CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-273

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Interdisciplinary Review Team for QT Studies Consultation:

Thorough QT Study Review

NDA	22-273
Trade Name	Fludara®
Generic Name	Fludarabine Phosphate
Sponsor	Antisoma
Indication	Treatment of adult patients with B-cell chronic lymphocytic leukemia who have not responded to or whose disease has progressed during or after treatments.
Dosage Form	Tablet
Drug Class	Anti-metabolite, Cancer chemotherapy agent
Therapeutic Dosing Regimen	40 mg/m^2 (PO) for 5 days during each 28-day cycle
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Single dose: 43 mg/m^2 IV or 56 mg/m^2 PO of 2F-ara-AMP (highest dose shown to be safe) Multiple dose: 25 mg/m^2 IV or 40 mg/m^2 PO of 2F-ara-AMP (highest dose shown to be safe)
Submission Number and Date	Aug 1, 2008
Clinical Division	DDOP / HFD 150

1 SUMMARY

1.1 Overall Summary of Findings

There was no apparent QT prolonging effect of fludarabine (25 mg/m^2 IV and 40 mg/m^2 PO) in this QT study. However, QTc prolongation less than 10 ms cannot be excluded in the absence of positive and placebo controls.

In this randomized, uncontrolled, single-dose, open-label, parallel study, patients with B-cell CLL received 40 mg/m^2 PO (n=42) or 25 mg/m^2 IV infusion over 30 minutes (n=14). Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the Upper One-Sided 95% CIs for Fludarabine (40 mg/m^2 PO and 25 mg/m^2 IV) (FDA Analysis)

Treatment	Time (hour)	ΔQTcI (ms)	Upper 95% CI (ms)
Fludarabine 40 mg/m^2 PO	18	2.1	(7.3)
Fludarabine 25 mg/m^2 IV	18	-2.7	(7.7)

One subject had a QTcI change > 60 ms from baseline. This was not associated with adverse events related to QT prolongation.

The was no evidence of dose- or exposure-response when analyzing the association between 2F-ara-A concentrations and ΔQTcI prolongations following 40 mg/m^2 PO and 25 mg/m^2 IV (single dose) with mean C_{max} of 279 and 808 ng/mL, respectively. No exposure-response was observed for 2F-ara-Hx concentrations and ΔQTcI prolongation.

The tested doses of 25 mg/m^2 IV and 40 mg/m^2 PO (single doses) are the therapeutic (and maximum tolerated) doses of fludarabine for first- and second-line treatment of CLL, respectively. The highest expected clinical exposure scenario (severe renal impairment: 2-fold increase) for 40 mg/m^2 PO will be covered by 25 mg/m^2 IV producing 10-fold higher C_{max} compared to 40 mg/m^2 PO and showed no detectable prolongations of the QT-interval. The QT effects in patients with severe renal impairment receiving 25 mg/m^2 IV are unknown.

1.2 QT Interdisciplinary Review Team's Comments

- Fludarabine at the dose of 25 mg/m^2 i.v. prolonged the PR interval with a maximum mean effect of 11 ms and 12 ms observed 0.17 and 0.5 hr post-infusion. (90% upper bound of ΔPR was 23 ms and 21 ms respectively).
    - This was not observed for the 40-mg/m^2 PO group with the largest upper bound of the 90% CI being 9.8 ms.
    - There was no evidence of exposure-response between ΔPR and 2F-ara-A and 2F-ara-Hx concentrations.
    - There were 9 instances of clinically asymptomatic 1st degree AV block in patients who had a normal PR interval at baseline. One patient developed a Mobitz type 1 second degree AV block.
    - However, since there were no clinically significant blocks (complete AV block or Mobitz type 2) in this study and very few post-marketing reports of complete heart block (sections 5.4.3, 5.4.4), we do not think this finding is clinically significant for the PO formulation at the current dose since exposures are lower. This may change if higher doses of the PO formulation are used.
- Since the above changes were observed only with the IV formulation we did not include any labeling recommendations regarding the same for the PO formulation at the proposed dose. We defer consideration of labeling changes for the IV formulation with respect to PR effects to the review division.

2 PROPOSED LABEL

The sponsor has not included any information regarding QT effects in the PI. We recommend including a description of study results in section 12.2 (Pharmacodynamics). Our recommendations for labeling are suggestions only. We defer all final labeling decisions to the review division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, uncontrolled, open-label, parallel study, patients with B-cell CLL were administered a single dose of FLUDARA 40 mg/m^2 PO (n = 42) or FLUDARA 25 mg/m^2 IV (n=14). The maximum increase in the baseline-corrected mean change in QTcI (individual-corrected QT interval) for each treatment arm was less than 10 ms.

3 BACKGROUND

3.1 MARKET APPROVAL STATUS

Following the initial approval of fludarabine phosphate in the UK in 2000, the drug has been approved in a total of 75 countries.

3.2 PRECLINICAL INFORMATION

Source: IB, Nov 12, 2007

"**The effects on the respiratory and cardiovascular** systems were examined in anesthetized rats. Heart rate was significantly decreased after a single intravenous application of 2F-ara-AMP at a dose of 25 mg/m^2 or more (which produced a plasma Cmax of 2F-araA 5- to 25-times greater than seen in humans following doses of 25 mg/m^2 or 40 mg/m^2 PO). At lower doses, the heart rate normalized within 60 minutes, while at the dose of 100 mg/kg the heart rate was still 23% below the pre-treatment value after 60 minutes. Effects on heart rate were accompanied by an increase in carotid arterial blood flow. A slight lowering of amplitude in the T wave of ECGs was seen, which achieved statistical significance only at the 5 and 10 minute time points after a dose of 100 mg/kg IV. A small but significant increase in blood pressure (10 mm Hg) was also noted at this dose.

"**The effects of 2F-ara-A and 2F-ara-AMP** were also tested on isolated rat atria (Study Report AT55); both decreased contraction rates but did not affect contractile force. The effects were not antagonized by atropine, nor did 2F-ara-A or 2F-ara-AMP antagonize the positive inotropic and chronotropic actions of isoproterenol, indicating that the negative chronotropic effect of 2F-ara-AMP is independent of the parasympathetic and sympathetic nervous systems, respectively.

"**In the 4-week dog study with a 4-week** recovery period (Study Report A22370), where fludarabine phosphate was administered daily intragastrically (i.g.) (doses of 4, 16 and 60 mg/kg) electrocardiograms were obtained in test-week 1, 3, 4, and 8, predose and 1 hour post-dose. Post-dosing ECGs were conducted within range of the maximum plasma concentrations (Tmax = 0.5 - 1.5 hrs). Visual assessment of ECGs collected did not reveal any test substance-related abnormalities of the heart rate or ECG parameters **including QRS and QT–interval. Based on** exposure (Cmax) levels in the dog at the tested doses (between 20-100µM at

tested 60 mg/kg) there is a considerable safety margin (20-100 fold) compared to the suggested human dose and expected exposure levels (~ 1 μM at the proposed oral dose of 40mg/m^2."

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety, CTD- 2.7.4 and IB-Nov 12, 2007

"The safety database of oral fludarabine phosphate in this application provides data on 558 patients treated with the oral formulation of fludarabine phosphate. This includes 516 patients treated with oral fludarabine phosphate tablets; the other patients received oral fludarabine as a solution.

"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). The estimate is based on worldwide sales, assuming that each patient received the recommended dose of 40 mg/m^2 body surface/day, the average body surface being 1. 7 m^2 and each patient receiving an average of four complete cycles. The number of patients treated with fludarabine phosphate tablets has been rising steadily each year since its first launch in the United Kingdom in 2001. Period Safety Update Reports (PSUR) based on global medical safety surveillance that included all adverse reactions (ADR) reports, including spontaneous reports, case reports from the literature and reports from serious adverse events (SAEs) from clinical trials have been reported. 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.

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"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/m^2/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.

Reviewer's Comments: There are no reports of AEs related to QT prolongation i.e. sudden cardiac death, seizures, and significant ventricular arrhythmias.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of fludarabine phosphate's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted the CSR for 0004B1-100-GL/0004B1-400-GL, electronic datasets and waveforms to the ECG warehouse.

4.2 QT ASSESSMENT

4.2.1 Title

Phase 1 and Phase 4 Study of a Single Fixed Dose of Oral Fludarabine Phosphate in Adult Patients with B-cell Malignancies

4.2.2 Protocol Number

0004B1-100-GL (Phase I) /0004B1-400-GL (Phase IV)

4.2.3 Study Dates

April 29, 2008 to May 31, 2008

4.2.4 Objectives

The objectives of this study were to:

- Determine the plasma and urine pharmacokinetics of fludarabine phosphate (2F-ara-AMP), fludarabine (2F-ara-A), and the hypoxanthine analog of fludarabine phosphate (2F-ara-Hx) following oral or intravenous (IV) administration.
- Assess the effect of oral or IV fludarabine phosphate on cardiac safety as determined by evaluation of all electrocardiogram (ECG) parameters, with special focus on the drug's effect on corrected QT (QTc) interval duration.
- Assess the relationship between pharmacokinetic data and QTc duration.

4.2.5 Study Description

4.2.5.1 Design

This was a 1-day, open-label, single-, fixed-dose study in adult subjects with B-cell CLL or low-grade non-Hodgkin's lymphoma (NHL) who were receiving or were scheduled to receive a fludarabine phosphate-containing treatment regimen.

4.2.5.2 Controls

No controls were used in this study.

4.2.5.3 Blinding

The study was unblinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Two treatment arms are used in study.

1. 40 mg/m^2 of fludarabine phosphate oral tablets
2. 25 mg/m^2 of fludarabine phosphate IV infusion over 30 minutes

4.2.6.2 Sponsor's Justification for Doses

"Fludarabine phosphate oral tablets are approved for marketing in 75 countries worldwide, but not in the United States, for the first-line treatment of adult patients with B-cell CLL and for the treatment of adult patients whose disease has not responded to, or whose disease has progressed during, treatment with at least one standard alkylating agent containing regimen. The recommended dose is 40 mg/m^2 orally once daily for 5 days every 4 weeks. Thus, the oral dose of fludarabine phosphate that was used in this study represents the usual daily dose of the drug when taken orally.

"Fludarabine phosphate for injection is approved for marketing in the United States and elsewhere for second-line treatment of CLL. The recommended dose is 25 mg/m^2 given as a 30-minute IV infusion once daily for 5 days every 4 weeks. Thus, the IV dose of fludarabine phosphate that was used in this study represents the usual daily dose of the drug when administered as an IV infusion. This IV dose results in a higher maximum Cmax of 2F-ara-A than that observed after 5 days of dosing with 40 mg/m^2 of fludarabine phosphate orally."

Reviewer's Comment: The tested doses of 25 mg/m^2 IV and 40 mg/m^2 PO (single doses) are the therapeutic and maximum tolerated doses of fludarabine for first- and second-line treatment of CLL, respectively. The highest expected clinical exposure scenario (severe renal impairment: 2-fold increase) for 40 mg/m^2 PO will be covered by 25 mg/m^2 IV (10-fold higher Cmax compared to 40 mg/m^2 PO). However, the therapeutic dose for second-line treatment of CLL is 25 mg/m^2 IV and the highest expected clinical exposure scenario will therefore not be covered in this study.

4.2.6.3 Instructions with Regard to Meals

Doses will not be administered with food. Meals are to be consumed and doses taken at the same time on each occasion.

Reviewer's Comment: It is adequate to administer fludarabine under fasted conditions since no food effect on systemic exposure has been identified.

4.2.6.4 ECG and PK Assessments

Table 2: Sampling Schedule

Study Day	-1	1
Intervention	No treatment (Baseline)	Single dose
12-Lead ECGs	Record ECGs###	Record ECGs###
PK Samples for drug	None collected	Collected###

###-1, -0.05, 0.17, 0.5, 1, 2, 4, 6, 10, 14, 18, and 23 hr post dosing.

Reviewer's Comment: The ECG and PK assessments are adequate to capture the QT effect at peak 2F-ara-A and 2F-ara-Hx *(metabolite) concentrations ($t_{max, A}$=1-2 hr, $t_{max, Hx}$=1-6 hr).*

4.2.6.5 Baseline

Baseline ECGs were obtained by continuous ambulatory ECG monitoring for 24 hours during the screening period prior to fludarabine phosphate administration. Time-matched baseline adjustment was used in the data analysis.

4.2.7 ECG Collection

Continuous 12-lead ECG recording was performed for 24 hours during the pretreatment screening period and during the 1-day treatment period. Triplicate ECGs were extracted at the time points specified above.

Subjects were not allowed to receive any other antineoplastic medications or any medications that are known to prolong the QTc interval during the 24-hour pretreatment screening period or during the 1-day treatment period of the study.

The ECG analysis was conducted in lead II or, when not analyzable, in lead V5 or the most appropriate lead.

All ECG data were analyzed by a central laboratory ——————————
——————The ECGs were read by an independent cardiologist who was blinded to the subject identifiers, treatment and evaluation time point; the same cardiologist read all of the ECGs for a given subject.

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4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 56 subjects were enrolled in the study: 42 subjects (28 men and 14 women of mean age 65.0 years) received treatment with a single 40-mg/m^2 oral dose of fludarabine phosphate, and 14 subjects (13 men and 1 woman of mean age 61.1 years) received treatment with a single 25-mg/m^2 IV dose of fludarabine phosphate. All of the subjects had a diagnosis of B-cell CLL. Relevant exclusion criteria included myocardial infarction within 3 months ,unstable angina pectoris, cardiac insufficiency (New York Heart Association [NYHA] Class III - IV), uncontrolled arrhythmia, or uncontrolled hypertension, history of risk factors for torsades de pointes (e.g., heart failure, hypokalemia, family history of long QT Syndrome) and use of concomitant medications that prolonged the QT/QTc interval.

All of the enrolled subjects received their assigned treatment and completed the 1-day study.

4.2.8.2 Statistical Analyses

All 42 of the enrolled subjects in the oral dosing cohort and all 14 of the enrolled subjects in the IV dosing cohort received the protocol-specified single dose of fludarabine phosphate. Therefore, all subjects enrolled are included in the analysis.

4.2.8.2.1 Primary Analysis

The QTcB and QTcF values obtained during day 1 at 10 and 30 minutes and at 1, 2, 4, 6, 10, 14, 18, and 23 hours after fludarabine phosphate dosing began were compared with the time-matched baseline QTcB and QTcF values that were obtained during the 24-hour pretreatment screening period, using a repeated measures analysis of variance (ANOVA). The following model was used:

Parameter (QTcF or QTcB value) = Subject + Visit + Assessment Time + Visit × Assessment Time + Error

Subject, visit (screening or day 1), assessment time, and visit-by-assessment time were included as fixed effects in the model. The repeated measures were taken over the assessment time. A 2-sided 90% CI was calculated for the least squares mean QTc change from baseline for each treatment group. No adjustment for multiple comparisons was performed.

Table 3: Change From Time-matched Baseline QTcB (Delta-QTcB) and QTcF (Delta-QTcF) Interval after a Single Oral (40 mg/m2) or a Single IV (25 mg/m2) Dose of Fludarabine Phosphate

Time Point	Statistic	Fludarabine Phosphate Cohort			
		40 mg/m^2 Orally (N = 42)		25 mg/m^2 IV (N = 14)	
		Delta-QTcB (msec)	Delta-QTcF (msec)	Delta-QTcB (msec)	Delta-QTcF (msec)
1 Hour Predose	n	42	42	13	13
	Mean	-2.95	-1.45	-0.36	0.48
	95% CI	-9.49, 3.59	-7.89, 4.99	-9.77, 9.05	-8.91, 9.88
	Median	-4.30	-3.50	-2.00	1.00
	Min, Max				
3 Min Predose	n	42	42	14	14
	Mean	-6.19	-3.60	-4.46	-0.81
	95% CI	-12.39, 0.02	-10.32, 3.13	-12.72, 3.80	-9.54, 7.91
	Median	-5.00	-9.00	-6.15	-0.15
	Min, Max				
10 Min Postdose	n	42	42	14	14
	Mean	-2.48	-2.06	-5.25	5.41
	95% CI	-8.89, 3.93	-9.18, 5.05	-12.76, 2.26	-3.72, 14.54
	Median	1.15	-4.15	-3.00	8.65
	Min, Max				
30 Min Postdose	n	42	42	14	14
	Mean	-5.89	-3.09	-9.44	-2.43
	95% CI	-13.89, 2.11	-10.61, 4.43	-18.71, -0.16	-9.46, 4.60
	Median	-9.20	-3.15	-11.70	-1.70
	Min, Max				

Time Point	Statistic	Fludarabine Phosphate Cohort			
		40 mg/m^2 Orally (N = 42)		25 mg/m^2 IV (N = 14)	
		Delta-QTcB (msec)	Delta-QTcF (msec)	Delta-QTcB (msec)	Delta-QTcF (msec)
1 Hour Postdose	n	42	42	14	14
	Mean	-3.91	-3.91	-7.43	-1.62
	95% CI	-11.67, 3.85	-10.45, 2.64	-15.25, 0.39	-7.32, 4.08
	Median	-4.65	-7.65	-4.00	0.50
	Min, Max				
2 Hours Postdose	n	42	42	14	14
	Mean	-2.96	-1.93	-3.21	-1.85
	95% CI	-9.74, 3.82	-7.72, 3.86	-13.56, 7.13	-12.46, 8.76
	Median	-1.50	2.50	-4.15	2.00
	Min, Max				
4 Hours Postdose	n	41	41	14	14
	Mean	-2.09	-5.95	-5.18	-0.16
	95% CI	-10.59, 6.41	-11.57, -0.33	-13.49, 3.13	-11.48, 11.15
	Median	-8.70	-7.70	-3.00	0.65
	Min, Max				
6 Hours Postdose	n	41	41	14	14
	Mean	-2.62	-5.19	-6.12	-3.21
	95% CI	-9.05, 3.82	-10.98, 0.60	-14.98, 2.74	-11.11, 4.70
	Median	-5.70	-6.70	-10.00	2.00
	Min, Max				

Source: Table 9 in Sponsor's CSR

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Table 4: Change From Time-matched Baseline QTcB (Delta-QTcB) and QTcF (Delta-QTcF) Interval After a Single Oral (40 mg/m2) or a Single IV (25 mg/m2) Dose of Fludarabine Phosphate (Continued)

Time Point	Statistic	Fludarabine Phosphate Cohort			
		40 mg/m^2 Orally (N = 42)		25 mg/m^2 IV (N = 14)	
		Delta-QTcB (msec)	Delta-QTcF (msec)	Delta-QTcB (msec)	Delta-QTcF (msec)
10 Hours Postdose	n	41	41	14	14
	Mean	-0.60	0.29	-2.41	-5.79
	95% CI	-5.91, 4.72	-4.95, 5.52	-14.78, 9.97	-17.79, 6.22
	Median	-3.00	3.00	-4.35	-10.70
	Min, Max	[redacted]			
14 Hours Postdose	n	40	40	14	14
	Mean	-3.80	-1.87	-0.78	0.69
	95% CI	-10.55, 2.96	-8.12, 4.37	-13.21, 11.65	-9.77, 11.14
	Median	-9.15	-1.65	-10.35	-1.50
	Min, Max	[redacted]			
18 Hours Postdose	n	40	40	14	14
	Mean	1.06	0.55	0.76	1.59
	95% CI	-5.22, 7.34	-5.66, 6.76	-12.71, 13.70	-10.09, 13.26
	Median	-1.85	-1.50	6.50	2.80
	Min, Max	[redacted]			
23 Hours Postdose	n	41	41	14	14
	Mean	-6.88	-6.45	-2.69	-5.24
	95% CI	-14.17, 0.41	-12.83, -0.08	-13.89, 8.52	-17.95, 7.47
	Median	-5.70	-3.70	2.20	0.35
	Min, Max	[redacted]			

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Source: Table 9 in Sponsor's CSR

4.2.8.2.2 Categorical Analysis

For absolute values of QTcB and QTcF intervals counts, the number and percentage of subjects whose values exceeded the normal range (females, 470 ms; males, 450 ms) were summarized by cohort (oral or IV) and assessment time for each gender and overall. Counts of subjects with borderline prolongation (females > 470 ms and < 501 ms; males > 450 ms and < 501 ms) and counts of subjects with prolonged intervals (> 501 ms) were also summarized for each cohort (oral or IV). The sponsor's results are presented in Table 5.

Table 5: Number and Percentage of Subjects with Borderline Prolonged and Prolonged QTcB or QTcF after a Single Oral (40 mg/m^2) or a Single IV (25 mg/m^2) Dose Fludarabine Phosphate

		Fludarabine Phosphate Cohort							
		40 mg/m^2 Orally (N = 42)				25 mg/m^2 IV (N = 14)			
		QTcB		QTcF		QTcB		QTcF	
Time Point	Baseline	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)
1 Hour Predose	High	2 (4.8)	0	0	0	2 (14.3)	0	1 (7.1)	0
	Normal	2 (4.8)	0	0	0	1 (7.1)	0	1 (7.1)	0
	Low	0	0	0	0	0	0	0	0
	Total	4 (9.5)	0	0	0	3 (21.4)	0	2 (14.3)	0
3 Minutes Predose	High	1 (2.4)	0	0	0	2 (14.3)	0	0	0
	Normal	0	0	0	0	0	0	2 (14.3)	0
	Low	0	0	0	0	0	0	0	0
	Total	1 (2.4)	0	0	0	2 (14.3)	0	2 (14.3)	0
10 Min Postdose	High	4 (9.5)	0	0	0	2 (14.3)	0	0	0
	Normal	1 (2.4)	0	0	0	1 (7.1)	0	2 (14.3)	0
	Low	0	0	0	0	0	0	0	0
	Total	5 (11.9)	0	0	0	3 (21.4)	0	2 (14.3)	0
30 Min Postdose	High	3 (7.1)	0	0	0	2 (14.3)	0	1 (7.1)	0
	Normal	2 (4.8)	0	0	0	0	0	1 (7.1)	0
	Low	0	0	0	0	0	0	0	0
	Total	5 (11.9)	0	0	0	2 (14.3)	0	2 (14.3)	0
1 Hour Postdose	High	2 (4.8)	0	0	0	3 (21.4)	0	1 (7.1)	0
	Normal	4 (9.5)	0	0	0	0	0	0	0
	Low	0	0	0	0	0	0	0	0
	Total	6 (14.3)	0	0	0	3 (21.4)	0	1 (7.1)	0

[a] Borderline prolonged for females: > 470 msec and ≤ 501 msec; borderline prolonged for males: > 450 msec and ≤ 501 msec
[b] Prolonged for both females and males: > 501 msec

		Fludarabine Phosphate Cohort							
		40 mg/m^2 Orally (N = 42)				25 mg/m^2 IV (N = 14)			
		QTcB		QTcF		QTcB		QTcF	
Time Point	Baseline	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)	Borderline Prolonged[a] n (%)	Prolonged[b] n (%)
2 Hours Postdose	High	2 (4.8)	0	0	0	2 (14.3)	0	0	0
	Normal	3 (7.1)	0	0	0	1 (7.4)	0	1 (7.1)	0
	Low	0	0	0	0	0	0	0	0
	Total	5 (11.9)	0	0	0	3 (21.4)	0	1 (7.1)	0
4 Hours Postdose	High	3 (7.1)	0	0	0	2 (14.3)	0	1 (7.1)	0
	Normal	2 (4.8)	1 (2.4)	0	0	1 (7.4)	0	1 (7.1)	0
	Low	0	0	0	0	0	0	0	0
	Total	5 (11.9)	1 (2.4)	0	0	3 (21.4)	0	2 (14.3)	0
6 Hours Postdose	High	3 (7.1)	0	0	0	1 (7.4)	0	0	0
	Normal	1 (2.4)	0	0	0	1 (7.4)	0	0	0
	Low	0	0	0	0	0	0	0	0
	Total	4 (9.5)	0	0	0	2 (14.3)	0	0	0
10 Hours Postdose	High	3 (7.1)	0	0	0	3 (21.4)	0	1 (7.1)	0
	Normal	1 (2.4)	0	0	0	1 (7.4)	0	0	0
	Low	0	0	0	0	0	0	0	0
	Total	4 (9.5)	0	0	0	4 (28.6)	0	1 (7.1)	0

[a] Borderline prolonged for females: > 470 msec and ≤ 501 msec; borderline prolonged for males: > 450 msec and ≤ 501 msec
[b] Prolonged for both females and males: > 501 msec

Source: Table 10 in Sponsor's CSR

For the change from time-matched baseline values of QTcB and QTcF intervals, the number and percentage of subjects with interval changes between 5 and 20 ms, between 21 and 30 ms, between 31 and 60 ms, and > 60 ms were presented by cohort (oral or IV) and assessment time. The sponsor's results are presented in Table 6.

Table 6: Number and Percentage of Subjects with Changes from Time-matched Baseline QTcB or QTcF of > 30 to 60 ms and > 60 ms After a Single Oral (40 mg/m^2) or a Single IV (25 mg/m^2) Dose Fludarabine Phosphate

Time Point	Baseline Value Relative to Normal Range	Fludarabine Phosphate Cohort							
		40 mg/m^2 Orally (N = 42)				25 mg/m^2 IV (N = 14)			
		Delta-QTcB		Delta-QTcF		Delta-QTcB		Delta-QTcF	
		> 30-60 msec	> 60 msec	> 30-60 msec	> 60 msec	> 30-60 msec	> 60 msec	> 30-60 msec	> 60 msec
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 Hour Predose	Above	1 (2.4)	0	0	0	0	0	0	0
	Within	5 (11.9)	0	5 (11.9)	1 (2.4)	0	0	1 (7.1)	0
	Below	0	0	0	0	0	0	0	0
	Total	6 (14.3)	0	5 (11.9)	1 (2.4)	0	0	1 (7.1)	0
3 Min Predose	Above	1 (2.4)	0	0	0	1 (7.1)	0	0	0
	Within	5 (11.9)	0	7 (16.7)	0	0	0	1 (7.1)	0
	Below	0	0	0	0	0	0	0	0
	Total	6 (14.3)	0	7 (16.7)	0	1 (7.1)	0	1 (7.1)	0
10 Min Postdose	Above	1 (2.4)	0	0	0	1 (7.1)	0	0	0
	Within	7 (16.7)	0	5 (11.9)	2 (4.8)	0	0	1 (7.1)	0
	Below	0	0	0	0	0	0	0	0
	Total	8 (19.1)	0	5 (11.9)	2 (4.8)	1 (7.1)	0	1 (7.1)	0
30 Min Postdose	Above	2 (4.8)	0	0	0	0	0	0	0
	Within	4 (9.5)	2 (4.8)	8 (19.1)	1 (2.4)	2 (14.3)	0	0	0
	Below	0	0	0	0	0	0	0	0
	Total	6 (14.3)	2 (4.8)	8 (19.1)	1 (2.4)	2 (14.3)	0	0	0
1 Hour Postdose	Above	3 (7.1)	0	0	0	0	0	0	0
	Within	6 (14.3)	1 (2.4)	5 (11.9)	0	1 (7.1)	0	0	0
	Below	0	0	0	0	0	0	0	0
	Total	9 (21.4)	1 (2.4)	5 (11.9)	0	1 (7.1)	0	0	0

Time Point	Baseline Value Relative to Normal Range	Fludarabine Phosphate Cohort							
		40 mg/m^2 Orally (N = 42)				25 mg/m^2 IV (N = 14)			
		Delta-QTcB		Delta-QTcF		Delta-QTcB		Delta-QTcF	
		> 30-60 msec	> 60 msec	> 30-60 msec	> 60 msec	> 30-60 msec	> 60 msec	> 30-60 msec	> 60 msec
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
14 hours Postdose	Above	0	0	0	0	1 (7.1)	0	0	0
	Within	4 (9.5)	1 (2.4)	5 (11.9)	0	3 (21.4)	0	3 (21.4)	0
	Below	0	0	0	0	0	0	0	0
	Total	4 (9.5)	1 (2.4)	5 (11.9)	0	4 (28.6)	0	3 (21.4)	0
18 hours Postdose	Above	1 (2.4)	0	0	0	1 (7.1)	0	0	0
	Within	1 (2.4)	1 (2.4)	3 (7.1)	1 (2.4)	3 (21.4)	0	2 (14.3)	0
	Below	0	0	0	0	0	0	0	0
	Total	2 (4.8)	1 (2.4)	3 (7.1)	1 (2.4)	4 (28.6)	0	2 (14.3)	0
23 hours Postdose	Above	3 (7.1)	0	1 (2.4)	0	1 (7.1)	0	1 (7.1)	0
	Within	6 (14.3)	0	5 (11.9)	0	2 (14.3)	0	3 (21.4)	0
	Below	0	0	0	0	0	0	0	0
	Total	9 (21.4)	0	6 (14.3)	0	3 (21.4)	0	4 (28.6)	0

Source: Table 12 in Sponsor's CSR

4.2.8.3 Safety Analysis

There were no deaths, SAEs or discontinuations due to AEs in the study.
A total of 5 treatment-emergent adverse events (thrombocytopenia, 1 subject; hyperglycemia, 1 subject; blood glucose increased, 1 subject; blood lactic dehydrogenase [LDH] increased, 1 subject; and dizziness, 1 subject), were reported in 5 of the 42 subjects (12%) who were treated with a single 40-mg/m^2 oral dose of fludarabine phosphate, and a total of 2 treatment-emergent adverse events (blood bilirubin increased and blood LDH increased).were reported in 1 of the 14 subjects (7%) who were treated with a single 25-mg/m^2 IV dose of fludarabine phosphate.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Both plasma and urine samples were collected from all 56 patients. Mean derived PK parameters of 2F-ara-A after a single oral dose and IV infusion are summarized in Table 7 and Table 8, respectively.

Table 7: Summary of 2F-ara-A Plasma PK Parameters in Orally Dosed Patients (40 mg/m^2)

Parameters	C_{max} ng/mL	T_{max} hr	AUC_{last} hr•ng/mL	$AUC_{0-\infty}$ hr•ng/mL	t½ hr	AUC_{extr} %	F_{oral} %
N	42	42	42	41	41	41	NA
$N_{missing}$	0	0	0	1	1	1	NA
N_{Obs}	42	42	42	42	42	42	NA
Mean	279	1.8	2390	3030	9.7	20.1	57.7%
SD	137	1.1	901	1010	2	6.24	NA
Minimum	40.5	0.5	534	691	3.8	9.81	NA
Median	281	2	2290	2910	9.8	19.3	NA
Maximum	751	6	4200	4660	14	37.9	NA
CV%	48.9	60	37.7	33.4	21	31	NA

NA: not applicable.

Source: Sponsor's Table 4 in CSR appendix 16.1.13 on page 909.

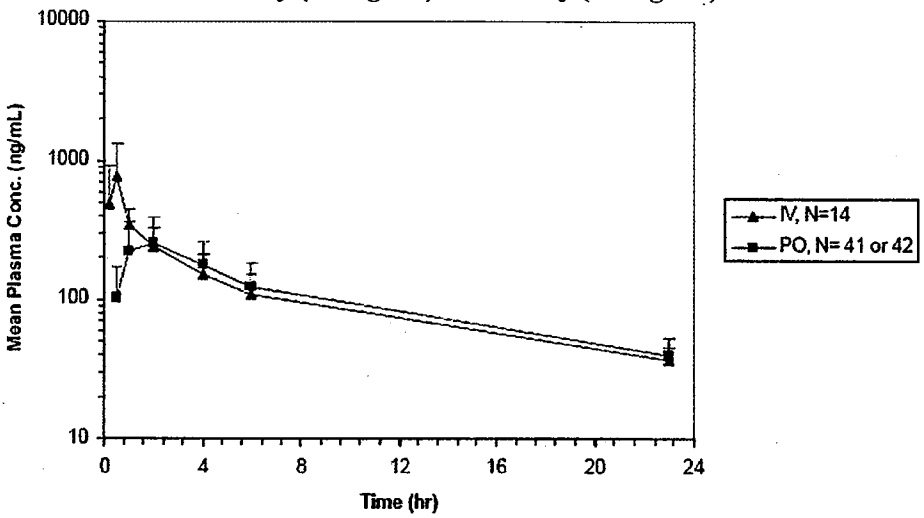
Table 8: Summary of 2F-ara-A Plasma PK Parameters in Intravenously Dosed Patients (25 mg/m^2)

Parameters	C_{max} ng/mL	T_{max} hr	AUC_{last} hr•ng/mL	$AUC_{0-\infty}$ hr•ng/mL	t½ hr	AUC_{extr} %
N	14	14	14	14	14	14
$N_{missing}$	0	0	0	0	0	0
N_{Obs}	14	14	14	14	14	14
Mean	808	0.36	2700	3280	11	18.3
SD	544	0.17	670	658	4.1	6.3
Minimum	372	0.17	1920	2610	7.3	10.3
Median	608	0.5	2550	2990	11	19.5
Maximum	2170	0.5	3830	4460	22	26.9
CV%	67.3	48	24.8	20	36	34.4

Source: Sponsor's Table 3 in CSR appendix 16.1.13 on page 909.

Mean plasma concentration-time curves for 2F-ara-A after a single oral dose and IV dose of 2F-ara-AMP are depicted in Figure 1.

Figure 1: Mean (+ SD) 2F-ara-A Plasma Concentration vs. Time Profiles in Intravenously (25 mg/m2) and Orally (40 mg/m2) Dosed Patients

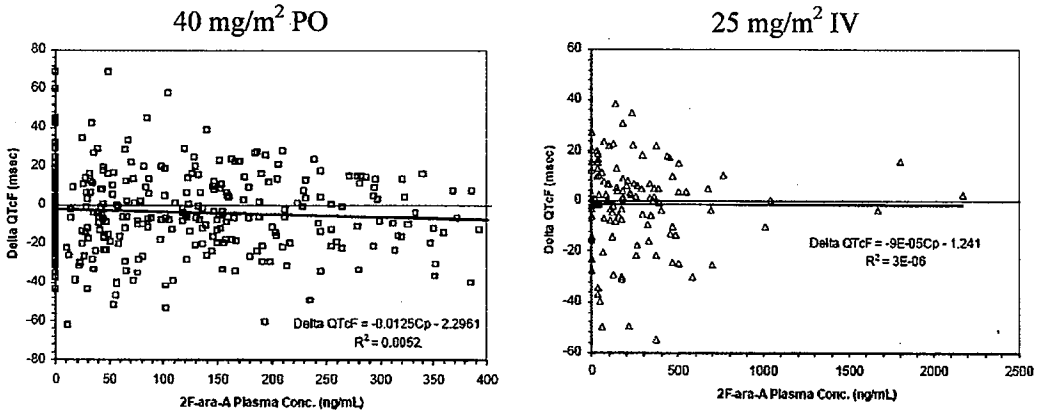


Source: Sponsor's Figure 1 in CSR Appendix 16.1.13 on page 913.

4.2.8.4.2 Exposure-Response Analysis

The relationship between ΔQTcF (change from baseline) and 2F-ara-A is presented in Figure 2.

Figure 2: Pooled ΔQTcF Values as a Function of Time-matched 2F-ara-A (Fludarabine) Plasma Concentrations in Subjects After a (Left) Single Oral (40 mg/m^2) and (Right) Intravenous (25 mg/m^2) Dose of Fludarabine Phosphate



Source: Sponsor's Figure 5 and 6 in CSR on pages 48 and 49.

Reviewer's Analysis: Sponsor's proposed QTcF correction method does not adequately remove the QT-RR correlation (see Figure 3). A plot of ΔQTcI vs. 2F-ara-A and 2F-ara-Hx (metabolite) concentrations is presented in Figure 7.

5 REVIEWERS' ASSESSMENT

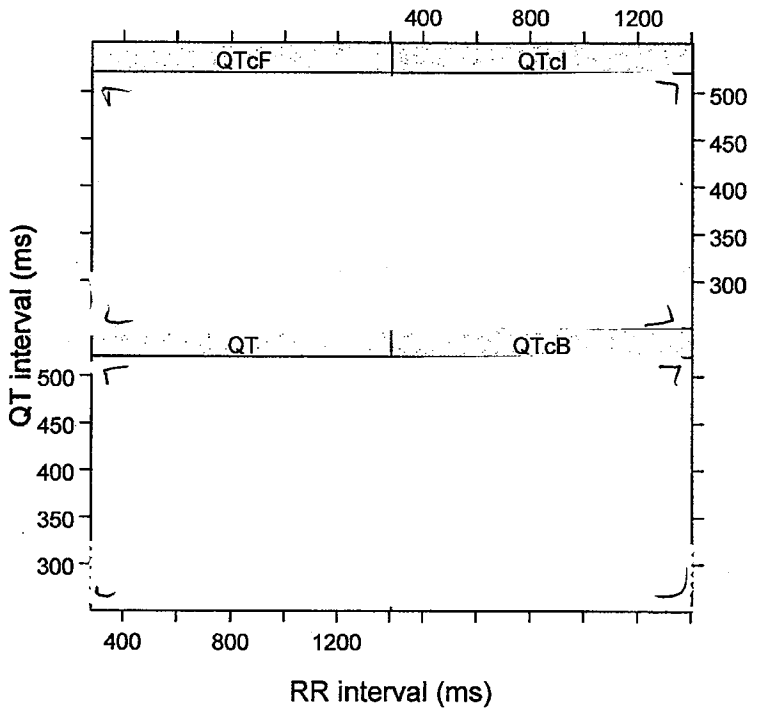
5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

In addition to the Bazett (QTcB) and Fridericia (QTcF) correction methods used by the sponsor, the reviewer investigated the individual correction method. Specifically, QT values were corrected on an individual basis (QTcI) via linear regressions of the pre-dose (Day -1) results on RR. To evaluate and compare the appropriateness of these correction methods, we performed regression of the QTc values at post dose on RR for each individual and used the average sum of squared slopes (MSSS) as the criterion. The smaller this value is, the better the correction. The results are presented in Table 9. The scatter plots of each method versus RR are also presented in Figure 3. It appears that QTcI is the best correction method for the study data. Therefore the reviewer will use QTcI as the primary correction method in analysis presented in Section 5.2. Results for QTcF will also presents for reference in the primary analysis.

Table 9: Mean Sum of Squared Slopes (MSSS) for Different QT-RR Correction Methods

		Treatment					
		25mg/m^2		40mg/m^2		All	
		N	MSSS	N	MSSS	N	MSSS
Correction Method	Gender						
QTcB	F	1	0.0000	14	0.0058	15	0.0054
	M	13	0.0041	28	0.0043	41	0.0042
	All	14	0.0038	42	0.0048	56	0.0045
QTcF	F	1	0.0088	14	0.0092	15	0.0092
	M	13	0.0065	28	0.0038	41	0.0047
	All	14	0.0067	42	0.0056	56	0.0059
QTcI	F	1	0.0189	14	0.0026	15	0.0037
	M	13	0.0012	28	0.0016	41	0.0015
	All	14	0.0025	42	0.0019	56	0.0021

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



b(4)

b(4)

5.2 Statistical Assessments

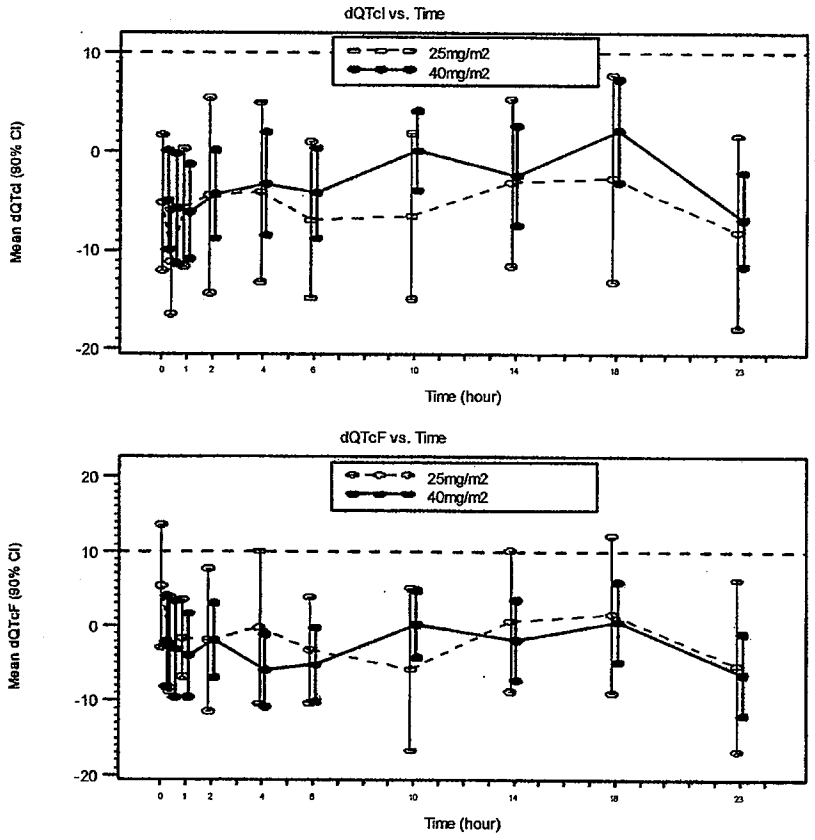
5.2.1 QTc Analysis

A summary of the unadjusted means for both ΔQTcI and ΔQTcF are presented in Table 10. When using QTcI, the largest upper bound of 90% CI of ΔQTcIs are 7.7 ms and 7.3 ms for the 25 mg/m^2 IV group and 40 mg/m^2 PO group, respectively. Figure 4 also displays the mean time profile of ΔQTcI and ΔQTcF for 14 patients receiving fludarabine 25 mg/m^2 IV and 42 patients receiving 40 mg/m^2 PO.

Table 10: Summary of ΔQTcI and ΔQTcF by Treatment

Time (hr)	ΔQTcI						ΔQTcF					
	25mg/m² IV			40mg/m² PO			25mg/m² IV			40mg/m² PO		
	N	Mean	Upper 90% CI	N	Mean	Upper 90% CI	N	Mean	Upper 90% CI	N	Mean	Upper 90% CI
0.17	14	-5.2	1.7	42	-4.9	0.1	14	5.4	13.7	42	-2.1	4.0
0.5	14	-11.2	-5.9	42	-5.8	-0.3	14	-2.4	3.9	42	-3.1	3.4
1	14	-5.7	0.3	42	-6.1	-1.3	14	-1.6	3.5	42	-3.9	1.7
2	14	-4.4	5.4	42	-4.4	0.1	14	-1.9	7.7	42	-1.9	3.0
4	14	-4.1	4.9	41	-3.3	1.9	14	-0.2	10.1	41	-5.9	-1.1
6	14	-6.9	1.0	41	-4.2	0.3	14	-3.2	3.9	41	-5.2	-0.2
10	14	-6.5	1.9	41	0.1	4.1	14	-5.8	5.1	41	0.3	4.8
14	14	-3.1	5.3	40	-2.5	2.6	14	0.7	10.1	40	-1.9	3.5
18	14	-2.7	7.7	40	2.1	7.3	14	1.6	12.1	40	0.6	5.9
23	14	-8.1	1.6	41	-6.8	-2.1	14	-5.2	6.2	41	-6.4	-1.0

Figure 4: Mean and 90% CI ΔQTcI and ΔQTcF Timecourse



5.2.2 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose absolute QTcI values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and > 500 ms. Majority of the subjects' absolute QTcI were below 480 ms. All subjects who had high post dose QTcI values (>480 ms) in both treatment groups also had high baseline values except for one subject in the 25 mg/m^2 group who had a high post dose (between 480 ms and 500 ms) but < 480 ms baseline value.

Table 11: Categorical Analysis for QTcI

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500 ms
Baseline	56	34 (60.7%)	17 (30.4%)	3 (5.4%)	2 (3.6%)
25mg/m2	14	10 (71.4%)	1 (7.1%)	3 (21.4%)	0 (0.0%)
40mg/m2	42	31 (73.8%)	8 (19.0%)	2 (4.8%)	1 (2.4%)

Table 12 lists the categorical analysis results for ΔQTcI. There was one subject in the 40mg/m^2 group who had ΔQTcI > 60 ms, but this subject's absolute QTcI for both post dose and baseline were below 480 ms.

Table 12: Categorical Analysis of ΔQTcI

Treatment Group	N	Value<=30 ms	30<Value<=60 ms	Value>60 ms
25mg/m^2	14	13 (92.9%)	1 (7.1%)	0 (0.0%)
40mg/m^2	42	37 (88.1%)	4 (9.5%)	1 (2.4%)

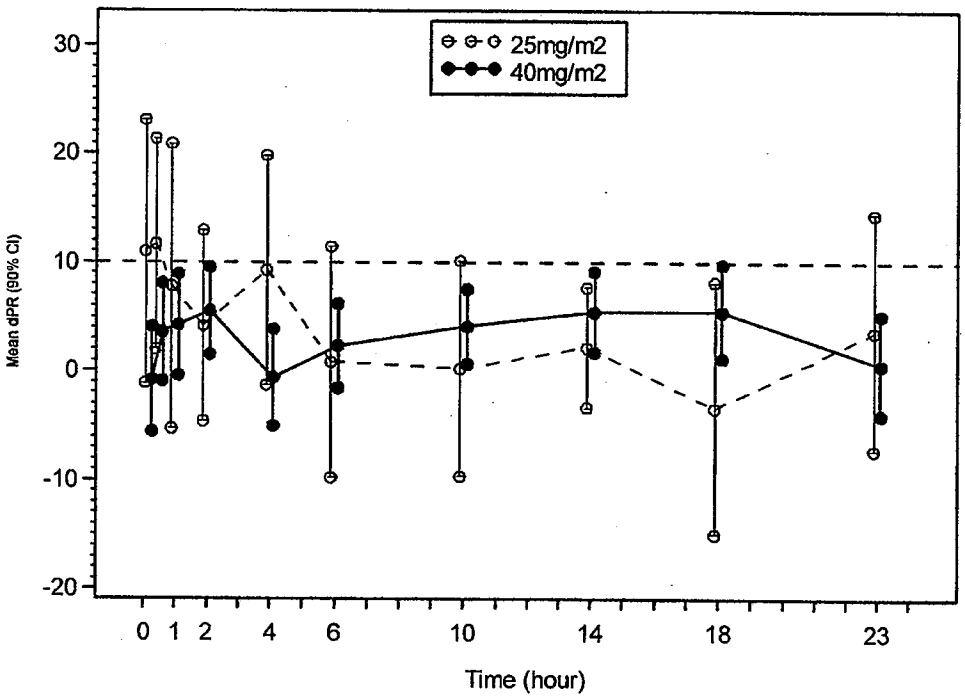
5.2.3 PR Analysis

Table 13 and Figure 5 present a summary of the unadjusted mean of ΔPR for each treatment. When the largest 90% upper bound of ΔPR are 23.1 ms and 9.8 ms for the 25 mg/m^2 IV group and 40 mg/m^2 PO group, respectively.

Table 13: Summary of ΔPR by Treatment

Time (hr)	25mg/m² IV				40mg/m² PO			
	N	Mean	Lower 90% CI	Upper 90% CI	N	Mean	Lower 90% CI	Upper 90% CI
0.17	14	11.0	-1.1	23.1	39	-0.7	-5.6	4.1
0.5	14	11.7	2.0	21.4	38	3.6	-0.9	8.1
1	14	7.8	-5.3	20.9	39	4.3	-0.4	8.9
2	14	4.2	-4.6	12.9	39	5.5	1.5	9.5
4	14	9.3	-1.3	19.8	38	-0.6	-5.0	3.9
6	14	0.8	-9.8	11.4	39	2.3	-1.5	6.2
10	14	0.2	-9.7	10.2	39	4.1	0.7	7.5
14	14	2.2	-3.4	7.7	38	5.4	1.7	9.1
18	14	-3.4	-15.0	8.2	36	5.5	1.2	9.8
23	14	3.6	-7.2	14.5	37	0.6	-4.0	5.2

Figure 5: Mean and 90% CI ΔPR Timecourse



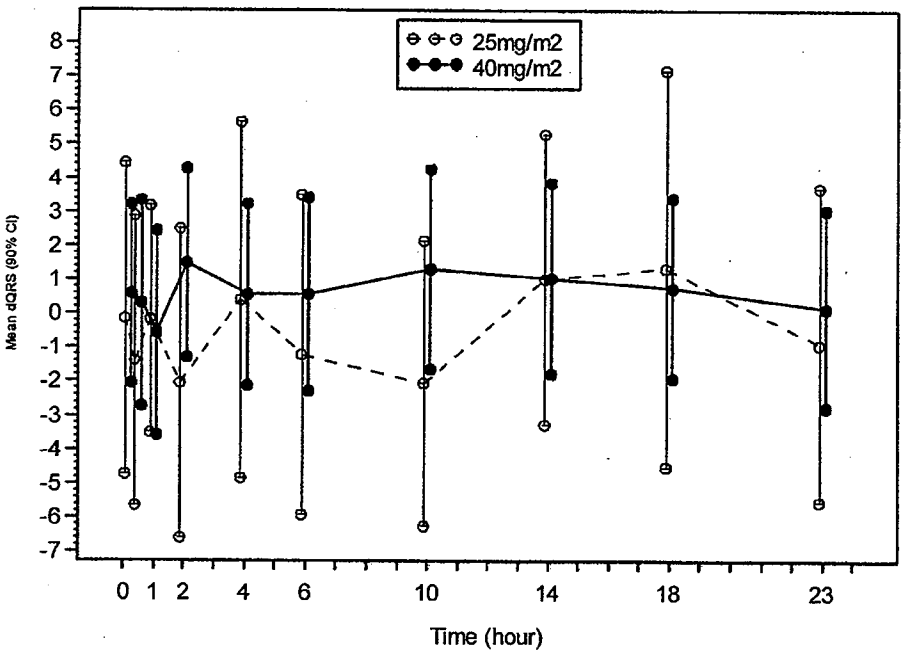
5.2.4 QRS Analysis

Table 14 and Figure 6 present a summary of the unadjusted mean of ΔQRS for each treatment. When the largest 90% upper bound of ΔQRS are 7.2 ms and 4.3 ms for the 25-mg/m^2 IV group and 40-mg/m^2 PO group, respectively.

Table 14: Summary of ΔQRS by Treatment

	25mg/m^2 IV				40mg/m^2 PO			
Time (hr)	N	Mean	Lower 90% CI	Upper 90% CI	N	Mean	Lower 90% CI	Upper 90% CI
0.17	14	-0.1	-4.7	4.4	42	0.6	-2.0	3.2
0.5	14	-1.4	-5.6	2.9	42	0.3	-2.7	3.3
1	14	-0.2	-3.5	3.2	42	-0.6	-3.6	2.4
2	14	-2.0	-6.6	2.5	42	1.5	-1.3	4.3
4	14	0.4	-4.8	5.7	41	0.6	-2.1	3.2
6	14	-1.2	-5.9	3.5	41	0.6	-2.3	3.4
10	14	-2.0	-6.2	2.2	41	1.3	-1.6	4.3
14	14	1.0	-3.3	5.3	40	1.0	-1.8	3.9
18	14	1.3	-4.5	7.2	40	0.7	-1.9	3.4
23	14	-0.9	-5.5	3.7	41	0.2	-2.8	3.1

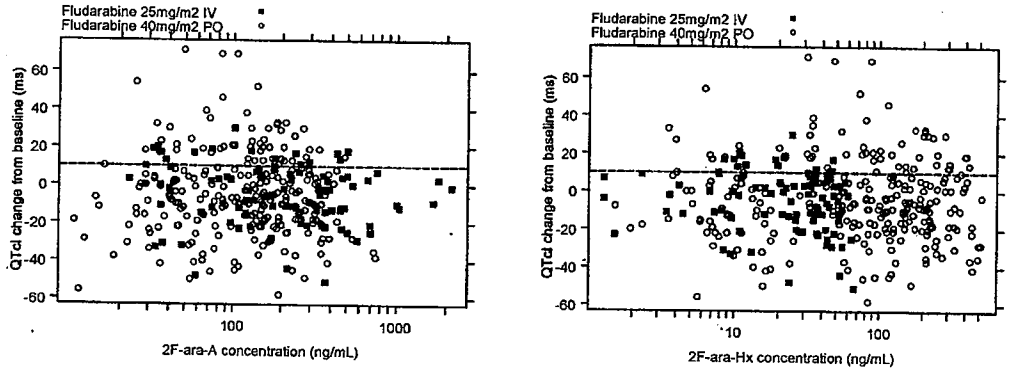
Figure 6: Mean and 90% CI ΔQRS Timecourse



5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

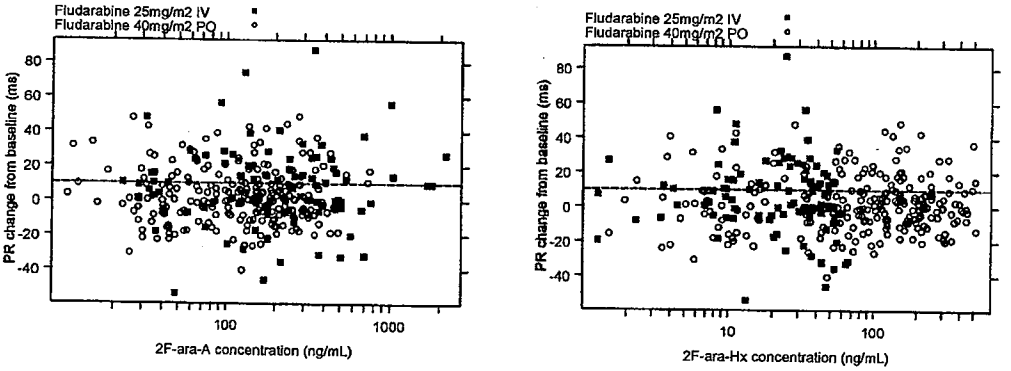
The relationship between ΔQTcI and 2F-ara-A and 2F-ara-Hx concentrations is shown in Figure 7 with no evident exposure-response relationship.

Figure 7: ΔQTcI vs. (Left) 2F-ara-A and (Right) 2F-ara-Hx (metabolite) concentrations



The relationship between ΔPR and 2F-ara-A and 2F-ara-Hx concentrations is visualized in Figure 8 with no evident exposure-response relationship.

Figure 8: ΔPR vs. (Left) 2F-ara-A and (Right) 2F-ara-Hx (metabolite) concentrations



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

Two subjects had an absolute QTcI >500 ms at baseline and one of these subjects in the 40mg/m^2 PO fludarabine group had an absolute value > 500 ms post-treatment as well.

There was one subject whose ΔQTcI was above 60 ms in 40-mg/m^2 PO group. These can be expected in this patient population with co-morbidities. None of these changes were associated with adverse events related to QT prolongation.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 72% of the ECGs were annotated in the primary lead II. On review of subsets of the other ECGs predominantly lead V5 or the most appropriate lead has been used as stated in the protocol. Less than 3.5% of ECGs reported to have significant QT bias, according to the automated algorithm. While this is a little higher than QT bias with most studies with healthy volunteers (1%), the histogram was symmetric and this appears reasonable considering that this was a study in a patient population. Overall, ECG acquisition and interpretation in this study appears acceptable for detecting large effects.

5.4.3 PR, QRS Interval and other ECG effects

This study was conducted with a heterogeneous population, with many baseline ECG abnormalities, including a couple of atrial fibrillation/flutter patients.

Based on interpretation of 12 lead ECGs by [redacted] and the CSR, the only findings were: b(4)

- Nine instances of non-clinically significant 1st degree AV blocks, with no cases of increase in PR interval over normal at baseline
- Four instances of atrial flutter and/or atrial fibrillation (2 patients had baseline atrial fibrillation)
- Some patients who received the study drug showed an increase in the PR interval and one developed Mobitz type I second degree AV block.

Fludarabine appears to increase the PR interval at several time points and the largest 90% upper bound of ΔPR are 23.1 ms and 9.8 ms for the 25-mg/m^2 IV group and 40-mg/m^2 PO group, respectively. This effect appears to be more prominent with the i.v. formulation. However, since the CI's are wide and there were no clinically significant blocks (complete AV block or Mobitz type 2) the interpretation of this data is difficult especially in this population of patients with several baseline ECG abnormalities (see also section 5.4.4).

The largest 90% upper bound of ΔQRS are 7.2 ms and 4.3 ms for the 25-mg/m^2 IV group and 40-mg/m^2 PO group, respectively indicating no clinically significant effects.

5.4.4 MGPS Datamining Analysis for Heart Block

A MGPS data mining analysis was conducted using the AERS database to look for reports of heart blocks with fludarabine. The signal scores (EBGM values) for fludarabine were less than 1 suggesting that the incidence rate was similar to the incidence rate in the general population.

Configuration: CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 123
Dimension: 2 **Selection Criteria:** Generic name(Fludarabine) + PT(...)
4 rows

Generic name	Level 1	Level 2	PT	HLT	HLGT	SOC	N	EBGM	EB05	EB9
Fludarabine	Purine Analogues	Immun&Neopl	Atrioventricular block	Cardiac conduction disorders	Cardiac arrhythmias	Card	3	0.655	0.256	1.4
Fludarabine	Purine Analogues	Immun&Neopl	Atrioventricular block complete	Cardiac conduction disorders	Cardiac arrhythmias	Card	3	0.618	0.241	1.3
Fludarabine	Purine Analogues	Immun&Neopl	Atrioventricular block second degree	Cardiac conduction disorders	Cardiac arrhythmias	Card	1	0.542	0.127	1.6
Fludarabine	Purine Analogues	Immun&Neopl	Bundle branch block	Cardiac conduction disorders	Cardiac arrhythmias	Card	1	0.603	0.141	1.8

ID:	123
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	10/10/2008 00:00:00
Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	Empirica Signal Administrator
Created On:	10/17/2008 10:04:32 EDT
User:	Suchitra Balakrishnan
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 10/10/2008 00:00:00 loaded on 2008-10-16 09:58:56.0

Dimension: 2 **Selection Criteria:** Generic name(Fludarabine) + PT(Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Bifascicular block, Bundle branch block)
These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<table>
<tr><td>Therapeutic dose</td><td colspan="2">PROPOSED: 40 mg/m^2 fludarabine phosphate (2F-ara-AMP) once daily PO for 5 days. Repeat regimen every 4 weeks for up to 3 cycles.</td></tr>
<tr><td>Maximum tolerated dose</td><td colspan="2">Single dose: 43 mg/m^2 IV or 56 mg/m^2 PO of 2F-ara-AMP (highest dose shown to be safe)
Multiple dose: 25 mg/m^2 IV or 40 mg/m^2 PO of 2F-ara-AMP (highest dose shown to be safe)</td></tr>
<tr><td>Principal adverse events</td><td colspan="2">Most frequent adverse events are myelosuppression, fever, diarrhea, nausea/vomiting, increased cough, anorexia, asthenia, and infection.
Myelosuppression (granulocytopenia, leucopenia, thrombocytopenia and anemia) is dose-limiting toxicity</td></tr>
<tr><td rowspan="2">Maximum dose tested</td><td>Single Dose</td><td>90 mg PO (ca. 56 mg/m^2) [Study ME95101] given as 9 10 mg tablets (n=18)
70 mg IV (ca. 43 mg/m^2) [Study TB03-1105] given as a 30 min infusion (n=1)
60 mg IV (ca. 37 mg/m^2) [Study TB03-1105] given as a 30 min infusion (n=9)</td></tr>
<tr><td>Multiple Dose</td><td>50 mg PO once daily for 5 days (ca. 31 mg/m^2) [Study BL03-1109 (n=16) for solution and Study ME94204 (n=16) for 5 tablets]
50 mg IV as a 30 min infusion once daily for 5 days [Study BL03-1109 (n=16) and ME94204 (n=16)]</td></tr>
<tr><td>Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>2F-ara-A; mean (%CV):
<table>
<tr><th>Route</th><th>Dose mg</th><th>Cmax µM</th><th>$AUC_{0-\infty}$ µM•hr</th><th>n</th><th>Study</th></tr>
<tr><td>PO</td><td>90</td><td>1.68 (34.8%)</td><td>10.6 (32.8%)[a]</td><td>18</td><td>ME95101</td></tr>
<tr><td>IV</td><td>60</td><td>3.53 (35%)</td><td>14.6 (36%)</td><td>12[b]</td><td>TB03-1105</td></tr>
<tr><td>IV</td><td>50</td><td>5.4 (93.8%)</td><td>10.73 (26.8%)</td><td>15</td><td>ME95101</td></tr>
</table>
[a] AUC_{0-24hr}
[b] Includes (2) pats. given 50 mg and (1) pat. given 70 mg</td></tr>
<tr><td></td><td>Multiple Dose</td><td>2F-ara-A; mean (%CV):
<table>
<tr><th rowspan="2">Route</th><th rowspan="2">Dose mg</th><th colspan="2">Cmax µM</th><th colspan="2">AUC_{0-24hr} µM •hr</th><th rowspan="2">n</th><th rowspan="2">Study</th></tr>
<tr><th>Day 1</th><th>Day 5</th><th>Day 1</th><th>Day 5</th></tr>
<tr><td>PO</td><td>50</td><td>0.974 (46%)</td><td>1.325 (39%)</td><td>7.282 (52%)</td><td>12.871 (47%)</td><td>16</td><td>BL03-1109</td></tr>
<tr><td>IV</td><td>50</td><td>3.725 (47%)</td><td>4.745 (52%)</td><td>12.8 (39%)</td><td>21.8 (35%)</td><td>16</td><td>BL03-1109</td></tr>
</table></td></tr>
<tr><td>Range of linear PK</td><td colspan="2">50, 70, or 90 mg single PO doses of 2F-ara-AMP given once daily as 5, 7, or 9 ten mg tablets to 18 patients. [Study ME95101]</td></tr>
<tr><td>Accumulation at steady state</td><td colspan="2">Mean (%CV):
PO: 50 mg (5 tablets) once daily for 5 days [Study ME94204] R (accumulation) = 2.28 (69.4%)
IV: 50 mg as a 30 min infusion once daily for 5 days [Study ME94204] R= 2.12 (50.6%)</td></tr>
<tr><td>Metabolites</td><td colspan="2">2F-ara-A (obligate precursor to 2F-ara-ATP)
2F-ara-ATP (ultimate intracellular active metabolite)
2F-ara-Hx (hypoxanthine analog; inactive)</td></tr>
<tr><td rowspan="2">Absorption</td><td>Absolute/Relative Bioavailability</td><td>Mean (%CV) Absolute Oral Bioavailability of 2F-ara-A:
57.1% (36.5%) 50 mg single dose (tablets); Day 5 [Study ME94204]
56% (49-64% CI) for 50 mg single dose (tablets); Day 1 [Study ME95101]
54% (46-63% CI) for 70 mg single dose (tablets); Day 1 [Study ME95101]
54% (46-62% CI) for 90 mg single dose (tablets); Day 1 [Study ME95101]
57.7% for 40 mg/m^2 single dose (tablets); Day 1 [Study 0004B1-100-GL/0004B1-400-GL]</td></tr>
<tr><td>Tmax</td><td>• Tmax for 2F-ara-A after PO 2F-ara-AMP; median (range):
50 mg single dose (tablets); 1.1 (0.5-2.0) hr [Study ME95101]
70 mg single dose (tablets); 1.2 (0.5-2.0) hr [Study ME95101]
90 mg single dose (tablets); 1.2 (0.67-3.0) hr [Study ME95101]</td></tr>
</table>

<table>
<tr><td></td><td></td><td>40 mg/m^2 single dose (tablets); 2.0 (0.5-6.0) hr [Study 0004B1-100-GL/0004B1-400-GL]
• Tmax for 2F-ara-Hx after PO 2F-ara-AMP; median (range):
40 mg/m^2 single dose (tablets); 1.0 (1.0-6.0) hr [Study 0004B1-100-GL/0004B1-400-GL]</td></tr>
<tr><td>Distribution</td><td>Vd/F or Vd</td><td>2F-ara-A; mean (%CV):
Vss: 153 L (34.6%) [Study ME95101]
Vss: 247 L (44.1%) CLL pats. [Study ME94204]
Vss: 176 L (33.0%) NHL pats. [Study ME94204]</td></tr>
<tr><td></td><td>% bound</td><td>2F-ara-A; mean (%CV):
24.0 (19.6%), 29.4 (35.4%), 19.3 (31.1%), bound at 0.2, 1, 5 µg/mL, (0.7, 3.5, 17.5 µM) respectively [Study 93440, 94611]</td></tr>
<tr><td>Elimination</td><td>Route</td><td>• Renal excretion of 2F-ara-A as % of 2F-ara-AMP dose;
IV: 60.5% of a 20 mg/m^2 single dose excreted within 6 days [Study 94615]
IV: 43.0% of a 50 mg single dose excreted within 8 days [Study ME94204]
IV: 37% of a 25 mg/m^2 single dose excreted within 23 hours [Study 0004B1-100-GL/0004B1-400-GL]
PO: 24% of a 50 mg single dose excreted within 8 days [Study ME94204]
PO: 19% of a 40 mg/m^2 single dose excreted within 23 hours [Study 0004B1-100-GL/0004B1-400-GL]
• Renal excretion of 2F-ara-Hx as % of 2F-ara-AMP dose;
IV: 17.3% of a 20 mg/m^2 single dose excreted within 6 days [Study 94615]
IV: 13% of a 25 mg/m^2 single dose excreted within 23 hours [Study 0004B1-100-GL/0004B1-400-GL]
PO: 25% of a 40 mg/m^2 single dose excreted within 23 hours [Study 0004B1-100-GL/0004B1-400-GL]
• Renal excretion of 2F-ara-AMP as % of 2F-ara-AMP dose;
IV: ~0% of a 25 mg/m^2 single dose excreted within 23 hours [Study 0004B1-100-GL/0004B1-400-GL]
PO: ~0% of a 40 mg/m^2 single dose excreted within 23 hours [Study 0004B1-100-GL/0004B1-400-GL]</td></tr>
<tr><td></td><td>Terminal t½</td><td>• Mean (%CV) for 2F-ara-A:
21.8 hr (12.4%) Day 5 after a single 50 mg IV dose and 22.5 hr (21.8%) Day 5 after a single 50 mg PO dose of tablets [Study ME94204]
26.5 hr (38.9%) Day 1 after a single 90 mg PO dose (fasted) and 26.9 hr (47.2%) Day 1 after a single 90 mg PO dose (fed) [Study ME96079]
• Mean (%CV) for 2F-ara-Hx ranged from 4.9 hr to 16.3 hr (30.7%, n=4) after single or 5 daily IV doses given as a 30 min infusion [Study 94615]</td></tr>
<tr><td></td><td>CL/F or CL</td><td>CLs (plasma) for 2F-ara-A after IV doses of 2F-ara-AMP; mean (%CV):
226 (58.8%) mL/min after single doses of 50 mg (n=2), 60 mg (n=9) or 70 mg (n=1) combined [Study TB03-1105]
248 (26.0%) mL/min after a single dose of 50 mg [Study ME95101]
145 (24%) mL/min on Day 5 after single daily IV dose of 50 mg [Study ME94204]</td></tr>
<tr><td>Intrinsic Factors</td><td>Age</td><td>Not studied specifically (CLL and NHL patients are generally elderly)</td></tr>
<tr><td></td><td>Sex</td><td>
Pharmacokinetics of 2F-ara-A in Male and Female Patients in Study ME94204
<table>
<tr><th>Parameter</th><th>IV Dose</th><th></th><th>PO Dose</th><th></th></tr>
<tr><th>mean ± sd</th><th>Male (n=8)</th><th>Female (n=11)</th><th>Male</th><th>Female</th></tr>
<tr><td>Cmax µg/mL</td><td>1.10 ± 0.21</td><td>1.34 ± 0.57</td><td>0.266 ± 0.136</td><td>0.325 ± 0.132</td></tr>
<tr><td>tmax hr</td><td>NR[b]</td><td>NR</td><td>1.3 ± 0.8</td><td>1.9 ± 0.8</td></tr>
<tr><td>AUC_{96-120} µg•hr/mL</td><td>5.17 ± 1.48</td><td>4.52 ± 1.33</td><td>2.33 ± 1.08</td><td>2.96 ± 1.19</td></tr>
<tr><td>t½ hr</td><td>22.2 ±</td><td>21.5 ± 2.5</td><td>21.5 ± 4.8[c]</td><td>23.2 ± 5.1</td></tr>
</table>
</td></tr>
</table>

			3.2			
	CLs	mL/min	133 ± 31	154 ± 36	NA[d]	NA
	Vz[a]	L	251 ± 50	274 ± 78	NA	NA

Race

Not studied specifically

Hepatic & Renal Impairment

Study BL03-4107, open label multiple dose PK study and protein binding study of IV fludarabine phosphate given to patients with and without renal impairment

parameter	unit	group 1		group 2		group 3	
		single	multiple	single	multiple	single	multiple
dose (n)	[mg/m²]	25 (10)	25 (10)	25 (9)	20 (9)	25 (2)	15 (2)
$C_{min(d1)}$	[µM]	0.13±0.04	-	0.16±0.04	-	0.36±0.03	-
$C_{min(d3)}$		-	0.23±0.09**	-	0.26±0.05***	-	0.31±0.05
$C_{min(d4)}$		-	0.2±0.08	-	0.28±0.09	-	0.34±0.14
$C_{min(d5)}$		-	0.23±0.07**	-	0.23±0.06	-	0.33±0.14
C(IT)		6.0±9.2*	3.7±1.8***	3.0±0.8	2.9±0.9	3.1±0.1	2.9±0.2
AUC(0-24h)	[µM·h]	9.2±4.1	13.4±4.8**	10.0±2.6	13.4±3.1	18.1±0.4	17.1±5.1
AUC		13.4±4.1	20.9±5.4**	15.6±3.6	20.4±4.8	29.0±1.1	29.5±11.0
$t_{½\lambda z}$	[h]	23±8	20±4**	23±7	22±4	20±3	24±3
CL_{cr}	[mL/min/m²]	48±15	51±27**	38±14	47±11	13±6	14±0
CL		92±34	93±36**	77±19	71±18	39±1	41±11
CL_R		59±37	55±22	43±19***	41±10***	14±0	16±2
CL_{NR}		33±24	37±21**	34±6***	33±13***	25±2	26±13

- **Group 1 - creatinine clearance > 70 mL/min/1.73 m²**
- **Group 2 - creatinine clearance 30 to 70 mL/min/1.73 m²**
- **Group 3 - creatinine clearance < 30 mL/min/1.73 m²**

Patients with hepatic impairment were not studied specifically

Extrinsic Factors

Drug interactions

No in vivo clinical DDI studies were conducted. In vitro CYP inhibition or induction studies with human liver microsomes or hepatocytes suggest that CYP-mediated drug-drug interactions with 2F-ara-AMP or 2F-ara-A are unlikely. In vitro studies showed that 2F-ara-A is a weak substrate and poor or non-inhibitor of P-gp and consequently there is low probability of 2F-ara-A drug-drug interactions mediated by P-gp activity.

Food Effects

Study ME96029, randomized single dose PK study of fludarabine phosphate given IV or as tablets to fasted or fed patients given a high fat meal.

Mean pharmacokinetic parameters of 2F-ara-A after a single oral dose of 90 mg fludarabine phosphate (SH T 586 C) in patients with B-CLL and Lg-NHL in fasted or non-fasted conditions

Treatment	AUC(0-24h) [µg·h/mL]	AUC(0-48h) [µg·h/mL]	Cmax [ng/mL]	tmax [h]	t1/2λz [h]
Fasted					
mean ± s.d.	3.05 ± 1.56 (n=16)	3.91 ± 1.77 (n=15)	488 ± 279 (n=16)	1.3 ± 0.74 (n=16)	26.5 ± 10.3 (n=14)
Non-fasted					
mean ± s.d.	3.28 ± 1.48 (n=16)	4.23 ± 1.76 (n=15)	442 ± 181 (n=16)	2.2 ± 1.0 (n=16)	26.9 ± 12.7 (n=14)

AUC(0-24h)	area under the plasma level-time curve from time of dosing to 24 h post administration
AUC(0-48h)	area under the plasma level-time curve from time of dosing to 48 h post administration
Cmax	maximum plasma level
tmax	time-point of maximum plasma level
t1/2λz	terminal half-life

Expected High Clinical Exposure Scenario

For the proposed 40 mg/m² fludarabine phosphate (2F-ara-AMP) once daily PO dose, the projected worst case Cmax may be 11.2 µM and this concentration has been exceeded by a factor of 2 after single 50 mg IV infusions (patient 17; 20.2 µM) [Study ME95101]. This projection assumes a bioavailability of 56%, linear exposure as demonstrated in Study ME95101, a 2-fold accumulation to steady-state and a 4-fold potential inter-patient variability.

The projected worst case AUC may be 32 µM•hr and this value has been exceeded slightly after a single 50 mg IV infusion (patient 106; 38.5 µM•hr) [Study BL03-1109]. This projection assumes a bioavailability of 56%, linear exposure, a 2-fold accumulation to steady-state and a 2-fold potential inter-patient variability in the AUC at steady-state.

6.2 TABLE OF STUDY ASSESSMENTS

Procedure	Screening (Day -13 to Day 0)	Day 1 Predose	Day 1 Postdose
Informed consent	X		
Demographics	X		
Medical history[a]	X		
Pathology/hematology documentation of B-cell CLL or low-grade NHL[b]	X		
Serum pregnancy test[c]	X		
Physical examination	X		
Eastern Cooperative Oncology Group (ECOG) performance status	X		
Vital signs	X	X[g]	
Continuous 12-lead ECG (24 hours)	X	X[h]	X[h]
Clinical laboratory tests[d]	X		X
Adverse events[e]	X	X	X
Blood samples for pharmacokinetics[f]		X	X
Urine collection			X[i]

[a] All prior therapies for B-cell chronic lymphocytic leukemia (CLL) or non-Hodgkin's leukemia (NHL), including the total cumulative dose and concomitant medications, were also to be recorded at the US site.
[b] US site only.
[c] Beta-human chorionic gonadotropin (ß-hCG) for women of childbearing potential only.
[d] Complete blood cell (CBC) count and serum chemistry panel.
[e] Adverse events were to be reported for 23 hours after fludarabine phosphate dosing on day 1. Adverse events that occurred before fludarabine phosphate dosing were also to be reported if the investigator judged these to be related to the study procedures.
[f] Blood samples were obtained predose and at 10 and 30 minutes and 1, 2, 4, 6, and 23 hours after intake of oral fludarabine phosphate or the start of the fludarabine phosphate IV infusion.
[g] Predose vital signs only included height and weight to allow for calculation of body surface area.
[h] Continuous 12-lead electrocardiogram (ECG) monitoring started 1 hour before fludarabine phosphate dosing and continued for a total of 24 hours.
[i] Urine was collected from 0 to 6 hours and from 6 to 23 hours postdosing with fludarabine phosphate.

Source: table 2 from CSR for 0004B1-100-GL/0004B1-400-GL

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/s/

Christine Garnett
11/14/2008 01:14:42 PM
BIOPHARMACEUTICS

Christoffer Tornoe
11/14/2008 01:39:37 PM
BIOPHARMACEUTICS

Joanne Zhang
11/17/2008 08:50:48 AM
BIOMETRICS
Lihan Yan was the primary statistical reviewer.

Suchitra Balakrishnan
11/17/2008 09:08:11 AM
MEDICAL OFFICER

Norman Stockbridge
11/19/2008 07:41:38 AM
MEDICAL OFFICER

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: Oral Fludarabine Phosphate

Generic name: Oral Fludarabine Phosphate

Type of dosage form and strength(s): immediate release tablet, 10 mg

Indication(s): the Applicant's proposed indication is, "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"

NDA number, type: NDA 22-273, 1S

Applicant name: Xanthus Pharmaceuticals, Inc.

Submission date (letter date):	15-Nov-2007	N	000	
	22-Feb-2008	N	000	BS

OCP Division name: Division of Pharmaceutical Evaluation V
OND: Division name: Division of Drug Oncology Products
OCP Reviewer name: Gene M. Williams, Ph.D.
OCP Team Leader name: NAM Atiqur Rahman, Ph.D.

Table of Contents

1. Executive Summary

The Applicant seeks approval of a New Drug Application (NDA 22-273/N-000) for Fludarabine Phosphate Film-Coated Tablets under Section 505b(2) of the Food, Drug, and Cosmetic Act (21 CFR 314.50) for the same indication as the approved intravenous drug product, FLUDARA FOR INJECTION. The recommended regimen of Fludarabine Phosphate Film-Coated Tablets is 40 mg/m^2 daily for five consecutive days on a 28 day cycle. The recommended dose of FLUDARA FOR INJECTION is 25 mg/m^2 administered intravenously over a period of approximately 30 minutes daily for five consecutive days on a 28 day cycle. The oral dose was selected to approximate the AUC of the IV product and results in an AUC of approximately 95% of that of the IV product.

The Applicant conducted efficacy/safety clinical studies in support of the NDA. The decision for the approval of this NDA submission is not based primarily on results obtained from bioequivalence studies or other evidence of pharmacokinetic similarity.

There are no recommendations for clinical pharmacology-related Phase 4 commitments or other clinical pharmacology-related recommendations other than changes to the proposed package insert.

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

The applicant has proposed that patients with severe renal impairment not receive oral fludarabine. Our recommendation is that patients with severe renal impairment not be excluded from treatment, but have their dose reduced by 50%.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

There are no clinical pharmacology-related recommended Phase 4 commitments.

1.3 Recommendations to the Applicant

With the exception of changes to the package insert, there are no recommendations for the applicant.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Fludarabine phosphate for injection is approved under the trade name Fludara. The current NDA is for the use of oral fludarabine phosphate for the same indication for which Fludara is approved: 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.

b(4)

The current application adds new clinical data [redacted] It also contains new *in vitro* metabolism data and new QT information.

2F-ara-A is an active metabolite of fludarabine and the clinical activity of fludarbine is thought to result from 2F-ara-A rather than the parent drug. The dose (40 mg/m^2) for the clinical studies in the current submission was selected to approximate the AUC of fludarabine's active metabolite, 2-ara-F, that occurs following administration of the package insert dose (25 mg/m^2) of the IV product. However, the FDA made clear during the development process that approval could be pursued via two distinctly different approaches:

1. a pharmacokinetcs approach. This would require either:
   a. compelling exposure-response models for efficacy and toxicity and sufficient similarity of concentrations, or
   b. bioequivalence of both AUC and Cmax for all active moieties. This would entail mass balance accounting to assure that all active moieties were identified.
2. a clinical approach. This would entail showing that safety and efficacy from oral administration approximates that from IV administration.

The Applicant has chosen the second option: a clinical approach. Neither exposure-response modeling nor bioequivalence and mass balance data that would satisfy the pharmacokinetics approach were performed.

Consistent with the package insert for the IV product, the focus of the pharmacokinetics program was to characterize 2F-ara-A pharmacokinetics. Absolute bioavailability of 2F-ara-A from the oral formulation is approximately 60%. Tmax is approximately 1.6 hours and terminal half-life is the same across routes of administration: approximately 22 hours. Data accumulated with both formulations support that the pharmacokinetics of 2F-ara-A are linear across doses and across time. The accumulation factor (AUC Day 5 ÷ AUC Day 1) with oral administration was 2.3.

Neither fludarabine nor 2F-ara-A are substrates or inhibitors of CYP enzymes. Food did not effect bioavailability (AUC and Cmax).

b(4)

A review by the CDER IRT concluded that there was no apparent QT prolonging effect of fludarabine (25 mg/m^2 IV and 40 mg/m^2 PO) in the QT study. However, QTc prolongation less than 10 ms cannot be excluded as the study lacked positive and placebo controls.

2. Question-Based Review

2.1. General attributes of the drug

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

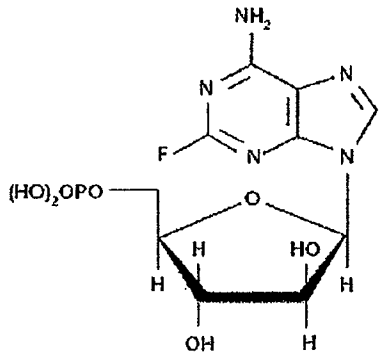
Fludarabine phosphate for injection is approved under the trade name Fludara. The current NDA is for the use of oral fludarabine phosphate for the same indication for which Fludara is approved.

b(4)

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The molecular formula for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-_-D-arabinofuranosyl) (2-fluoro-ara-AMP). The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ and the molecular weight is 943.48 grams per mole. A structural representation is shown below as **FDA Figure 1.**

FDA Figure 1. Fludarabine phosphate



Fludarabine phosphate possesses no chiral centers or external olefinic bonds, thus precluding the existence of stereoisomers or geometricisomers.

Fludarabine phosphate tablets are film-coated, capsule shaped, salmon pink in color, and marked on one side with 'LN' in a regular hexagon. A single strength, 10 mg, is being marketed.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The below (indent, font change) are reproduced from the Applicant's proposed package insert.

b(4)

b(4)

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The below (indent, font change) is reproduced from the Applicant's proposed package insert.

b(4)

2.2. General clinical pharmacology

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

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.

Modeling and simulation using the PK data derived in Study ME95101 predict that the systemic exposure (AUC) produced by an oral dose of 40 mg/m^2 (the clinical trials dose and the package insert dose for the current oral application) would be 95% of that of a 30 min iv infusion of 25 mg/m^2 (the package insert dose for the iv product). However, a study directly measuring the

confidence interval for the ratio of the AUCs of the oral and iv products at their package insert doses has not been performed.

The primary efficacy study, Study ME96029, is a single-arm, open-label study of FLUDARABINE PHOSPHATE conducted in 78 patients with CLL refractory to at least one prior standard alkylating-agent containing regimen. The primary efficacy variable in this study is clinical response rate. In the Applicant's analysis the overall objective response, according to NCI criteria, was 51 %, including 18% complete responses and 33% partial responses. The overall response rate, according to IWCLL criteria, was 46%, including 21% complete responses and 26% partial responses.

In a second single-arm, open-label study, FLUDARABINE PHOSPHATE oral tablets were administered to 81 previously untreated B-CLL patients (Study 303080). The overall response rate, according to NCI criteria, was 80%, including 12% complete responses and 68% partial responses. The overall response rate, according to IWCLL criteria, was 72%, including 37% complete responses and 35% partial responses.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoint was response rate by NCI criteria. No biomarkers for safety or efficacy were assessed in the efficacy/safety and pharmacokinetic studies

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The performance of the bioanalytical methods will be reviewed in Section 2.6.

No mass balance study was performed. Neither parent fludarabine nor any other moiety was measured in plasma following oral dosing.

The package insert for the iv product does not include a description of parent fludarabine pharmacokinetics, but does include the following statements (font change): Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2-fluoro-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2-fluoro-ara-A pharmacokinetics.

Renal excretion of 2F-ara-A was approximately 42% of the administered iv or oral dose. No data for the biliary or fecal excretion of 2F-ara-A are known. Following iv administration the metabolite 2F-ara-Hx was excreted renally and accounted for 9 - 17% of the administered dose.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Previous studies with the iv product have been unable to correlate concentrations and efficacy in cancer patients. The current study with oral administration did not include assessment of concentrations in the efficacy studies.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Previous studies with the iv product have shown correlations between concentrations and the cytotoxicity of fludarabine phosphate. There was a significant inverse correlation between the plasma AUC of 2F-ara-A and the absolute granulocyte count. A rank order of AUC values with the corresponding severity of neutropenia developed by each patient was also shown. White blood cell (WBC) toxicity was related to 2F-ara-A plasma concentrations and, therefore, to the administered dose. A positive correlation of total 2F-ara-A plasma clearance with hemoglobin and hematocrit was also observed, suggesting that the capacity of the compound to depress hematopoiesis is dose related.

2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

The Applicant submitted a QT study in month eight of the review cycle. The study has been reviewed by CDER's Interdisciplinary Team for QT (the IRT). Section **1.1 OVERALL SUMMARY OF FINDINGS** from the IRT review is reproduced, below (indent, font change).

1.1 OVERALL SUMMARY OF FINDINGS

There was no apparent QT prolonging effect of fludarabine (25 mg/m2 IV and 40 mg/m2 PO) in this QT study. However, QTc prolongation less than 10 ms cannot be excluded in the absence of positive and placebo controls.

In this randomized, uncontrolled, single-dose, open-label, parallel study, patients with Bcell CLL received 40 mg/m2 PO (n=42) or 25 mg/m2 IV infusion over 30 minutes (n=14). Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the Upper One-Sided 95% CIs for Fludarabine (40 mg/m^2 PO and 25 mg/m^2 IV) (FDA Analysis)

Treatment	Time (hour)	ΔQTcI (ms)	Upper 95% CI (ms)
Fludarabine 40 mg/m^2 PO	18	2.1	(7.3)
Fludarabine 25 mg/m^2 IV	18	-2.7	(7.7)

One subject had a QTcI change > 60 ms from baseline. This was not associated with adverse events related to QT prolongation.

The was no evidence of dose- or exposure-response when analyzing the association between 2F-ara-A concentrations and ΔQTcI prolongations following 40 mg/m2 PO and 25 mg/m2 IV (single dose) with mean Cmax of 279 and 808 ng/mL, respectively. No exposure-response was observed for 2F-ara-Hx concentrations and ΔQTcI prolongation. The tested doses of 25 mg/m2 IV and 40 mg/m2 PO (single doses) are the therapeutic (and maximum tolerated) doses of fludarabine for first- and second-line treatment of CLL, respectively. The highest expected clinical exposure scenario (severe renal impairment: 2-fold increase) for 40 mg/m2 PO will be covered by 25 mg/m2 IV producing 10-fold higher Cmax compared to 40 mg/m2 PO and showed no detectable prolongations of the QT-interval. The QT effects in patients with severe renal impairment receiving 25 mg/m2 IV are unknown.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and regimen were selected to approximate the AUC of 2F-ara-A that occurs with the recommended dose of the approved iv product. There are no unresolved dosing or administration issues.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

FDA Table 1 summarizes the pharmacokinetic parameters.

FDA Table 1. Applicant's Table, page 4 of Clinical Study Report AN60

Table: 2F-ara-A (ZK 159155) pharmacokinetics following once daily repeated i.v. and p.o. doses of 50 mg fludarabine phosphate on 5 consecutive days

parameter	unit	route of administration	
		i.v.	p.o.
C(24h,d1)	[µg/mL]	0.046 ± 0.032	0.025 ± 0.014
C(24h,d5)		0.097 ± 0.048	0.055 ± 0.023
C_{max}		1.24 ± 0.46	0.298 ± 0.133
t_{max}	[h]	-	1.6 ± 0.8
AUC(96-120h)	[µg·h/mL]	4.79 ± 1.39	2.68 ± 1.15
AUC(96-192h)		7.65 ± 2.70	4.42 ± 1.50
AUC(96-∞)		8.03 ± 2.94	4.74 ± 1.52
$t_{½}$	[h]	21.8 ± 2.7	22.5 ± 4.9
MRT	[h]	24.0 ± 8.8	30.5 ± 14.6
CL	[mL/min]	145 ± 35	-
CL_R		63.0 ± 19.9	66.3 ± 26.5
V_z	[L]	264 ± 67	-
V_{ss}		205 ± 88	-
R		2.12 ± 1.07	2.28 ± 1.59
%Ae(0-8d)	[%]	43.0 ± 8.4	24.1 ± 12.0
f_1 (plasma)	[%]	-	51.1 (40.1 - 65.1) 57.1 ± 20.8 (n=16)
f_2 (urine)	[%]	-	53.8 (40.0 - 72.4) 61.3 ± 25.5 (n=12)

n	number of evaluable patients after respective route of adm.
C(24h,d1/d5)	plasma level at the end of the dosing interval after the first and fifth dose, respectively
C_{max}	maximum plasma level
t_{max}	time to reach maximum plasma level
AUC	area under the plasma level-time curve
MRT	mean residence time at steady state
$t_{½}$	terminal half-life in plasma
CL, CL_R	total and renal clearances
V_z, V_{ss}	apparent volumes of distribution during terminal phase and at steady state
R	accumulation factor
%Ae(0-8d)	renally excreted dose portion within 8 days as percent of the total dose
f	systemic 2F-ara-A availability (geom. mean with confidence interval and arithm. mean ± SD) based on plasma level (f_1) and renal excretion data (f_2)

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Fludarabine is cytotoxic; studies in healthy subjects were not performed.

2.2.5.3 What are the characteristics of drug absorption?

Maximum plasma concentrations of 2F-ara-A occur 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 from fludarabine (2F-ara-AMP) is 50 - 65 %.

2.2.5.4 What are the characteristics of drug distribution? *(Include protein binding.)*

The volume of distribution of 2F-ara-A from iv fludarabine is approximately 200 L. Plasma protein binding of 2F-ara-A is approximately 25%.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not performed.

2.2.5.6 What are the characteristics of drug metabolism?

In the systemic circulation, fludarabine phosphate (2F-ara-AMP) is dephosphorylated to 2F-ara-A by "ubiquitous phosphatases." In addition to 2F-ara-A, circulating concentrations of 2F-ara-Hx ranging from 0.14 to 0.31 uM were found after 30 min infusions of 15 - 25 mg/m^2. Following iv administration 2F-ara-Hx was excreted renally and accounted for 9 - 17% of the administered dose.

No biotransformation of 2F-ara-A was detected *in vitro* after incubation with human liver microsomes or genetically engineered V79 cells expressing human liver CYP1A2 or 3A4.

2.2.5.7 What are the characteristics of drug excretion?

Renal excretion of 2F-ara-A was approximately 40 - 55% of the administered iv or oral dose. No data for the biliary or fecal excretion of 2F-ara-A are known. Following iv administration the metabolite 2F-ara-Hx was excreted renally and accounted for 9 - 17% of the administered dose.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

A published study with the iv product has demonstrated that plasma concentrations and AUC values increase proportionally with dose for doses of up to 260 mg/m^2, a dose approximately 10-fold greater than the current therapeutic daily dose of 25 mg/m^2. These data are show below **(FDA Table 2.)**.

FDA Table 2. Excerpted from Applicant's Table 2.7.2.7, page 41 of Clinical Summary – Clinical Pharmacology

Table 2.7.2.7: Mean 2F-ara-A Pharmacokinetics in Plasma of Cancer Patients after I.V. Administration of Fludarabine Phosphate

dose [mg/m²]	n	mode of adm.	$T_{½λ1}$ [h]	$t_{½λ2}$ [h]	$T_{½λz}$ [h]	MRT [h]	CL [mL/min/m²]	V_{ss} [L/m²]	V_z [L/m²]	ref.
260	7	infusion	0.10	1.2	9.5	9	72	41	60	Malspeis et al., 1990
160	6	2-5 min	0.09	1.6	9.7	10	78	47	66	
120	8		0.07	1.4	12.2	12	54	41	58	
100	3		0.09	1.5	10.8	12	73	53	71	
80	6		0.08	1.5	10.2	10	69	45	63	

Linearity with dose was also demonstrated across single oral doses of 50 – 90 mg (**FDA Table 3.**).

FDA Table 3. Applicant's Text Table 21, page 56 of Clinical Study Report AN61

Text Table 21: Adjusted Bioavailability (retransformed)

Treatment	N	Mean	Lower Conficence Interval	Upper Confidence Interval
[50mg/d] p.o.	15	0.56	0.49	0.64
[70mg/d] p.o.	15	0.54	0.46	0.63
[90mg/d] p.o.	15	0.54	0.46	0.62

2.2.5.9 How do the PK parameters change with time following chronic dosing? *(This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)*

In Study AN60 50 mg doses were given daily for 5 days. Independent of the route of administration 2F-ara-A plasma levels increased only through the fourth day, indicating obtainment of steady state on day 4. The observed mean drug accumulation factors at steady state were 2.12 (iv) and 2.28 (po). Based on half-lives of 21.8 h and 22.5 h, respectively, and the 24 h dose interval, the predicted accumulation factors are 1.87 and 1.91. It appears that clearance is reasonably constant across five days of dosing.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The Applicant's table summarizing the pharmacokinetic results for Study AN60 is reproduced, below (**FDA Table 4.**). The sources of the variability are unknown.

FDA Table 4. Applicant's Table, page 4 of Clinical Study Report AN60

Table: 2F-ara-A (ZK 159155) pharmacokinetics following once daily repeated i.v. and p.o. doses of 50 mg fludarabine phosphate on 5 consecutive days

parameter	unit	route of administration	
		i.v.	p.o.
C(24h,d1)	[µg/mL]	0.046 ± 0.032	0.025 ± 0.014
C(24h,d5)		0.097 ± 0.048	0.055 ± 0.023
C_{max}		1.24 ± 0.46	0.298 ± 0.133
t_{max}	[h]	-	1.6 ± 0.8
AUC(96-120h)	[µg-h/mL]	4.79 ± 1.39	2.68 ± 1.15
AUC(96-192h)		7.65 ± 2.70	4.42 ± 1.50
AUC(96-∞)		8.03 ± 2.94	4.74 ± 1.52
$t_{½}$	[h]	21.8 ± 2.7	22.5 ± 4.9
MRT	[h]	24.0 ± 6.8	30.5 ± 14.6
CL	[mL/min]	145 ± 35	-
CL_R		63.0 ± 19.9	66.3 ± 26.5
V_z	[L]	264 ± 67	-
V_{ss}		205 ± 88	-
R		2.12 ± 1.07	2.28 ± 1.59
%Ae(0-8d)	[%]	43.0 ± 8.4	24.1 ± 12.0
f_1 (plasma)	[%]	-	51.1 (40.1 - 65.1) 57.1 ± 20.8 (n=16)
f_2 (urine)	[%]	-	53.8 (40.0 - 72.4) 61.3 ± 25.5 (n=12)

n	number of evaluable patients after respective route of adm.
C(24h,d1/d5)	plasma level at the end of the dosing interval after the first and fifth dose, respectively
C_{max}	maximum plasma level
t_{max}	time to reach maximum plasma level
AUC	area under the plasma level-time curve
MRT	mean residence time at steady state
$t_{½}$	terminal half-life in plasma
CL, CL_R	total and renal clearances
V_z, V_{ss}	apparent volumes of distribution during terminal phase and at steady state
R	accumulation factor
%Ae(0-8d)	renally excreted dose portion within 8 days as percent of the total dose
f	systemic 2F-ara-A availability (geom. mean with confidence interval and arithm. mean ± SD) based on plasma level (f_1) and renal excretion data (f_2)

2.3. Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Data on the effect of renal impairment and pediatric data appear in the package insert for the iv product. No data on the effects of intrinsic factors on the pharmacokinetics of the oral product are reported.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

CLL is a disease most commonly seen in elderly patients. The absorption, distribution, metabolism and excretion data presented and discussed previously applies to elderly patients since demographic data for patients participating in bioavailability studies shows that approximately 90% of the population studied was older than 50 years and approximately 40% was older than 65 years.

No dosage regimen adjustments are recommended.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

No studies of oral fludarabine have been conducted. The package insert for the iv product includes information on clinical dosing to pediatric patients and is reproduced, below (indent, font change). There are no pharmacokinetic data from pediatric patients.

b(4)

b(4)

2.3.2.2 Gender

No dosage regimen adjustments are recommended.

2.3.2.4 Race

No dosage regimen adjustments are recommended.

2.3.2.5 Renal impairment

The following (indent, font change) is reproduced from the package insert of the iv product. Identical language appears in the proposed package insert for the oral product.

b(4)

While the renal impairment studies were conducted with iv fludarabine phosphate, based on the equivalence in exposure between the 25 mg/m^2 therapeutic iv dose and the suggested 40 mg/m^2 oral dose similar dose reductions are recommended for oral fludarabine phosphate treatment in renally impaired patients.

The language recommending
is a recent change to the iv package insert and is under review by the Agency. The recommendation is

b(4)

Based on the pharmacokinetics data and discussion with the reviewing medical officer, our recommendation is that patients with severe renal impairment not be excluded from treatment, but have their dose reduced by 50%.

b(4)

2.3.2.6 Hepatic impairment

No dosage regimen adjustments are recommended.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

No pharmacogenetics information appears in the application.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no pregnancy and lactation use information in the application. The following (indent, font change) is reproduced from the proposed package insert for the oral product. It is a near duplication of the package insert for the iv product

b(4)

2.3.2.9 Are there other human factors that are important to understanding the drug's efficacy and safety?

No other intrinsic factors known to be important to efficacy and safety have been identified.

2.4. Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

With the exception of food and drugs, no studies were conducted to assess correlations between extrinsic factors and the pharmacokinetics of fludarabine.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

With the exception of food and drugs, which appear in other sections of this review, no dosage regimen changes are recommended.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

No. Section 2.2.5.6. discusses the inability of CYP P450 enzymes to metabolize fludarabine and Section 2.4.2.3 discusses the inability of fludarabine to inhibit CYP P450 enzymes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No biotransformation of 2F-ara-A was detected *in vitro* after incubation with human liver microsomes or genetically engineered V79 cells expressing human liver CYP1A2 or 3A4. There are no data indicating that metabolism is influenced by genetics.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

An *in vitro* study of the ability of fludarabine and 2F-ara-A to inhibit CYPs 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 was conducted. Neither fludarabine not 2F-ara-A resulted in more than 27% inhibition at the highest concentrations tested (100 uM). Steady-state Cmax for 2F-ara-A following the clinical dose (40 mg/m^2/day) is approximately 1 uM. Fludarabine appears to not be an inhibitor of CYP enzymes at relevant concentrations.

The ability of fludarabine to induce CYP enzymes was not investigated.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The ability of fludarabine to act as substrate or inhibitor of P-glycoprotein transport or other metabolic/transporter pathways was not investigated.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Oral fludarabine was administered as monotherapy.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Because of the toxicities associated with the regimen, anti-emetics are likely to be co administered.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

In vitro drug metabolism and CYP profiling and CYP inhibition studies have not indicated a potential for pharmacokinetic drug-drug interactions.

The following (indent, font change) is reproduced from the BOXED WARNING that appears at the beginning of the package insert for the iv product.

> In a clinical investigation using FLUDARA FOR INJECTION in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of FLUDARA FOR INJECTION in combination with pentostatin is not recommended.

The below (indent, font change) is reproduced from the proposed BOXED WARNING for the oral product.

[ ] b(4)

A drug interaction was observed in B-CLL and acute myelogenous leukemia (AML) patients during combination therapy with fludarabine and ara-C. Clinical studies and *in vitro* experiments with cancer cell lines demonstrated elevated intracellular ara-CTP (5'-triphosphate of ara-C) levels in leukemic cells in terms of intracellular peak concentrations, as well as intracellular exposure (AUC) with fludarabine and ara-C combination treatment, and ara-C treatment subsequent to fludarabine therapy. Plasma concentration of ara-C and the elimination rate of ara-CTP were not affected.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No nonclinical pharmacodynamic studies have been performed to specifically evaluate possible interactions of fludarabine with other drugs that may be co-administered.

Based on the data available the potential for pharmacodynamic drug interactions appears small.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

The ability of fludarabine and 2F-ara-A to act as an inducer of CYP enzymes, a substrate of p-glycoprotein or an inhibitor of p-glycoprotein has not been investigated.

2.4.2 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The clinical activity of oral fludarbaine doses lower than 40 mg/m^2 is largely unknown. Thus, it is possible that a lower dose could provide less toxicity while retaining efficacy. This could be considered an insignificant omission, as the drug development program was based on oral fludarabine substituting for the iv product which is currently marketed.

2.5. General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

There is no data on dissoltuoion or permeability in the section 5 of the NDA. The Office of New Drug Quality Assessment (ONDQA) reviewer indicates that the Applicant classifies fludarabine as a BCS Class 1 substance: high solubility – high permeability.

A single dose strength of 10 mg has been studied and is planned for marketing.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The to-be-marketed formulation was used in the pivotal clinical trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

In the oral dosing portion of Study ME96079 patients were given single oral doses of 90 mg fludarabine phosphate as 9 immediate release tablets after a high- fat meal (fed) or overnight fast in a cross-over design. Each meal contained 960 kilocalories with 513 kcal contributed from fat. Blood samples were collected for 48 h post-dose. The results are shown, below, as **FDA Table 5.** and **FDA Table 6.** It is important to note that the 95% confidence interval, rather than the 90% confidence interval commonly used for regulatory decision making, is reported in **FDA Table 6.** The 90% confidence interval would be narrower than the reported 95% confidence interval. No confidence interval was reported for Cmax.

FDA Table 5. Applicant's Table TT 6 from page 32 of Clinical Study Report AZ85

TT 6: **Mean pharmacokinetic parameters of 2F-ara-A after a single oral dose of 90 mg fludarabine phosphate (SH T 586 C) in patients with B-CLL and Lg-NHL with or without concomitant food intake**

Treatment	AUC(0-24h) [µg·h/mL]	AUC(0-48h) [µg·h/mL]	Cmax [ng/mL]	tmax [h]	t1/2λz [h]
Fasted					
mean ± s.d.	3.05 ± 1.56 (n=16)	3.91 ± 1.77 (n=15)	488 ± 279 (n=16)	1.3 ± 0.74 (n=16)	26.5 ± 10.3 (n=14)
Non-fasted					
mean ± s.d.	3.28 ± 1.48 (n=16)	4.23 ± 1.76 (n=15)	442 ± 181 (n=16)	2.2 ± 1.0 (n=16)	26.9 ± 12.7 (n=14)

AUC(0-24h) area under the plasma level-time curve from time of dosing to 24 h post administration.
AUC(0-48h) area under the plasma level-time curve from time of dosing to 48 h post administration.
Cmax maximum plasma level
tmax time-point of maximum plasma level
t1/2λz terminal half-life

FDA Table 6. Except of Applicant's Table TT 7 from page 32 of Clinical Study Report AZ85

Estimations of bioavailability
Study 96079

Standard: Fasting regimen
Test: Breakfast regimen

Pharmacokinetic Parameter	Treatments	Bioavailability	Lower confidence limit	Upper confidence limit
AUC 0-24h [ng*h/ml]	Test vs Standard	110.653	94.9528	128.948
AUC 0-48h [ng*h/ml]	Test vs Standard	111.397	94.5195	131.287

The confidence level equals 95%
The bioavailability and the confidence limits are presented on the original scale in percentage terms

2.5.4 When would a fed BE study be appropriate and was one conducted?

Such a study would not be appropriate and was not conducted.

2.5.5 How do the dissolution conditions and specifications ensure *in vivo* performance and quality of the product?

Dissolution specifications for this immediately released product will be determined by the Office of New Drug Quality Assessment.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

A single strength is being marketed.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

The NDA is not for a modified release formulation of an approved immediate release product.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or in vivo data to evaluate BE?

Unapproved products or altered approved products were not used as active controls

2.5.9 What other significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE need to be addressed?

There are no other significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE.

2.5 Analytical section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In all studies of the oral product, only 2F-ara-A was measured.

2.6.2 Which metabolites have been selected for analysis and why?

For the oral product, only the active metabolite 2F-ara-A was measured.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total 2F-ara-A was measured. Protein binding in human plasma was approximately 25%. Measurement of total drug appears appropriate.

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?
2.6.4.3 What are the accuracy, precision, and selectivity at these limits?
2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
2.6.4.5 What is the QC sample plan?

Five *in vivo* studies submitted in the NDA contributed to this review. In all five studies 2F-ara-A concentrations were measured using an HPLC method with fluorescence detection after derivatization with chloracetaldehyde. The quality control data from each study is reproduced, below, in **FDA Table 7.**

FDA Table 7. Analytical Methods QC Data

	accuracy			intra-assay variability			inter-assay variability		
	10 ng/mL	50 ng/mL	200 ng/mL	10 ng/mL	50 ng/mL	200 ng/mL	10 ng/mL	50 ng/mL	200 ng/mL
Study ME95101, Report AN61	102.4%	100.9%	100.5%	9.1%	6.6%	4.6%	18.2%	9.5%	6.2%
Study ME94204 Report AT41/AN60	99.5%	104.3%	94.3%	22.8%	10.8%	11.0%	8.7%	5.7%	6.4%
Study ME96079, Report AZ85	102.7%	102.7%	101.0%	7.1%	7.3%	5.5%	14.1%	6.4%	8.5%
Study 94615 Report AU92	QC data not reported								
Study 94615 Report AW74	QC data not reported								

Study 94615 was a small study conducted in Japan that included quantitation of 2F-ara-Hx in urine. Method validation for the bioanalytical method study was provided, but the in-assay quality control samples were not available. The data from Study 94615 does not impact the package insert language.

The Reviewer finds the data of sufficient quality to allow for interpretation of the studies performed and thus construction of the package insert.

3 Detailed Labeling Recommendations

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4 *Appendices*

4.1 ***Proposed Package Insert (Original)***

4.2 _____ b(4)

4.3 ***Minutes from pre-NDA meeting of July 30, 2007***

4.4 ***Cover Sheet and OCPB Filing/Review Form***

4.1 Proposed Package Insert (Original)

Appears This Way
On Original

29 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-273	Brand Name	oral fludarabine phosphate
OCPB Division (I, II, III, IV, V)	V	Generic Name	fludarabine phosphate
Medical Division	Drug Oncology	Drug Class	purine nucleotide anti-metabolite
OCPB Reviewer	Gene M. Williams, Ph.D.	Indication(s)	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
OCPB Team Leader	NAM Atiqur Rahman, Ph.D.	Dosage Form	10 mg tablet
		Dosing Regimen	40 mg/m^2 daily for the 1st 5-days of a 28-day cycle
Date of Submission	November 15, 2007	Route of Administration	oral
Estimated Due Date of OCPB Review		Sponsor	Xanthus Pharmaceuticals, Inc.
PDUFA Due Date	December 19, 2008	Priority Classification	1S
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	x	3	3	
Blood/plasma ratio:				
Plasma protein binding:	x	2	2 (reviewed under NDA for IV)	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	3	1	
multiple dose:	X	3	2	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	x	1	1 (reviewed under NDA for IV)	
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x	3	2	
Relative bioavailability -				
solution as reference:	x	2	0	
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1	1	
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		12	10	

Filability and QBR comments		
	"X" If yes	Comments
Application filable?	x	
Comments sent to firm?	x	Inquiry regarding need for BE studies; firm indicated that to-be-marketed formulation was studied.
QBR questions (key issues to be considered)	Does oral approximate PK of already approved IV?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gene Williams
12/4/2008 02:22:45 PM
BIOPHARMACEUTICS

Atiqur Rahman
12/4/2008 03:37:23 PM
BIOPHARMACEUTICS

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