, Not Related
No data on whether SAE reported as "anemia" included "hemolytic anemia"

Forty-four serious adverse events were reported for 18 patients in Study 303080. For the most part, these SAEs were related to myelosuppression and infections, with 36.4% of these incidents considered either unrelated or with an unlikely relationship to study medication. The incidence of SAEs in Study 303080 is provided in **Table 39.**

Table 39: Serious Adverse Events - Study 303080

	Study 303080 (N=81) Serious Adverse Events	
HARTS Term	**n**	**%**
Total	18	22
Fever	6	7
Infection	3	4
Anemia	3	4
Autoimmune hemolytic anemia	3	4
Pneumonia	2	3
Overdose	2	3
Kidney function abnormal	2	3
Infarct	1	1
Thrombocytopenia	1	1
Respiratory disorder	1	1
Kidney pain	1	1
Acute kidney failure	1	1
Rash	1	1
Amylase increased	1	1
Abdominal pain	1	1
Vomiting	1	1
Diarrhea	1	1
Sepsis	1	1
Atrial fibrillation	1	1
Heart failure	1	1
Peripheral edema	1	1
Dyspnea	1	1

In Study LRF-CLL4, SAEs other than death were reported in 4.7% (9/191) of patients who received fludarabine phosphate only. Patients in this study may have received PO or IV fludarabine phosphate.

Serious adverse events were reported in 24 of 80 patients (30%) participating in fludarabine phosphate oral pharmacokinetic studies. Of these, SAEs in 14 patients (18%) were considered drug-related. The most common SAEs (overall and those considered drug-related) in Phase 1/2 studies were infection, pneumonia, chills/fever, and fever.

7.1.3 Dropouts and Other Significant Adverse Events

Many of the adverse events in Study ME96029 were tolerable without dosage

adjustment; those events that required a reduction in dosage frequency generally improved or resolved after dosage reduction. A total of 32% (25/78) of patients in Study ME96029 withdrew because of an adverse event. Leukopenia and thrombocytopenia were the most common adverse events which each caused withdrawal in 5% (4/78) of patients. The next most common events causing withdrawal were infection and hemolytic anemia which each caused withdrawal in 4% (3/78) of patients.

Gastrointestinal adverse events infrequently required dose reduction or postponement of treatment. In Study ME96029 there was one withdrawal (Patient 148) because of abdominal pain due to intestinal obstruction judged not related to study drug. The patient subsequently was determined to have had transformation to Richter's disease and died about one month after withdrawal because of progression of disease. There were no other withdrawals because of gastrointestinal toxicity, although two patients (Patients 33 and 37) had severe anorexia at the time of withdrawal because of lack of efficacy. Patient 33 also had mild nausea/vomiting and diarrhea and Patient 37 also had mild nausea/vomiting. Patient 67 had severe nausea/vomiting and weight loss at the time of withdrawal because of pneumonia.

Sixteen adverse events resulting in withdrawal from Study 303080 were reported in 1.6% of patients (13/81) (**Table 40**). Of these 16 events, 1 was considered not related, 4 were considered unlikely related, 4 were considered possibly related, 5 were considered probably related, and 2 were considered definitely related. Adverse events requiring dosage adjustment were not examined in Study 303080.

Table 40: Patients Prematurely Discontinued Due to AEs, Study 303080

Cycle Number	Patient Number	Adverse event by HARTS preferred term (outcome)	Relationship to study drug
1	1002	Infarct (recovered completely)	Unlikely
	1004	Thrombocytopenia (recovered completely)	Probable
	28004	Autoimmune hemolytic anemia (complete recovery)	Probable
3	23001	Pneumonia (recovered completely)	Probable
	33003	Sepsis (recovered completely)	Definite
4	35006	Infection (recovered completely) Anemia (continuing) Fever (recovered completely)	Unlikely None Unlikely
5	7002	Anemia (recovered completely)	Probable
	10003	Foot drop (recovered completely)	Probable
	13002	Infection (recovered with residual effects)	Unlikely
	13003	Autoimmune hemolytic anemia (complete recovery)	Definite
	15004	Bronchitis (recovered completely)	Possible
	33002	Rash (outcome unknown) Face edema (outcome unknown)	Possible Possible
	34001	Autoimmune hemolytic anemia (complete recovery	Possible

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events – Comparison of Oral and IV Drug Delivery

Safety-related events with oral fludarabine have been compared to safety related events with IV fludarabine as assessed in the MDAH (T83-1275) and SWOG (83-78) studies. Safety evaluations of these studies were based on reports of adverse events by the investigator and by review of all patient documentation and graded according a MDAH and SWOG toxicity grading system.

The most common adverse events observed with oral fludarabine included myelosuppression (neutropenia, thrombocytopenia and anemia), infection, diarrhea, nausea and vomiting, fever, cough, anorexia, constipation, weakness (asthenia) and pain. The incidences of adverse events were similar in the SWOG and MDAH studies with IV fludarabine. In the MDAH Study anemia was reported in 15% of patients, neutropenia in 18% of patients, thrombocytopenia in 8% of patients, pancytopenia in 2% of patients and myelosuppression and unspecified blood abnormalities in 6% of patients. In the SWOG study, anemia and neutropenia were each reported in 28% of patients, leukopenia was reported in 31% of patients, thrombocytopenia was reported in 50% of patients, and myelosuppression was reported in 6% of patients. In Study ME96029 that used fludarabine phosphate tablets, the most prominent adverse events were related to bone marrow suppression. Adverse events reported included anemia in 9% of patients (anemia in 3% and hemolytic anemia in 6%), thrombocytopenia in 3%, and pancytopenia in 3%. Overall frequencies of hemato-suppression included anemia in 65% of patients, granulocytopenia in 79%, leucopenia in 64%, thrombocytopenia in 62% of patients.

Fever was reported with less frequency in study ME96029 (26% of patients) compared to the MDAH and SWOG studies (60% and 69% respectively. Weakness was reported in 13% of patients in the Study ME96029, 9% of patients in the MDAH study and in 65% of patients in the SWOG study. In Study ME96029 nausea and/or vomiting were reported as adverse events for 5 patients (6%), and diarrhea also was reported as an adverse event for 5 patients. In the MDAH and SWOG studies nausea and vomiting was reported as adverse events in 36% and 31% of patients; diarrhea was reported in 15% and 13% of patients. Anorexia was reported in 19% (15/78 patients) of patients in study ME96029, in 7% of patients in the MDAH study and in 34% of the patients in the SWOG study. While the incidence of gastrointestinal events

With respect to serious adverse events, the same pattern of serious adverse events was seen in the SWOG and MDAH studies for IV fludarabine phosphate compared to oral fludarabine phosphate in ME96029, with fever, pneumonia, infection, hemolysis, leukopenia and anemia as most frequent serious adverse events.

7.1.6 Laboratory Findings

See above

7.1.7 Vital Signs

No special analysis of vital signs were conducted in the trials presented in this report.

7.1.8 Electrocardiograms (ECGs)

The study reports for each of the conducted clinical studies with oral fludarabine phosphate (ME96029, 303080 and the PK studies), as well as post-market surveillance data were examined in an attempt to uncover signals that may suggest a significant risk for drug induced cardiac repolarization with oral fludarabine phosphate. In addition to searching for dose response or concentration effect relationships, other important considerations for the assessment of potential drug-induced altered cardiac repolarization include the extent of human exposure, the population studied or exposed, the clinical setting for drug exposure, type and timing of cardiac repolarization assessments performed, measured QT effects, detected QT outlier populations and cardiac rhythm adverse event reporting.

The paucity of reported adverse events that would be indicative of a causal mechanism involving fludarabine phosphate altered cardiac repolarization collected over the past approximate 16 year marketing history of fludarabine phosphate suggests that clinical consequences from drug induced QT prolongation are not taking place with use of this agent. This is reinforced by the fact that patients who are receiving this agent are being closely medically supervised during their treatment. The lack of cardiac adverse events, despite oral doses of fludarabine phosphate ranging to 50 mg/m2/day, during clinical testing in a Phase 1 research environment is consistent with that conclusion. The cardiac rhythm disturbances reported during clinical trials with oral fludarabine phosphate have been atrial in origin and would have required ECG evaluation to diagnose, providing opportunity to detect QT prolongation were this to occur. The safety database for fludarabine phosphate does not demonstrate a signal for clinical signs of drug induced altered cardiac repolarization associated with this drug. Taken together, these data suggest that the probability that fludarabine phosphate produces a clinically significant prolongation of the QT interval in cancer patients being treated with this agent is very low.

7.1.9 Immunogenicity

There is no new relevant information.

7.1.10 Human Carcinogenicity

There is no new relevant information.

7.1.11 Special Safety Studies

There is no new relevant information.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Fludarabine has no known potential for abuse..

7.1.13 Human Reproduction and Pregnancy Data

FDA Pregnancy Category D
A genotoxic potential of fludarabine phosphate was demonstrated in the Chinese hamster ovary cell chromosomal aberration assay and the mouse micronucleus test.

Interference with the process of spermatogenesis was expected for a compound known to inhibit DNA-synthesis. This assumption was confirmed by testicular changes at generally toxic doses observed in repeated dose toxicity studies in mice and rats.
The results from the embryotoxicity studies and the peri-/postnatal study revealed clear evidence of a toxic potential of fludarabine phosphate towards development. Fetotoxicity was evident as increased postnatal mortality and growth retardation of the rat pups (30 mg/kg/day). Teratogenic effects were recognized in rats (40 mg/kg/day, dose-finding study) and rabbits (8 mg/kg/day) where malformations were recorded with incidences clearly above spontaneous rates. While the low doses established in both studies (1 mg/kg/day; rats and rabbits) were below the threshold for embryotoxic and teratogenic effects, 100% embryo mortality precluded the assessment of possible teratogenic effects at the dose levels of 100 (rat, dose-finding study) and 25 mg/kg/day (rabbit, dose-finding study). Because the dosing periods covered the entire organogenesis, stage specificity of teratogenic effects could not be evaluated. Theoretically, the teratogenic properties of fludarabine phosphate could be directly linked to its inhibitory activity on DNA synthesis. The dose response characteristics described above are consistent with such a non-specific cytotoxic mechanism.

The most important issue with regard to quantitative risk assessment is the occurrence of maternal and developmental toxic responses at dose levels close to the therapeutic dose, particularly in the rabbit. Although no adverse effects were evident in either species at 1 mg/kg/day, indications of maternal toxicity and/or slight impairment of fetal development occurred after dosages as low as 10 or 5 mg/kg/day in rats or rabbits. Severe embryotoxic including teratogenic effects were recorded at 30-to-40 mg/kg/day in rats and at 8 mg/kg/day in rabbits. Due to the lack of pharmacokinetic data in rats and rabbits at this dose-range, a comparison of systemic fludarabine phosphate burden under experimental conditions with therapeutic systemic exposure is not possible. Thus, based on the absolute intravenous doses and considering possible species differences in distribution, metabolism and excretion of the compound, a relevant risk of embryotoxic/teratogenic effects has to be assumed after therapeutic treatment of pregnant women following intravenous or oral administration (0.7 to 1.4 mg/kg/day).

7.1.15 Assessment of Effect on Growth

No data was reported.

7.1.16 Overdose Experience

High doses of intravenous fludarabine phosphate have been associated with irreversible central nervous system toxicity characterized by delayed blindness, coma, and death. High doses are also associated with severe thrombocytopenia and neutropenia due to bone marrow suppression.

Two patients in study 303080 conducted with oral fludarabine phosphate (patients 14003 and 15003) took overdoses of study medication. Patient 14003 had 20% and 33% overdoses during cycles 3 and 6 respectively, and experienced no side effects. During cycles 1 and 2, patient 15003 took the correct dose of 80 mg/day for the full cycle of 5 days but took 50 mg/day for two additional days (25% overdose each cycle). The only clinical consequences reported were mild constipation and pain and the patient made a full recovery. Neither patient withdrew due to these overdoses.

There is no known specific antidote for fludarabine phosphate overdose. Treatment consists of drug discontinuation and supportive therapy.

7.2 Adequacy of Patient Exposure And Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The duration of exposure was based on therapeutic results. Treatment appeared to be reasonably tolerated..

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Prior evaluation of the safety of intravenously administered fludarabine.

7.2.3 Adequacy of Overall Clinical Experience

AE's associated with fludarabine treatment have been well described. The safety database of oral fludarabine phosphate in this application provides data on 502 patients treated with the oral formulation of fludarabine phosphate. This includes 474 patients treated with oral fludarabine phosphate tablets. Seventy-eight of these patients who received fludarabine phosphate monotherapy were diagnosed with B-CLL that was refractory to or had relapsed during or after treatment with at least one alkylating agent –containing regimen (Study ME96029). This is the population for which the sponsor is seeking approval for oral fludarabine phosphate. In addition, 92 B-CLL, NHL and low grade NHL patients were

treated with oral fludarabine phosphate monotherapy in pharmacokinetic studies, and 81 previously untreated B-CLL patients received oral fludarabine phosphate monotherapy treatment in Study 303080. Additionally, limited safety data are available from Study LRF CLL4, where 122 B-CLL patients received oral fludarabine phosphate monotherapy and 129 patients received a combination treatment of oral fludarabine phosphate and cyclophosphamide, both as initial B-CLL therapy. Finally, post-marketing safety surveillance data are available from over ——— patients treated with oral fludarabine phosphate in regions of the world where this formulation is approved. b(4)

Across all of these studies in the clinical development program, oral fludarabine phosphate therapy was generally well tolerated. The most commonly reported adverse events and WHO toxicities reported across all studies with oral fludarabine phosphate typically included myelosuppression, fever, cough, nausea, vomiting, diarrhea, asthenia, anorexia, and infections. These events were usually mild or moderate in severity with non-hematological Grade 3-4 events occurring in up to 8% of patients and hematological grade 3-4 toxicities occurring in up to 25% of patients. Adverse events and toxicities observed with oral fludarabine phosphate did not significantly differ from the adverse event profile of the IV formulation of fludarabine phosphate, with the exception of mild/moderate nausea/vomiting and diarrhea which seemed to occur at slightly higher rates in patients treated with oral fludarabine phosphate, based on reported WHO toxicities, compared to patients treated with IV fludarabine phosphate. Post-marketing experience in clinical practice with oral fludarabine phosphate over the past 6 years shows that, based on voluntary reported adverse drug reactions during the marketed period, the safety profile of oral fludarabine phosphate has not significantly changed from when oral fludarabine phosphate was initially approved in 2000 in the UK. Taken together, these data indicate that the safety profile of oral fludarabine phosphate therapy for B-CLL patients is both predictable and manageable.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new information was provided. Animal and/or In-Vitro Testing was adequate based on previous submissions.

7.2.5 Adequacy of Routine Clinical Testing

Adequate

7.2.6 Adequacy of Metabolic. Clearance. and Interaction Workup

Adequate

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Evaluation for potential adverse events was adequate. No new recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

Data was of high quality and was complete. All relevant information was submitted.

7.3 Summary Of Selected Drug- Related Adverse Events. Important Limitations Of Data. And Conclusions

There is extensive data regarding the AE profile of IV and PO fludarabine. The most common adverse events observed with oral fludarabine included myelosuppression (neutropenia, thrombocytopenia and anemia), infection, diarrhea, nausea and vomiting, fever, cough, anorexia, constipation, weakness (asthenia) and pain. The incidences of adverse events were similar in the SWOG and MDAH studies with IV fludarabine. In the MDAH Study anemia was reported in 15% of patients, neutropenia in 18% of patients, thrombocytopenia in 8% of patients, pancytopenia in 2% of patients and myelosuppression and unspecified blood abnormalities in 6% of patients. In the SWOG study, anemia and neutropenia were each reported in 28% of patients, leukopenia was reported in 31% of patients, thrombocytopenia was reported in 50% of patients, and myelosuppression was reported in 6% of patients. In Study ME96029 that used fludarabine phosphate tablets, the most prominent adverse events were related to bone marrow suppression. Adverse events reported included anemia in 9% of patients (anemia in 3% and hemolytic anemia in 6%), thrombocytopenia in 3%, and pancytopenia in 3%. Overall frequencies of hemato-suppression included anemia in 65% of patients, granulocytopenia in 79%, leucopenia in 64%, thrombocytopenia in 62% of patients.

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7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Because of the large amount of safety data already available it was not felt to be worthwhile to pool safety data. .

7.4.2 Explorations for Predictive Factors

Predictive factors including dose dependency, time dependency, drug-demographic interactions, and drug-disease interactions were not explored in the current study.

7.4.3 Causality Determination

AE's occurring with Fludarabine treatment likely represent the effect of the drug in the population of patients with B-CLL.

8.0 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen for oral fludarabine is 40 mg/m2 daily for 5 days every 28 days dependent on observed drug toxicity.

8.2 Drug-Drug Interactions

Fludarabine in combination with pentostatin is not recommended because of the risk of severe pulmonary toxicity.

8.3 Special Populations

Renal Impairment:
- Reduce dose by 20% in adult patients with moderate renal impairment (creatinine clearance 30 to 70 mL/min/1.73 m2).
- Not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m2).

8.4 Pediatrics

In accordance with 21 CFR 314.55 the sponsor requests a waiver of the requirements to conduct studies in pediatric patients. CLL is not a disease that is prevelant in pediatric patients.

8.5 Advisory Committee Meeting

An ODAC meeting to discuss this application is not planned.

8.6 DSI Inspection

Foreign Sites audited:

Site audited in Belgium
Professor Dr. Gregor E.G. Verhoef
U.Z. Gasthuisberg, Trial Bureau Hematologie
Herestraat 49, B-3000 Leuven, Belgium
Dates of inspection: November 20-21, 2000

Site audited in Italy: Professor Sante Tura
Instituto di Ematologia "L. e A. Seragnoli"
Universita degli Studi, Via Massarenti 9, I-40138, Bologna, Italy
Date of inspection: November 23, 2000

Basis for Site Selection: Prof. Verhoef's center enrolled ten subjects (being the largest number of subjects enrolled), and Prof. Tura's center enrolled five subjects all of whom were treatment responders. Thus, inspection of these sites is critical for approval of this drug.

Methodology: An inspection assignments was issued to the field offices through the International and Technical Operations Branch of the Division of Emergency and Investigational Operations, FDA.

Overall Assessment Of Findings And General Recommendations
At both study sites, there was sufficient documentation at this site to assure that all audited subjects did exist, met the inclusion and exclusion criteria, and were available for the duration of the study and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded (exceptions noted), completed the study, and had their outcome captured as specified in the protocols and amendments.

Instances of deviations from protocol or inaccurate record keeping or problems with drug accountability were found, which were not of clinical significance to require exclusion of any subject from data analysis.

Thus, it was recommended that data from all of the subjects at the center in Leuven, Belgium and Bologna, Italy.

8.7 Proposed Phase 4 Study

Title	A Phase 4 randomised multicentre study to evaluate the efficacy and safety of front-line therapy with oral fludarabine phosphate versus chlorambucil in patients with progressive B-cell chronic lymphocytic leukaemia (B-CLL)
Rationale	Oral fludarabine phosphate has received marketing approval in the United States under 21 CFR 314 subpart H ("accelerated approval") for the treatment of relapsed or refractory B-CLL, based on a surrogate endpoint reasonably likely to predict clinical benefit. However, direct demonstration of clinical benefit of oral fludarabine phosphate, which would support regular approval of the drug, has not yet been performed. In addition, although oral fludarabine phosphate is approved for front-line therapy of B-CLL in certain territories outside the United States, the comparative clinical benefit of oral fludarabine phosphate vs. a standard front-line therapy for B-CLL has never been demonstrated. Chlorambucil is also approved and commonly used as monotherapy for the treatment of B-CLL, including front-line therapy for B-CLL. Two recent randomised Phase 3 trials studied chlorambucil as front-line therapy for B-CLL.1, 2 Combining chlorambucil and IV fludarabine phosphate led to increased toxicity without any increase in efficacy, so consequently chlorambucil is not used in combination with either the IV or oral formulation of the drug.3 This present trial is designed to demonstrate the comparative clinical benefit of oral fludarabine phosphate monotherapy vs chlorambucil monotherapy, as front-line therapy for B-CLL.
Study design	This study is a multicentre, randomised, active control study of oral fludarabine phosphate monotherapy versus chlorambucil monotherapy in patients with progressiv B-CLL. Patients will be randomised to receive either oral fludarabine phosphate 40 mg/m2 p.o days 1-5 every 28 days (Arm A), or chlorambucil 40 mg/m2 po every 28 days (Arm B). Treatment on each arm will be provided for 6 months or until disease progression, if sooner
Objectives	The primary efficacy endpoint of the trial is progression-free survival (PFS) duration calculated from the date of randomisation to the date of disease progression or relaps as documented by an independent response review panel, or the date of death from a cause, whichever occurs earlier. Secondary endpoints include complete response (CR) rate; overall response (OR) rat (CR + nodular partial response (nPR) + partial response (PR)); and safety.
Population	Patients with previously untreated Rai stage I-IV B-CLL experiencing progression of their disease

Sample Size Justification	The estimated median PFS following treatment with oral fludarabine monotherapy is estimated at 20 months, based on 4 recent clinical trials of IV or oral fludarabine phosphate monotherapy in patients with previously untreated B-CLL.3-6 The estimated median PFS following this proposed dose and schedule of chlorambucil is 11.7 months, based on 2 recent clinical trials.2, 3 Approximately 200 patients will provide 90% power to detect a statistically significant difference (α=0.05, two tailed) in PFS between the two treatment arms, assuming a 2.5 year enrolment and 1.5 year follow up period.
Number of centres and geographical location	Approximate number of patients: 200 Approximately 20-30 centres Regions: United States, Europe, and other territories

8.8 Literature Review

1. Angelopoulou MA, Poziopoulos C, Boussiotis VA, et al. Fludarabine monophosphate in refractory B-chronic lymphocytic leukemia: maintenance may be significant to sustain response. Leuk Lymphoma 1996;21:321;324.
2. Anaissie EJ, Kontoyiannis DP, O'Brien S, et al. Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Intern Med 1998;129(7):559-566.
3. Bergmann L, Fenchel K, Jahn B, et al. Immunosuppressive effects and clinical response of fludarabine in refractory chronic lymphocytic leukemia. Ann Oncol 1993;4:371-375.
4. Bezares R, Murro H, Marquez M, et al. A multicentric trial on chronic lymphocytic leukemia with fludarabine. An interim analysis. Br J Hematol 1998;102:Abstract P-0767.
5. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48(1):198-206.
6. Boogaerts MA, Van Hoof A, Catovsky D, et al. Activity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia. J Clin Oncol 2001;19(22):4252-4258.
7. Bosch F, Ferrer A, Lopez-Guillermo A, et al. Fludarabine, cyclophosphamide and mitoxantrone in the treatment of resistant or relapsed chronic lymphocytic leukaemia. Br J Haematol 2002;119:976-984.
8. Brockman RW, Schabel Jr FM, Montgomery JA. Biologic activity of 9-β-Darabinofuranosyl-2-fluoroadenine, a metabolically stable analog of 9-β-D-arabinofuranosyladenine. Biochem Pharmacol 1977;26:2193-2196.
9. Brown JR, Stock W, Katzen HI, et al. Early estimates of safety for alemtuzumab combined with fludarabine for the treatment of relapsed/refractory B-cell chronic lymphocytic leukemia: Phase II multicenter study. Blood 2006;108:Abstract 4989.
10. Catovsky D, Richards S, Hillmen P. Early results from LRF CLL4: A UK multicenter randomized trial. Blood 2005;106:Abstract 716.
11. Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet 2007;370:230-239.
12. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;87:4990-4997.

13. Clavio M, et al. First line fludarabine treatment of symptomatic chronic lympho-proliferative diseases: clinical results and molecular analysis of minimal residual disease. Eur J Haematol 1998;61(3):197-203.
14. Delpoeta G, DelPrincipe MI, Maurillo L, et al. The addition of rituximab to fludarabine improves clinical outcome in untreated patients with ZAP-70 negative chronic lymphocytic leukemia. Cancer 2005;104(12):2743-2752.
15. Döhner H, Fischer K, Bentz M, et al. p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias. Blood 1995;85(6):1580-1589.
16. Eichhorst BF, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood 2006; 107(3):885-891.
17. Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. J Clin Oncol 2005;23:7024-7031.
18. Fabbri A, Lenoci M, Gozzetti A, et al. Low-dose oral fludarabine plus cyclophosphamide in elderly patients with chronic lymphoproliferative disorders. Hematol J 2004;5:472-474.
19. Fenchel K, Bergmann L, Wijermans P, et al. Clinical experience with fludarabine and its immunosuppressive effects in pretreated chronic lymphocytic leukemias and low-grade lymphomas. Leuk Lymphoma 1995;18:485-492.
20. Foran JM, Oscier D, Orchard J, et al. Pharmacokinetic study of single doses of oral fludarabine phosphate in patients with"low-grade" non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia. J Clin Oncol 1999;17:1574-1579.
21. Friedberg JW, et al. Oral fludarabine has significant activity in patients with previously untreated chronic lymphocytic leukemia, and leads to increased STAT1 levels in vivo. Leuk Res 2004;28(2):139-147.
22. Gandhi V, Kemena A, Keating MJ, Plunkett W. Cellular pharmacology of fludarabine triphosphate in chronic lymphocytic leukemia cells during fludarabine therapy. Leuk Lymphoma 1993;10:40-56.
Xanthus Pharmaceuticals, Inc.
23. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. Clin Pharmacokinet 2002;41(2):93-103.
24. Gillis S, Dann EJ, Cass Y, et al. Activity of fludarabine in refractory chronic lymphocytic leukemia and low grade non-Hodgkin's lymphoma—the Jerusalem experience. Leuk Lymphoma 1994;15:173-175.
25. Gjedde SB, Hansen MM. Salvage therapy with fludarabine in patients with progressive B-chronic lymphocytic leukemia. Leuk Lymphoma 1996;21:317-320.
26. Grever MR, Kopecky KJ, Coltman CA, et al. Fludarabine monophosphate: a potentially useful agent in chronic lymphocytic leukemia. Nouv Rev Fr Hematol 1988;30:457-459.
27. Hallek M, Kuhn-Hallek I, Emmerich B. Prognostic factors in chronic lymphocytic leukemia. Leukemia 1997;11(Suppl 2):S4-13.

28. Hallek M, Langenmayer I, Nerl C, et al. Elevated serum thymidine kinase levels identify a subgroup at high risk of disease progression in early, nonsmoldering chronic lymphocytic leukemia. Blood 1999;93(5):1732-1737.
29. Hallek M, Schmitt B, Wilhelm M, et al. Fludarabine plus cyclophosphamide is an efficient treatment for advanced chronic lymphocytic leukaemia (CLL): results of a phase II study of the German CLL Study Group. Br J Haematol 2001;114:342-348.
30. Hendry L, Bowen A, Matutes E, et al. Fludarabine, cyclophosphamide and mitoxantrone in relapsed or refractory chronic lymphocytic leukemia and low grade non-Hodgkin's lymphoma. Leuk Lymphoma 2004;45:945-950.
31. Hensel M, Fischer K, Haas R, et al. Fludarabine phosphate in the treatment of advanced-stage chronic lymphocytic leukemia. Ann Hematol 1994;67:Abstract 190.
32. Hiddeman W, Rottmann R, Wormann B, et al. Treatment of advanced chronic lymphocytic leukemia by fludarabine. Results of a clinical phase-II study. Ann Hematol 1991;63:1-4.
33. Hillmen P, Richards S, Catovsky D. Comparison of oral and intravenous fludarabine in the LRF CLL4 trial. Blood 2005;106(11):Abstract 722.
34. Hocepied AM, Falkson CI, Falkson G. A phase II trial of fludarabine in patients with previously treated chronic lymphocytic leukemia. S Afr Med J 1996;86(5):549-550.
35. International Workshop on Chronic Lymphocytic Leukemia. Chronic lymphocytic leukemia: recommendations for diagnosis, staging, and response criteria. Ann Intern Med 1989;110:236-238.
36. Johnson S, Hiddemann W, Corffier B, et al. Fludarabine in the treatment of chronic lymphocytic leukaemia. Ann Oncol 1994;5:Abstract 277.
37. Johnson S, Smith AG, Loffler H, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. The French Cooperative Group on CLL. Lancet 1996;347(9013):1432-1438.
38. Keating MJ, Kantarjian H, Talpaz M, et al. Fludarabine: a new agent with major activity against chronic lymphocytic leukemia. Blood 1989;74:19-25.
39. Keating MJ, O'Brien S, Kantarjian H, et al. Long-term follow-up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent. Blood 1993;82:2878-2884.
40. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005;23(18):4079-4088.
41. Keating MJ, et al. Fludarabine: a new agent with marked cytoreductive activity in untreated chronic lymphocytic leukemia. J Clin Oncol 1991;9(1):44-49.
42. Kemena A, O'Brien S, Kantarjian H, et al. Phase II clinical trial of fludarabine in chronic lymphocytic leukemia on a weekly low-dose schedule. Leuk Lymphoma 1993;10:187-193.
43. Knauf WU, Kreuser E, Pottgieller E, Thiel E. In vitro and in vivo effectiveness of fludarabine in B-cell chronic lymphocytic leukemia (B-CLL). Ann Hematol 1992;65:A80, Abstract 203.

44. Kowal M, Dmoszynska A, Lewandowski K, et al. Efficacy and safety of fludarabine and cyclophosphamide combined therapy in patients with refractory/recurrent B-cell chronic lymphocytic leukaemia (B-CLL)-Polish multicentre study. Leuk Lymphoma 2004;45:1159-1165.
45. Leporrier M, Chevret S, Cazin B, et al. French Cooperative Group on Chronic Lymphocytic Leukemia. Randomized comparison of fludarabine, CAP and CHOP in 938 previously untreated stage B and C Chronic Lymphocytic Leukemia patients. Blood 2001;98(8):2319-2325.
46. Montillo M, Tedeschi A, Delfini C, et al. Effectiveness of fludarabine in advanced B-cell chronic lymphocytic leukemia. Tumori 1995;81:419-423.
47. Montserrat E, Bosch F, Rozman C. Treatment of B-cell chronic lymphocytic leukaemia: Current status and future perspectives. J Int Med 1997;242(Suppl 740):63-67.
48. Montserrat E, Lopez-Lorenzo JL, Manso F, et al. Fludarabine in resistant or relapsing B-cell chronic lymphocytic leukemia: the Spanish Group experience. Leuk Lymphoma 1996;21:467-472.
49. O'Brien SM, Kantarjian HM, Cortes J, et al. Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. J Clin Oncol 2001;19:1414-1420.
50. O'Brien S, Moore JO, Boyd TE, et al. Randomized Phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2007;25:1114-1120.
51. O'Brien ME, Matutes E, Cunningham D, et al. Fludarabine in lymphoproliferative disorders: The Royal Marsden Hospital experience. Leuk Lymphoma 1994;14Suppl2:17-23.
52. Puccio CA, Mittelman A, Lichtman SM, et al. A loading dose/continuous infusion schedule of fludarabine phosphate in chronic lymphocytic leukemia. J Clin Oncol 1991;9:1562-1569.
53. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000;343:1750-1757.
54. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukaemia. Blood 1975;46:219-234.
55. Robertson LE, O'Brien S, Kantarjian H, et al. A 3-day schedule of fludarabine in previously treated chronic lymphocytic leukemia. Leukemia 1995;9:1444-1449.
56. Rossi JF, van Hoof A, de Boeck K, et al. Efficacy and safety of oral fludarabine phosphate in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2004;22:1260-1267.
57. Sayala HA, Moreton P, Jones RA, et al. Final report of the UKCLL02 trial: A Phase II study of subcutaneous alemtuzumab plus fludarabine in patients with fludarabine refractory CLL (on behalf of the NCRI CLL trials sub-group). ASH 2006;108:34a
58. Schering Oncology. Fludara® (fludarabine phosphate) Product Monograph. 25 August 2006.
59. Schiavone EM, De Simone M, Palmieri S, et al. Fludarabine plus cyclophosphamide for the treatment of advanced chronic lymphocytic leukemia. Eur J Haematol 2003;71:23-28.

60. Schulz H, Klein SK, Rehwald U, et al. Phase 2 study of a combined immuno-chemotherapy using rituximab and fludarabine in patients with chronic lymphocytic leukemia. Blood 2002;100:3115-3120.
61. Seymour JF, Grigg AP, Szer J, Fox RM. Fludarabine and mitoxantrone: effective and well-tolerated salvage therapy in relapsed indolent lymphoproliferative disorders. Ann Oncol 2001;12:1455-1460.
62. Shustik C, et al. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Phase II study of oral fludarabine in untreated B-cell chronic lymphocytic leukemia. Blood 2005;106:Abstract 2977.
63. Shvidel L, Shtalrid M, Bairey O, et al. Conventional dose fludarabine-based regimens are effective but have excessive toxicity in elderly patients with refractory chronic lymphocytic leukemia. Leuk Lymphoma 2003;44:1947-1950.
64. Sorensen JM, Vena DA, Fallavollita A, Chun HG, Cheson BD. Treatment of refractory chronic lymphocytic leukemia with fludarabine phosphate via the group C protocol mechanism of the National Cancer Institute : five-year follow-up report. J Clin Oncol 1997;15:458-465.
65. Spriano M, Clavio M, Carrara P, et al. Fludarabine in untreated and previously treated B-CLL patients: a report on efficacy and toxicity. Haematologica 1994;79(3):218-224.
66. Stelitano C, Morabito F, Kropp MG, et al. Fludarabine treatment in B-cell chronic lymphocytic leukemia: response, toxicity and survival analysis in 47 cases. Haematologica 1999;84:317-323.
67. Thomas DA, O'Brien SM, Kantarjian HM, et al. Retreatment with fludarabine: outcome in 203 patients with relapsed or refractory CLL treated with salvage therapy (abstract P084), IWCLL-VIII International Workshop on CLL, Paris, 29-31 October 1999.
68. Tsimberidou AM, Keating MJ, Giles FJ, et al. Fludarabine and mitoxantrone for patients with chronic lymphocytic leukemia. Cancer 2004;100:2583-2591.
69. Tsimberidou AM, Wen S, O'Brien S, et al. Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2007;25(29):4648-4656.
70. Wierda W, O'Brien S, Faderl S, et al. A retrospective comparison of three sequential groups of patients with recurrent/refractory chronic lymphocytic leukemia treated with fludarabine-based regimens. Cancer 2006;106:337-345.
71. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. Clin Oncol 2005;23:4070-4078.
72. Wijermans PW, Gerrits WB, Haak HL. Severe immunodeficiency in patients treated with fludarabine monophosphate. Eur J Hematol 1993 ;50 :292-296.
73. Zinzani PL, Lauria F, Rondelli D, et al. Fludarabine in patients with advanced and/or resistant B-chronic lymphocytic leukemia. Eur J Hematol 1993 ;51 :93-97.
74. Zinzani PL, Bendandi M, Magagnoli M, et al. Results of a fludarabine induction and alpha-interferon maintenance protocol in pretreated patient with chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma. Eur J Haemaol 1997;59:82-88.

8.9 Postmarketing Risk Management Plan

Following the initial approval of fludarabine phosphate tablets in the UK in 2000, the drug has been approved in approximately 75 countries. An estimated ——patients have been exposed to fludarabine phosphate tablets as marketed by Bayer Schering Pharma AG in the 6-year-period from August 2000 till August 2006. b(4)

Periodic Safety Update Reports (PSUR) based on global medical safety surveillance that include all adverse reaction (ADR) reports, including spontaneous reports, case reports from the literature and reports from serious adverse events (SAEs) from clinical trials have been reported. Based on voluntary reporting, analysis of the August 2005- August 2006 PSUR shows that the safety profile of oral fludarabine phosphate has not significantly changed since initial market approval.

8.10 Other Relevant Materials

No new information is available.

9.0 0VERALL ASSESSMENT

9.1 Conclusions

The safety database of oral fludarabine phosphate in this application provides data on 502 patients treated with the oral formulation of fludarabine phosphate. This includes 474 patients treated with oral fludarabine phosphate tablets. Seventy-eight of these patients who received fludarabine phosphate monotherapy were diagnosed with B-CLL that was refractory to or had relapsed during or after treatment with at least one alkylating agent – containing regimen (Study ME96029). This is the population for which the sponsor is seeking approval for oral fludarabine phosphate. In addition, 92 B-CLL, NHL and Lg-NHL patients were treated with oral fludarabine phosphate monotherapy in pharmacokinetic studies, and 81 previously untreated B-CLL patients received oral fludarabine phosphate monotherapy treatment in Study 303080. Additionally, limited safety data are available from Study LRF CLL4, where 122 B-CLL patients received oral fludarabine phosphate monotherapy and 129 patients received a combination treatment of oral fludarabine phosphate and cyclophosphamide, both as initial B-CLL therapy. Finally, post-marketing safety surveillance data are available from over ——patients treated with oral fludarabine phosphate in regions of the world where this formulation is approved. b(4)

Across all of these studies in the clinical development program, oral fludarabine phosphate therapy was generally well tolerated. The most commonly reported adverse events and WHO toxicities reported across all studies with oral fludarabine phosphate typically included myelosuppression, fever, cough, nausea, vomiting, diarrhea, asthenia, anorexia, and infections. These events were usually mild or moderate in severity with non-hematological Grade 3-4 events occurring in up to 8% of patients and hematological

grade 3-4 toxicities occurring in up to 25% of patients. Adverse events and toxicities observed with oral fludarabine phosphate did not significantly differ from the adverse event profile of the IV formulation of fludarabine phosphate, with the exception of mild/moderate nausea/vomiting and diarrhea which seemed to occur at slightly higher rates in patients treated with oral fludarabine phosphate, based on reported WHO toxicities, compared to patients treated with IV fludarabine phosphate. Post-marketing experience in clinical practice with oral fludarabine phosphate over the past 6 years shows that, based on voluntary reported adverse drug reactions during the marketed period, the safety profile of oral fludarabine phosphate has not significantly changed from when oral fludarabine phosphate was initially approved in 2000 in the UK. Taken together, these data indicate that the safety profile of oral fludarabine phosphate therapy for B-CLL patients is both predictable and manageable.

9.2 Recommendation on Regulatory Action

The clinical reviewer recommends that oral fludarabine phosphate tablets receive accelerated approval for the 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. Accelerated approval is based on the absence of remission duration data for the indicated patient population. Accelerated approval is supported by comparable clinical outcomes including response rates, response duration, and progression free survival of intravenous and oral fludarabine treatment as well as a reasonable complete response (CR) rate of adequate duration in previously untreated CLL patients.

9.3 Recommendation On Postmarketing Actions

9.3.1 Risk Management Activity

Not applicable

9.3.2 Required Phase 4 Commitments

A randomized trial comparing oral and intravenous fludara, with or without other agents, in the first-line CLL setting.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

In progress by review team.

9.5 Comments To Applicant

None.

10.0 APPENDICES

10.1. Review Of Individual Study Reports

See clinical section

REFERENCES

See section 8.6.

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