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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-673

Medical Review(s)

Division Director's Memorandum

Date: February 1, 2005
NDA: 21-673
Sponsor: Genzyme Corporation (previously Ilex Products, Inc.)
Proprietary Name: CLOLAR™ (clofarabine) for Intravenous Infusion
Approval Date: December 28, 2004

Regulatory History

November 7, 2001: IND 63,641 submitted to this Division.

February 7, 2002: Orphan Drug designation granted for treatment of acute lymphoblastic leukemia (ALL).

March 14, 2002: Orphan Drug designation granted for treatment of acute myelogenous leukemia (AML).

March 7, 2003: FDA issued Written Request to obtain needed pediatric information on clofarabine.

July 8, 2003: Division grants Fast Track designation and accepts Ilex's plan for rolling submission for the treatment of pediatric primary refractory or relapsed ALL.

September 26, 2003: Ilex submits the first part (non-clinical) of the NDA.

October 14, 2003: FDA issued a revised Written Request.

March 30, 2004: Division received the last part of the NDA from Ilex.

July 14, 2004: Pediatric Exclusivity Board determined Ilex "fairly met" all terms in the Written Request and granted Pediatric Exclusivity.

August 6, 2004: Additional clinical data received; PDUFA clock extended 3 months beyond September 30, 2004.

December 1, 2004: Application discussed at Oncologic Drugs Advisory Committee (ODAC).

December 31, 2004: PDUFA goal date for this NDA with a priority review, extended clock.

Indication

Clofarabine is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

Clinical and Biostatistical Review (see reviews by Drs. Cohen, Johnson and Sridhara)

Clinical Trials: The NDA is supported by data from three clinical trials: two phase 2 (CLO-212 and CLO-222) and one phase 1 (ID99-383). See Table 1.

ID99-383 was a phase 1 open-label, non-randomized, dose escalation study for pediatric patients with hematological malignancies (ALL and AML) who have failed standard therapy

or for whom no such therapy existed. Patients received doses of clofarabine as 1-3 hr intravenous (IV) infusion daily × 5 days, every 2 to 6 weeks for a maximum of 12 cycles. The doses evaluated were 11.25, 15, 30, 40, 52 and 70 mg/m²/day. The objective of this study was to establish the maximum tolerated dose and obtain pharmacokinetic data in this population.

CLO-212 was a phase 2 open-label, non-randomized study in pediatric patients (1-20 yrs) with refractory or relapsed ALL. CLO-222 was a phase 2 open-label, non-randomized study in pediatric patients (1-20 yrs) with refractory or relapsed AML. The objective of the phase 2 studies was to examine clofarabine efficacy in the given population as well as to obtain data on clofarabine pharmacokinetics (PK) in the pediatric population.

Table 1
Submitted clinical trials (pediatric patients only)

Data Source	ALL N	AML N	ALL/AML N
Total	67	46	113
CLO-212	49		49
CLO-222		35	35
ID99-383 (MDACC)	17	8	25

Eligibility in Phase 2 Trials. AML patients were in relapse or refractory after 1 or more prior induction regimens. ALL patients were in relapse or refractory after 2 or more prior induction regimens.

Treatment in Phase 2 Trials. The clofarabine pediatric dose and schedule was 52 mg/m² administered IV over 1 to 2 hours daily for 5 consecutive days. Treatment cycles were repeated every 2 to 6 weeks following recovery or return to baseline organ function. The dosage was based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle.

Best Response AML Trial. Table 2 shows the results for Best Response in the AML Trial. Table 3 shows the response durations in responders not transplanted in the AML trial.

Table 2
Best response AML Trial*

Response Category	N=35	%
Complete Remission (CR)	0	0.0
Complete Remission-Absence of Total Platelet Recovery (CRp)	1	2.9
Partial Remission (PR)	8	22.9
Treatment Failure	19	54.3
Not Evaluable	7	20.0

* Not all responses confirmed with a second bone marrow exam

Table 3
Response Durations in AML Patients
Not Transplanted

Response Category	N*	Response Durations (Days)	N**	Response Durations (Days)
CR	0		0	
CRp	0		0	
PR	2	12, 34	0	

* Responses not confirmed

** Responses confirmed

Clinical Benefit: AML Trial. Clofarabine clinical benefit is difficult to assess in this trial because patients often received subsequent transplant; hence, clofarabine response duration can not be assessed. In addition, some patients went to transplant before clofarabine response could be confirmed and some patients went to transplant without a clofarabine response. Thus, in transplanted patients the response durations in responding patients and the time-to relapse and survival are an effect of clofarabine + transplant and the effect of clofarabine can not be isolated. Clofarabine effect on time-to relapse and survival can not be evaluated without a randomized trial. Clofarabine clinical benefit can only be assessed in patients who were not transplanted after clofarabine treatment.

Response Assessment: ALL Trial. Table 4 shows the response assessments for the ALL Trial. Table 5 shows response durations in responding patients not transplanted.

Table 4
Objective Responses ALL Trial

Response Category	N=49	
	N	%
Complete Remission (CR)	6	12.2
Complete Remission Without Total Platelet Recovery (CRp)	4	8.2
Partial Remission (PR)	5	10.2
Treatment Failure	26	53.1
Not Evaluable	8	16.3
Overall Remission (CR + CRp)*	10	20.4
CR+CRp+PR	15	30.6

*95% Confidence Interval for Independent Panel Response Rate of Overall Remission (CR + CRp): (0.10, 0.34)

Table 5
Response Durations in ALL Patients
Not Transplanted

Response Category	N*	Response Durations (Days)	N**	Response Durations (Days)
CR	2	43, 50	3	82, 93+, 160+
CRp	1	32	0	
PR	3	7, 16, 21	0	

* Responses not confirmed

** Responses confirmed

Clinical Benefit: ALL Trial. Clofarabine clinical benefit is difficult to assess in this trial because patients often went to transplant, so that clofarabine response duration can not be

assessed. In addition some patients went to transplant before clofarabine response could be confirmed and some patients went to transplant without a clofarabine response. See above discussion for clofarabine clinical benefit in AML trial.

Safety. The most common toxicities observed during clofarabine exposure were gastrointestinal system adverse events (including vomiting, nausea, and diarrhea), hematologic adverse events (including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia), and infection events.

Clofarabine can produce systemic inflammatory response syndrome/capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. Two patients died due to capillary leak syndrome and a third patient had grade 3 capillary leak syndrome.

The adverse effects are severe, but similar to other chemotherapy regimens in this very sick population.

ODAC Recommendations. The ODAC considered this NDA at its December 1, 2004 meeting. The Committee recommended accelerated approval under Subpart H for ALL (9 yes and 6 no) and against accelerated approval for AML (1 yes and 14 no).

Phase 4 commitments: Required for conversion to full approval

1. **Completion of study CLO-216:** This is a phase 1/2 Dose-Escalation Study of Clofarabine Plus Cytarabine and L-Asparaginase in Pediatric Patients with Refractory or Relapsed ALL, showing that an acceptable and potentially useful regimen has been developed for study in a phase 3 study. We expect the phase 1 part of this study to be completed by March 1, 2006, and the phase 2 part of the study, assuming a tolerated regimen is found in phase 1, by October 1, 2006. If either the phase 1 or 2 components fail to identify a useful and tolerated regimen, the applicant agreed to promptly develop an alternative plan to verify and describe clinical benefit.

	Phase 1	Phase 2
Protocol Submission:	Done	Done
Study Start:	June 1, 2005	June 1, 2006
Trial Completion:	March 1, 2006	October 1, 2006
Final Report Submission:	June 1, 2006 (interim report)	April 13, 2007

2. **Completion of a controlled clinical study to verify and describe the clinical benefit of clofarabine in pediatric ALL.** The proposed phase 3 study to be possibly conducted by the Children's Oncology Group (COG) does not appear to have a realistic chance of showing a clinical benefit of clofarabine in children with ALL in first relapse. The Division asked the applicant to submit, within 2 months of the NDA approval date, a new study protocol to show clofarabine clinical benefit in children with ALL. Timelines for study start, completion and submission of the study report will also be submitted. The Division recommended the applicant request a meeting to discuss this protocol within 30 days of receipt of the approval letter, so that a meeting can be scheduled to occur about one month after receipt of the protocol.

Clinical Pharmacology & Biopharmaceutic Review (see Dr. Ramchandani's review)

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) found the Clinical Pharmacology section of this NDA acceptable, with some revisions to the proposed label.

Clofarabine is a second generation purine nucleoside analog. Clofarabine pharmacokinetics were determined in 40 pediatric patients, ages 2 to 19 years (21 males/19 females), from 3 studies: a phase 1 dose escalation study and two phase 2 studies in ALL and AML patients. A population PK model was fit to the data from these studies. Clofarabine pharmacokinetics was best described by a 2-compartment model with first order elimination. Body weight was the best predictor in parameter models for all model parameters (CL, Q, V1 and V2). The applicant's model included baseline white blood cell (WBC) count as a predictor of the central compartment volume V1. The Agency's analysis determined that WBC counts were not correlated with the central volume estimates and inclusion of WBC in the parameter model did not reduce the population variance for the central volume. Based on a non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m² and 172 L/m², respectively. The terminal half-life was estimated to be 5.2 hours. No major PK differences were found between ALL and AML patients or between male and female patients. Intra-cellular concentrations of the active metabolite clofarabine triphosphate were also measured in some phase 1 study patients, however the data were too sparse for any meaningful evaluation.

Renal excretion of unchanged clofarabine, measured over a 24-hour period, accounts for 49-60% of the total clearance. *In vitro* studies using isolated hepatocytes indicate very limited hepatic metabolism, thus the pathways of non-renal elimination are unknown. The inhibition and induction potential of clofarabine for cytochrome p450 enzymes has not been studied. Clofarabine pharmacokinetics has not been evaluated in patients with renal or hepatic dysfunction.

No significant relationships were found between measures of clofarabine exposure and measures of clofarabine response or toxicity. The applicant's analysis only included those patients who had PK measurements. The Agency's re-analysis of this data included estimation of the exposure (AUC) of clofarabine in all the patients in the studies, based on the parameter model for clearance which was a function of body weight. However this did not change the outcome, and there were still no significant associations between AUC and measures of toxicity or response. This may be partly because the majority of the patients received the 52 mg/m² dose, which did not provide an adequate range of exposures to effectively evaluate the exposure-response relationship for clofarabine.

Recommendations:

1. Evaluate the pharmacokinetics of the active metabolite clofarabine triphosphate, both in future studies in adult and pediatric patients to better understand the exposure-response relationship for this drug and to help optimize dosing regimens in the future studies.
2. Examine the effect of renal impairment on the safety and pharmacokinetics of clofarabine in patients in future studies.

3. Explore the fate of the fraction of the clofarabine that is not eliminated by renal or hepatic routes as the studies have shown that clofarabine is not hepatically metabolized and that ~60% is renally excreted unchanged. The fate of the remaining 40% is not known.

Chemistry, Manufacturing and Controls (CMC) Review (see Dr. Sarker's review)

The CMC team recommended approval of this NDA.

CLOLAR™ (clofarabine) is formulated as a solution (1 mg/mL) and is supplied in a 20 mL, single-use vial. The 20 mL vial contains 20 mg of clofarabine formulated in 20 mL unbuffered normal saline. The inactive ingredients are sodium chloride, USP and water for injection, USP. The drug product is a clear, colorless liquid, free of foreign matter with a pH range of 4.5 to 7.5. The drug product is stored at 25°C (77°F); excursion permitted to 15°-30°C (59°-86°F). The drug product has to be diluted with 5% dextrose, USP or with 0.9% sodium chloride injection, USP prior to administration. Drug product infusion solutions are found to be stable up to 24 hours at room temperature. Based on primary and supportive stability data, an expiration dating period of 24 months was granted.

Clofarabine drug substance is a modified nucleoside, which is the one that is manufactured.

Clofarabine API (active pharmaceutical ingredient) is soluble in normal saline up to 1 mg/mL at room temperature.

Two different HPLC methods are utilized for analyzing the impurities in drug substance at release and stability respectively. Method A appears to be capable of analyzing the process impurities, whereas method B appears to be capable of analyzing the drug substance degradants. A third HPLC method, C has been utilized for drug product assay and degradants at release and stability. Based on primary and supportive stability data, a retest period of 6 months may be granted for the drug substance.

Nonclinical Review (see Drs. Goheer and Leighton's reviews)

The pharmacology and toxicology review team recommended approval of this NDA.

Clofarabine is a purine analogue pro-drug that needs to be converted to the 5'-triphosphate metabolite before induction of DNA damage and triggering of apoptosis. The exact mechanism of clofarabine triphosphate cytotoxicity remains to be fully explored but incorporation into DNA is probably its primary pharmacodynamic activity. Other sites of action (e.g., action at mitochondrial membranes, inhibition of ribonucleotide reductase) may also be involved in cytotoxicity. Clofarabine has demonstrated activity in dividing and quiescent cells.

Toxicology studies normally submitted to support an NDA application were provided in the submission. These include investigations of general toxicology, genetic toxicology, and developmental toxicology. Pharmacokinetic and ADME studies were also provided. These studies provide sufficient nonclinical information to support the approval of clofarabine. There are no outstanding nonclinical issues.

Data Integrity Issues

The Division of Scientific Investigation (DSI) investigated two sites (University of Texas, Houston, TX and Memorial Sloan-Kettering Cancer Center, New York, NY). DSI did not issue an FDA-483 for the Texas site.

DSI found that the investigator at the New York site did not always adhere to good clinical practices governing the conduct of clinical investigations. However, there was documentation to assure that all audited subjects existed, most study subjects met the eligibility criteria, and were available for the duration of the study, and that all enrolled subjects received the assigned study drug and had clinical and laboratory parameters recorded, completed the study, and most study subjects had their primary efficacy endpoints captured, though not always as specified in the protocols and amendments and correctly reported to the sponsor.

DSI recommended that the Division (1) exclude study subjects who did not meet inclusion criteria from the final data analysis, and (2) use an independent party to evaluate the tumor response data, the primary endpoint.

Tradename and Labeling Consultation (see DDMAC and DMETS reviews)

The Division of Drug Marketing, Advertising and Communications (DDMAC) reviewers, Joseph Grillo & Iris Masucci reviewed the draft labeling submitted in the NDA and provided their comments in a review signed July 27, 2004.

In a review signed August 24, 2004, the Division of Medication Errors and Technical Support (DMETS) had no objections to the use of the proprietary name, "Clolar". However, DMETS noted the name must be re-evaluated if the approval of the NDA is delayed beyond 90 days from August 24th. This re-evaluation will rule out any objections based upon approval of other proprietary or established names after August 24th. In this review, DMETS recommended labeling revisions to minimize potential errors with the use of this product. DMETS also noted that DDMAC found the proprietary name, "Clolar" acceptable from a promotional perspective.

On November 18, 2004, the Division requested a re-evaluation of the proprietary name "Clolar". In a review signed December 6, 2004, DMETS still had no objections to the name; however, referred to their labeling revision recommendations in the previous review.

Pediatric Considerations

As the indication the applicant is seeking is specifically for the pediatric population, the Division considers the pediatric studies completed for this NDA.

Conclusions and Recommendations: Accelerated Approval

The accelerated approval regulations (21 CFR Part 314.500) altered the evidentiary standard for approval endpoints for drugs that are intended to treat serious or life-threatening diseases. These drugs must either demonstrate an improvement over available therapy or provide therapy where none exists. In this setting, the FDA may grant approval based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.

In the 2 single-arm pediatric clinical trials in AML and ALL, the clofarabine effect on time-to-relapse and survival can not be assessed because many patients also had transplantation; and it is not possible to separate clofarabine effect from transplantation effect. In addition, clofarabine effect on time-to-relapse and survival can not be assessed without a randomized trial unless the effect is very large and it was not.

Thus we can only assess the clofarabine effect on response. Clofarabine effect on response duration can only be assessed in non-transplanted patients.

In the relapsed/refractory populations in these 2 clinical trials, a good complete response rate with good response durations has been accepted as evidence of clinical benefit resulting in regular approval. Generally partial responses are not accepted as evidence of clinical benefit, although very long duration partial responses could be considered.

In the pediatric AML single arm phase 2 trial there was only 1 CRp. The patient was transplanted, so Clofarabine effect on response duration can not be assessed. There were 2 PRs lasting 12 and 34 days. There was also 1 CRp in the Phase 1 trial. This is insufficient evidence to conclude there is clofarabine clinical benefit, or that these results are reasonably likely to predict clofarabine clinical benefit, in the AML population.

In the pediatric ALL single-arm phase 2 trial there were 6 CRs. Five of these CRs were not transplanted. Response durations in the 2 CRs not confirmed with a second bone marrow were 13 and 50 days. Response durations in the 3 CRs confirmed with a second bone marrow were 82, 93+ and 160+ days. There were 3 PRs in non-transplanted patients, all not confirmed with a second bone marrow, lasting 7, 16 and 21 days. The CRs are not of sufficient duration to be considered clinical benefit, however, the CR rate is reasonably likely to predict clinical benefit.

In order to convert this application to regular approval, the applicant committed to the following phase 4 commitments as outlined in the clinical and Biostatistical section above.

1. **Completion of study CLO-216.**
2. **Completion of a controlled clinical study to verify and describe the clinical benefit of clofarabine in pediatric ALL.**

/s/

Richard Pazdur, MD
Director, Division of Oncology Drug Products

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this page is the manifestation of the electronic signature.**

/s/

Dianne Spillman
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CSO

Richard Pazdur
2/2/05 08:02:35 AM
MEDICAL OFFICER

Clinical Team Leader Review of New NDA

NDA 21673
APPLICANT Ilex Products, Inc.
DRUG CLOLAR™ (Clofarabine)

DATE RECEIVED March 30, 2004

DATE RECEIVED ADDITIONAL CLINICAL DATA August 6, 2004

PROPOSED INDICATION Clofarabine is indicated for the treatment of pediatric patients 1 to 21 years old with refractory or relapsed acute leukemias.

CLINICAL TRIALS

The NDA is supported by data from three clinical trials, two Phase 2 and one Phase 1 (see Table 1). All Tables in this review are copied from the Medical Officer Review except Tables 5, 11 and 14.

Table 1
Submitted clinical trials (pediatric patients only)

Data Source	ALL n	AML n	ALL/AML n
Total	67	46	113
CLO-212	49		49
CLO-222		35	35
ID99-383 (MDACC)	17	8	25

Eligibility in Phase 2 Trials. AML patients were in relapse or refractory after 1 or more prior induction regimens. ALL patients were in relapse or refractory after 2 or more prior induction regimens.

Treatment in Phase 2 Trials. The clofarabine pediatric dose and schedule is 52 mg/m² administered IV over 1 to 2 hours daily for 5 consecutive days. Treatment cycles are repeated every 2 to 6 weeks following recovery or return to baseline organ function. The dosage is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle.

Patient Characteristics AML Trial (CLO-222). Patient characteristics for the AML phase 2 trial are shown in Table 2.

Table 2
Patient Characteristics AML Trial

Variable	N=35 (%)
Age Category	
0 to 2	2 (5.7)
>2 to < 12	16 (45.7)
>12 to < 16	7 (20.0)
>16 to 22	10 (28.6)
Sex	
Female	13 (37.1)
Male	22 (62.9)
Ethnicity	
Hispanic	7 (20.0)
Caucasian	19 (54.3)
Black	3 (8.6)
Asian	3 (8.6)
Other	3 (8.6)
Karnofsky Performance Status	
100	14 (40.0)
90	9 (25.7)
80	8 (22.9)
70	3 (8.6)
60	1 (2.9)

Prior Induction Regimens AML Trial. Table 3 shows the number of prior induction regimens. At least one prior induction regimen was required.

Table 3
Prior Induction Regimens AML Trial

Number of Prior Induction Regimens	ITT Patients (N=35)	
	n	%
1	5	14.3
2	12	34.3
3	8	22.9
4	4	11.4
5	6	17.1

Best Response AML Trial. Table 4 shows the results for Best Response in the AML Trial. Table 5 shows the response durations in responders not transplanted in the AML trial.

Table 4
Best response AML Trial*

Response Category	N=35	%
Complete Remission (CR)	0	0.0
Complete Remission-Absence of Total Platelet Recovery (CRp)	1	2.9
Partial Remission (PR)	8	22.9
Treatment Failure	19	54.3
Not Evaluable	7	20.0

* Not all responses confirmed with a second bone marrow exam

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On Original

Table 5
Response Durations in AML Patients
Not Transplanted

Response Category	N*	Response Durations (Days)	N**	Response Durations (Days)
CR	0		0	
CRp	0		0	
PR	2	12, 34	0	

* Responses not confirmed

** Responses confirmed

Survival by Response Category in AML Trial. Table 6 shows the survival results by response category in the AML Trial.

Table 6
Survival (weeks) By Response Category AML Trial

Response Category	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored
CRp	1	.	.	.	93.6	93.6	100.0
PR	8	30.3	24.3	.	7.7	67.9	50.0
Treatment Failure/Not Evaluable	26	12.4	5.4	22.1	1.6	84.9	15.4
Overall Remission(CR+CRp)	1	.	.	.	93.6	93.6	100.0
Remission(CR+CRp+PR)	9	24.3	24.3	.	7.7	93.6	55.6
All Patients	35	21.0	7.7	30.3	1.6	93.6	25.7

Responder Summary AML Trial. Table 7 shows the data for each individual responder.

Table 7
FDA Responder Summary AML Trial

Patient	014-0003	006-0013	009-0018	014-0002	014-0019	014-0027	015-0017	006-0036	014-0031
Time to first relapse (mo)	3	2	4*	26	10*	1	8	14	1
Time to 2nd relapse (mo)	12	1	-	27	-	3*	2*	16	1*
Time to 3rd or later relapse (mo)	3, 9*	2, 1*	-	7,2,9*	-	-	-	1,1*	-
Stem cell transplant (Y or N)	Y	N	N	Y	Y	N	N	Y (2)	N
Stem cell transplant response duration (mo)	5	-	-	6	6	-	-	12,16	-
Clofarabine response	CRp	PR							
Clofarabine response confirmed Y or N	Y	N	N	N	N	N	N	N	Y
Clofar response duration (d)**	519+	12	34	141	44+	14	410+	82+	53+
Clofarabine TTP or death (d)**	547+	54	67	161	78+	49	465+	130+	93+
Post-clofarabine SCT (Y or N)	Y	N	N	Y	Y	N	Y	Y	Y
Current status (Alive or Dead)	A	D	D	D	D	A	A	A	A
Post-clofarabine OS (w)	93.6+	7.7	24.3	30.3	39.0	29.0+	67.9+	16.4+	24.9+

* response duration for treatment immediately preceding clofarabine treatment

** censored at the time of last bone marrow evaluation

Clofarabine Clinical Benefit AML Trial. Clofarabine clinical benefit is difficult to assess in this trial because patients often went to transplant, so that clofarabine response duration can not be assessed. In addition some patients went to transplant before clofarabine response could be confirmed and some patients went to transplant without a clofarabine response. Thus in transplanted patients the response durations in responding patients and the time-to relapse and survival are an effect of clofarabine + Transplant and the effect of clofarabine can not be isolated. Clofarabine effect on time-to relapse and survival can not be evaluated without a randomized trial unless the effect is very large. Clofarabine clinical benefit can only be assessed in patients who were not transplanted after clofarabine treatment.

Patient Characteristics in ALL Trial (CLO-212). Patient characteristics in the ALL trial are shown in Table 8.

Table 8
Demographics and Performance Status ALL Trial

Variable		ITT Patients (N=49)
Age (years):	Mean	12.18
	Median	12
	Minimum	1
	Maximum	20
Age Category	0 to <=2	3 (6.1%)
	>2 to <=12	22 (44.9%)
	>12to<=16	11 (22.4%)
	>16 to <=22	13 (26.5%)
Sex:	Female	20 (40.8%)
	Male	29 (59.2%)
Ethnicity:	Caucasian	20 (40.8%)
	Hispanic	20 (40.8%)
	Other	3 (6.1%)
	Black	6 (12.2%)
Karnofsky Grade	n	%
100	15	30.6
90	12	24.5
80	7	14.3
70	8	16.3
60	4	8.2
50	2	4.1
Not assessed	1	2.0

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Prior Induction Regimens ALL Trial. The number of prior induction regimens is shown in Table 9.

Table 9
Prior Induction Regimens ALL Trial

Number of Prior Regimens	ITT Patients (N=49)	
	n	%
2	17	34.7
3	17	34.7
4	12	24.5
5	1	2.0

Response Assessment ALL Trial. Table 10 shows the response assessments for the ALL Trial. Table 11 shows response durations in responding patients not transplanted.

Table 10
Objective Responses ALL Trial

Response Category	N=49	
	n	%
Complete Remission (CR)	6	12.2
Complete Remission Without Total Platelet Recovery (CRp)	4	8.2
Partial Remission (PR)	5	10.2
Treatment Failure	26	53.1
Not Evaluable	8	16.3
Overall Remission (CR + CRp)*	10	20.4
CR+CRp+PR	15	30.6

*95% Confidence Interval for Independent Panel Response Rate of Overall Remission (CR + CRp): (0.10, 0.34)

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Table 11
Response Durations in ALL Patients
Not Transplanted

Response Category	N*	Response Durations (Days)	N**	Response Durations (Days)
CR	2	43, 50	3	82, 93+, 160+
CRp	1	32	0	
PR	3	7, 16, 21	0	

* Responses not confirmed

** Responses confirmed

Appears This Way
 On Original

Table 12 shows the FDA Responder Summary for the ALL trial.

Table 12
FDA Responder Summary ALL Trial

Patient	007-0018	014-0030	006-0047	018-0036	009-0045	014-0049	009-0024	009-0028	012-0014	014-0040
Time to 1st relapse (mo)	22	86	1	30	53	53	2	25	31	3
Time to 2nd relapse (mo)	2	35	3	10	48*	31	4*	25*	1	3
Time to 3 rd or later relapse (mo)	1*	18*	1, 1*	2, 31*	-	68*	-	-	1, 1, 2, 1*	1*
Stem cell transplant (Yes or No)	N	Y (2)	N	Y (2)	N	N	Y	Y	N	N
Stem cell transplant resp dur (mo)	-	27, 10	-	6, 29	-	-	2	20	-	-
Clofarabine response	CR	CR	CR	CR	CR	CR	CRp	CRp	CRp	CRp
Clofar response confirmed (Y or N)	N	Y	N	Y	Y	Y	Y	Y	Y	N
Clofar response duration (days)**	43	160+	50	82	57+	93+	237	77	142+	32
Clofarabine TTP or death (days)**	143	216+	76	108	82+	110+	259	96	168+	64
Post-clofarabine SCT (Y or N)	N	N	N	N	Y	N	Y	Y	Y	N
Current status (Alive or Dead)	D	A	A	A	A	A	A	A	D	D
Post-clofarabine OS (w)	58.6	32.7+	10.4+	28.3+	17.6+	16.3+	63.1+	44.0+	42.0	9.1

* response duration for treatment immediately preceding clofarabine treatment

** censored at the time of the last bone marrow evaluation

Clofarabine Clinical Benefit in ALL Trial. Clofarabine clinical benefit is difficult to assess in this trial because patients often went to transplant, so that clofarabine response duration can not be assessed. In addition some patients went to transplant before clofarabine response could be confirmed and some patients went to transplant without a clofarabine response. Thus in transplanted patients the response durations in responding patients and the time-to relapse and survival are an effect of clofarabine + Transplant and the effect of clofarabine can not be isolated. Clofarabine effect on time-to relapse and survival can not be evaluated without a randomized trial unless the effect is very large. Clofarabine clinical benefit can only be assessed in patients who were not transplanted after clofarabine treatment.

Phase 1 Study in Pediatric Patients with Refractory Hematologic Malignancies.

A Phase 1 study was conducted at MDA. Of 17 patients with ALL there were 2 CRs and 3 PRs. Of the 8 patients with AML there were 1 CRp and 2 PRs.

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Exposure to Clofarabine in Phase 2 Pediatric ALL and AML Studies.

Table 13

Median Total Exposure to Clofarabine by Cycle

Cycle	ALL		AML		ALL/AML	
	N	Median Total mg Clofarabine	N	Median Total mg Clofarabine	N	Median Total mg Clofarabine
1	67	350.0	46	309.0	113	340.0
2	43	275.5	25	328.0	68	282.5
3	15	250.0	9	275.0	24	255.0
4	3	185.0	4	180.0	7	185.0
5	2	222.5	2	195.0	4	222.5
6	1	185.0	1	380.0	2	282.5
7	1	185.0	1	300.0	2	242.5
8	1	180.0	1	225.0	2	202.5

Deaths on Clofarabine. During the clofarabine pediatric development program, 26 patients (16 ALL, 10 AML) died on-study or within 30 days of the last dose of clofarabine. None of these patients died during or immediately after the infusion of clofarabine.

Twelve patients died from progressive disease, 5 of whom also experienced at least one AE that contributed to death (i.e., at least one grade 5 AE): 383-001-004 (multi-organ failure), 212-014-0013 (hepatic disorder NOS and renal impairment NOS), 222-011-0028 (septic shock), 212-014-0050 (sepsis NOS), and 222-010-0037 (progressive AML).

Sepsis or septic shock contributed to the death of 7 patients, and renal impairment (reported as renal impairment NOS, renal failure NOS, or increased creatinine) was present in 3 patients who died (Patient 383-001-0016, Patient 212-014-0013 and Patient 212-006-0004). Multi-organ failure contributed to the death of 6 patients. Pulmonary hemorrhage, liver impairment (reported as hepatic disorder NOS or hepatocellular damage), or cardiac arrest each contributed to the death of 2 patients. Other causes of death in individual patients included acute vascular leak syndrome, hypotension, pulmonary edema, respiratory distress, and worsening pneumonia.

Four of the deaths were considered by the investigator to be related to treatment with clofarabine; 212-004-0031 died from drug-related acute vascular leak syndrome that contributed to cardiac arrest, 212-005-0037 died from drug-related respiratory failure and liver damage, 222-014-0029 died from drug-related septic shock and multi-organ failure, and 212-014-0040 died from drug related multi-organ failure.

Clofarabine Adverse Effects. Applicant Table 14 shows the drug related adverse events occurring in $\geq 5\%$ of pediatric patients by NCI CTC grade.

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Table 14
Drug-Related Adverse Events in $\geq 5\%$ of Pediatric Patients
Overall by NCI CTC Grade
ALL/AML (N=113)

Preferred Term ¹	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	%	n	%	n	%	n	%	n	%	n	%
Total Patients with Study Drug Related Adverse Events	111	98.2	2	1.8	32	28.3	59	52.2	15	13.3	3	2.7
Vomiting NOS	74	65.5	17	15.0	49	43.4	7	6.2	1	0.9	.	.
Nausea	71	62.8	12	10.6	49	43.4	10	8.8
Febrile Neutropenia	34	30.1	.	.	1	0.9	32	28.3	1	0.9	.	.
Headache NOS	28	24.8	12	10.6	13	11.5	3	2.7
Pyrexia	26	23.0	4	3.5	13	11.5	9	8.0
Pruritus NOS	25	22.1	9	8.0	16	14.2
Dermatitis NOS	24	21.2	6	5.3	12	10.6	6	5.3
Diarrhoea NOS	24	21.2	9	8.0	6	5.3	9	8.0
Mucosal Inflammation NOS	18	15.9	10	8.8	6	5.3	2	1.8
Fatigue	16	14.2	9	8.0	6	5.3	1	0.9
Anxiety NEC	14	12.4	5	4.4	9	8.0
Flushing	13	11.5	13	11.5
Anorexia	12	10.6	6	5.3	2	1.8	2	1.8	2	1.8	.	.
Palmar-Plantar Erythrodysesthesia Syndrome	12	10.6	3	2.7	5	4.4	4	3.5
Neutropenia	10	8.8	3	2.7	7	6.2	.	.
Rigors	10	8.8	6	5.3	4	3.5
Myalgia	8	7.1	3	2.7	5	4.4
Pain In Limb	8	7.1	3	2.7	4	3.5	1	0.9
Petechiae	8	7.1	4	3.5	2	1.8	2	1.8
Epistaxis	7	6.2	3	2.7	1	0.9	3	2.7
Tachycardia NOS	7	6.2	3	2.7	3	2.7	1	0.9
Abdominal Pain NOS	6	5.3	2	1.8	4	3.5
Appetite Decreased NOS	6	5.3	3	2.7	3	2.7
Irritability	6	5.3	5	4.4	1	0.9
Jaundice NOS	6	5.3	4	3.5	1	0.9	1	0.9
Rash Pruritic	6	5.3	2	1.8	4	3.5

¹ Patients with more than one occurrence of the same preferred term are counted only once.

Program:

Data Source: Table 3.5.17

The most common toxicities observed during exposure to clofarabine were gastrointestinal system AEs (including vomiting, nausea, and diarrhoea), hematologic adverse events (including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia), and infection events.

Capillary Leak Syndrome/SIRS. Clofarabine can produce systemic inflammatory response syndrome/ capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. Two patients died due to capillary leak syndrome and a third patient had grade 3 capillary leak syndrome.

ONCOLOGY DRUGS ADVISORY COMMITTEE RECOMMENDATIONS

The ODAC considered this NDA at its December 1, 2004 meeting. The questions for the Committee and the Committee's answers follow.

Questions to the Committee:

In the clofarabine single arm relapsed/refractory acute leukemia studies patients often went to early transplant without determining the clofarabine response duration, sometimes without confirming the clofarabine response with a second bone marrow exam and sometimes without a clofarabine response at all. Early transplant was particularly common in AML and interferes with assessment of response duration. Interpretation of time to relapse and survival in patients with clofarabine plus transplant is confounded because the contribution of clofarabine can not be determined. In addition interpretation of time to event endpoints requires a randomized trial unless the effects are very large.

1. Although the protocol required responses to be confirmed at least 3 weeks later, this was often not done. Do you consider an unconfirmed response useful for considering drug effect?

Yes: 12

No: 3

Discussion: Patients on study had baseline marrows and a response marrow after treatment with drug. Protocol studies required a confirmatory marrow 3-4 weeks later which did not occur in some patients. However, initial response was documented and thus initial "drug effect" on leukemia status was assessable

2. Transplantation, especially in AML patients, was common. Although it is possible that response to Clofarabine encouraged physicians to consider transplant when they otherwise would not have, there is no way to know this and there were no criteria for transplantation in the protocols. Some patients went to transplantation without a clofarabine response.

Do the transplantation data contribute to the assessment of the effectiveness of clofarabine:

In ALL?

Yes: 5

No: 10

In AML?

Yes: 2

No: 13

As noted, in refractory acute leukemias the FDA has considered a good complete response rate with complete responses of good duration to represent clinical benefit. There was clearly no substantial CR rate in AML and in ALL only 2 non-transplanted patients had a response duration of at least 3 months. The PR duration in AML is not assessable in many responders because they had early transplantation. There is somewhat more information in ALL.

3. Does the ODAC believe that the Clofarabine complete response rate with available response duration data is reasonably likely to predict a clinical benefit in ALL?

Yes: 9

No: 6

After further clarification on the implications of accelerated approval from a regulatory perspective, the majority of the committee felt that with the data presented in ALL population, the product should be approved under accelerated approval conditions.

4. Does the ODAC believe that the 2 clofarabine CRps (1 in phase 1 and 1 in phase 2) are reasonably likely to predict a clinical benefit in AML?

Yes: 1

No: 14

PHASE 4 COMMITMENTS BY APPLICANT

The Applicant has committed to conduct the following Phase 1-2 trial.

Clo-216: A Phase 1-2 dose-escalation study of clofarabine plus cytarabine and L-Asparaginase in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Patients will have had 2 or 3 prior induction regimens and will be relapsed or refractory. This is the same population as in the Phase 2 ALL trial submitted in this NDA. The trial will be conducted by the same investigators.

The trial will have the same limitations as the submitted Phase 2 single agent trial, namely most patients with a CR will go to transplant preventing an assessment of the effect of the induction

regimen on CR duration, time-to relapse or survival. The purpose of the trial is to identify an acceptable clofarabine combination regimen for testing in a Phase 3 randomized trial.

The Applicant submits the following timeline.

Trial initiation	6-1-05
Trial completion	10-1-06
Submit study report	4-13-07

The Children's Oncology Group (COG) is considering conducting a Phase 2 study in pediatric patients who have had 2 or 3 prior induction regimens and are relapsed or refractory. The regimens in the study would be:

1. Clofarabine in combination with etoposide and dexamethasone.
2. Clofarabine in combination with Cytosan and dexamethasone.

All patients would receive both regimens with alternate patients reversing the sequence.

This trial would have the same problems as the prior trials, namely most patients with a CR will go to transplant preventing an assessment of the effect of the induction regimen on CR duration, time-to relapse and survival.

The Applicant hopes the Children's Oncology Group (COG) will conduct a Phase 3 randomized trial in pediatric patients with ALL in first relapse, conditional on an acceptable clofarabine combination regimen identification in the Applicant's Phase 1-2 study. There is no commitment by COG to conduct such a clofarabine study at present and no COG commitment is expected until after completion of the clofarabine Phase 1-2 study. The design of the study the COG might conduct follows.

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1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

CONCLUSIONS

In the 2 single arm clinical trials in pediatric AML and ALL the clofarabine effect on time-to-relapse and survival can not be assessed because many patients also had transplantation and it is not possible to separate clofarabine effect from transplantation effect. In addition clofarabine effect on time-to-relapse and survival can not be assessed without a randomized trial unless the effect is very large and it is not.

Thus we can only assess the clofarabine effect on response. Clofarabine effect on response duration can only be assessed in non transplanted patients.

In the relapsed/refractory populations in these 2 clinical trials a good complete response rate with good response durations has been accepted as evidence of clinical benefit resulting in regular approval. Generally partial responses are not accepted as evidence of clinical benefit, although very long duration partial responses could be considered.

In the pediatric AML single arm Phase 2 trial there was only 1 CRp. The patient was transplanted, so Clofarabine effect on response duration can not be assessed. There were 2 PRs lasting 12 and 34 days. There was also 1 CRp in the Phase 1 trial. This is insufficient evidence to conclude there is Clofarabine clinical benefit or that these results are reasonably likely to predict Clofarabine clinical benefit.

In the pediatric ALL single arm Phase 2 trial there were 6 CRs. Five of these CRs were not transplanted. Response durations in the 2 CRs not confirmed with a second bone marrow were 13 and 50 days. Response durations in the 3 CRs confirmed with a second bone marrow were 82, 93+ and 160+ days. There were 3 PRs in non-transplanted patients, all not confirmed with a second bone marrow, lasting 7, 16 and 21 days. The CRs are not of sufficient duration to be considered clinical benefit, but the CR rate is reasonably likely to predict clinical benefit. However, the amount of evidence is small. This conclusion is based on only 6 patients with CRs and only 4 of the 6 were confirmed with a second bone marrow exam. The marginal nature of the evidence is indicated by the split ODAC vote (9-6).

The Subpart H regulations anticipate that in most instances the Applicant will have studies in progress to demonstrate clinical benefit at the time of accelerated approval. There are no such clofarabine studies in progress. In addition it is not clear that such clofarabine studies can be conducted. None of the studies proposed by the Applicant thus far has a realistic chance of demonstrating clofarabine clinical benefit in pediatric ALL.

The Applicant estimates there are approximately 500 patients each year in the United States who fit the proposed indication for this NDA. Not all of these patients would choose to use clofarabine

and those who do could be easily accommodated under an expanded access protocol or even single patient INDs.

In view of these considerations an approvable letter under Subpart H is appropriate with approval conditional on FDA review of the results of the Phase 1 part of the Phase 1-2 study to assure there is an acceptable clofarabine combination regimen for study in Phase 2 of the study and subsequently in a randomized trial to demonstrate clofarabine clinical benefit. Approval is also conditional on the Applicant's commitment to conduct a study that will demonstrate clofarabine clinical benefit. None of the studies proposed by the Applicant thus far has a realistic chance of demonstrating clofarabine clinical benefit in pediatric ALL.

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RECOMMENDATION

The NDA is approvable under Subpart H for the following indication.

" CLOLAR™ is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphocytic leukemia after at least two prior regimens. This approval is based on complete response rate. Clinical benefit has not been demonstrated".

Labeling revisions are required as a condition of an approvable letter under subpart H. See labeling revisions by the FDA review team.

Approval will be conditional on FDA review of the Phase 1 part of the Applicant's following Phase 1-2 study, showing that an acceptable clofarabine, cytarabine, PEG Asparaginase regimen has been developed for study in the Phase 2 part of the study and potentially in a Phase 3 study that has a realistic chance of demonstrating clofarabine clinical benefit in children with ALL.

Clo-216: A Phase 1-2 dose-escalation study of clofarabine plus cytarabine and L-Asparaginase in pediatric patients with refractory or relapsed acute lymphoblastic leukemia.

Trial initiation	6-1-05
Trial completion	10-1-06
Submit study report	4-13-07

Approval will also be conditional on the Applicant's submission of a protocol for a clinical study with a realistic chance of demonstrating clofarabine clinical benefit in children with ALL and the Applicant's commitment to conduct the study and submit the results in an acceptable time frame. None of the clinical studies proposed by the Applicant thus far has a realistic chance of demonstrating clofarabine clinical benefit in pediatric ALL.

JS

John R. Johnson, M.D.
Clinical Team Leader Oncology Drugs
December 20, 2004

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

/s/

John Johnson
12/22/04 11:21:43 AM
MEDICAL OFFICER

CLINICAL REVIEW

Clinical and Statistical Review

Application #	N021673
Drug Name	
Medical Reviewer	Martin H. Cohen, M.D.
Medical Team Leader	John R. Johnson, M.D.
Statistician	Rajeshwari Sridhara, Ph.D.
Documents reviewed	EDR Document: 2456412
	Location:
	<u>\\CDSESUB1\N21673\N 000\2004-03-29</u>
	<u>\\CDSESUB1\N21673\N 000\2004-08-02</u>
	<u>\\CDSESUB1\N21673\N 000\2004-08-05</u>
	<u>\\CDSESUB1\N21673\N 000\2004-10-06</u>

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Clinical Review for NDA 21-673

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Medical Reviewer Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA, while awaiting the comments of our outside consultants and the Oncologic Drugs Advisory Committee (ODAC), believes that accelerated approval should be given for both the pediatric AML and ALL indications. The reviewer believes that a favorable outcome (prolonged TTP of clofarabine \pm transplant compared to treatment regimens administered prior to the start of clofarabine treatment) has been demonstrated. This endpoint is not a traditional endpoint for acute leukemia studies, however. Clofarabine toxicity, while considerable, is what one might expect in a heavily pretreated population of pediatric acute leukemia.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Phase 3 trials, conducted in less refractory pediatric ALL and AML populations, comparing a clofarabine containing regimen \pm transplant to an appropriate control regimen \pm transplant should be submitted in timely fashion as a Special Protocol Assessment.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two Phase II pivotal studies have been conducted by ILEX in pediatric patients with refractory or relapsed ALL (CLO-212) or refractory or relapsed AML (CLO-222), in which clofarabine was used as a single agent.

In addition phase I/II pediatric and adult clofarabine studies conducted at The University of Texas MD Anderson Cancer Center (MDACC) were submitted.

B. Efficacy

In pediatric AML there was 1 CRp (2.9%) and 8 PR's among 35 treated patients. Twelve of 35 AML patients went on to transplant including the CRp patient, 6 PR's, 3 not-evaluable patients and 2 treatment failures. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In trial CLO-222 there were no CR's, only one CRp (2.9%) and 8 PR's. The CRp patient and 6 of the PR's went on to have a transplant. Long duration responses and prolonged survival were confined to patients who received a transplant. Four clofarabine plus transplant patients had longer time to progression (TTP) with that treatment then they had with the therapy that immediately preceded clofarabine. Three of these 4 patients also had longer TTP with clofarabine plus transplant then they had with their preceding transplant.

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In Pediatric ALL there were 6 CR's (12.2%), 4 CRp's (8.2%) and 5 PR's among 49 treated patients. Eight ALL patients went on to transplant including 2 CR's, 2 CRp's, 2 PR's, 1 not-evaluable patient and 1 treatment failure. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In study CLO-212 among the 6 CR patients 3 had ongoing responses at the time of data cutoff and 3 had relapsed. Using the criteria of longer TTP with clofarabine \pm transplant than to immediate prior therapy 2 of 6 CR patients, 3 of 4 CRp patients and 0 of 5 PR patients demonstrated benefit. With further follow-up benefit may be demonstrated in 3 additional CR patients and 1 PR patient.

C. Safety

The toxicity profile of clofarabine was as expected for a heavily pretreated acute leukemia pediatric patient population. The principal toxicities were nausea and vomiting, hematologic toxicity, fever and febrile neutropenia, hepatobiliary toxicity, infections and renal toxicity. Clofarabine can produce systemic inflammatory response syndrome/capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. Cardiac toxicity most often manifest as left ventricular systolic dysfunction with accompanying tachycardia may also occur. With attentive patient care, however, the drug was tolerable.

D. Dosing

The recommended clofarabine pediatric dose and schedule is 52 mg/m² administered by intravenous infusion (IVI) over 1 to 2 hours daily for 5 consecutive days. Treatment cycles are repeated every 2 to 6 weeks following recovery or return to baseline organ function. The dosage is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle.

E. Special Populations

Pediatrics -

The studies were performed in pediatric patients

Elderly -

No clofarabine data is available for elderly patients.

Renal or Hepatic Impairment -

The major route of clofarabine elimination is renal clearance. Clofarabine is likely not metabolized by the CYP450 enzyme system,

Gender -

Results appeared comparable for males and females

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Ethnicity -

There was no significant effect of race/ethnicity on either efficacy or safety results.

Pregnancy – Category D

Pregnancy studies have not been done in humans. Female patients with childbearing potential must have a negative serum pregnancy test before starting each cycle of clofarabine therapy. Men and women with reproductive potential must use an effective contraceptive method while taking the drug. If a patient becomes pregnant while taking clofarabine, she should be apprised of the potential hazard to the fetus. Because impairment of fertility is unknown, reproductive planning should be discussed with the patient, as appropriate.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: Clofarabine (Cl-F-Ara-A)
Proprietary Name: CLOLAR™
Applicant: Hex Products Inc
Drug Class: Antimetabolite: Second-generation purine nucleoside analogue

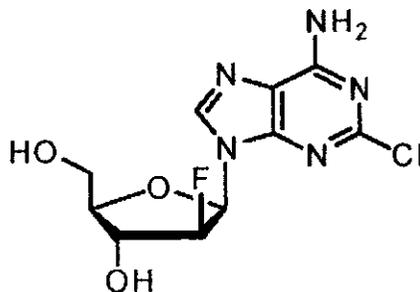
The chemical structure of clofarabine is 2-chloro-2'-fluoro-deoxy-9-β-arabinofuranosyladenine. The molecular formula is C₁₀H₁₁ClFN₅O₃. The molecular weight is 303.68.

CLOLAR (1 mg/mL) is supplied in a 20 mL, single-use vial. The 20 mL vial contains 20 mg clofarabine dissolved in 20 mL of 0.9% sodium chloride injection, United States Pharmacopeia (USP). The pH range of the solution is 4.5 to 7.5. The solution is clear and practically colorless, and free from foreign matter. The structural formula (**Figure 1**) follows:

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Figure 1: Clofarabine structural formula



Indication:

Current: None

Proposed: Clofarabine is indicated for the treatment of pediatric patients 1 to 21 years old with refractory or relapsed acute leukemias.

Dosage and Administration

Current Label: None

Proposed Label: The recommended clofarabine pediatric dose and schedule is 52 mg/m² administered IV over 1 to 2 hours daily for 5 consecutive days. Treatment cycles are repeated every 2 to 6 weeks following recovery or return to baseline organ function. The dosage is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle.

B. State of Armamentarium for Indication(s)

Drugs approved by the FDA for the treatment of pediatric ALL and AML are listed in **Table 1**.

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Table 1: FDA approved drugs for pediatric ALL and AML

Drug	Approved for Pediatric Acute Leukemias	
	ALL	AML
Asparaginase	X	
Corticosteroids		
Dexamethasone	X	X
Prednisolone	X	
Prednisone	X	X
Cyclophosphamide	X	X
Cytarabine	X	X
Daunorubicin	X	
Doxorubicin	X	X
Mercaptopurine	X	
Methotrexate	X	
Teniposide	X	
Thioguanine		X
Tretinoin		X Promyelocytic
Vincristine	X	X

C. Important Milestones in Product Development

Clofarabine was originally synthesized at the [redacted] as a hybrid molecule to incorporate the favorable properties of both fludarabine (Fludara®) and cladribine (Leustatin®). It is a nucleoside pro-drug that must be metabolized to its triphosphate conjugate by deoxycytidine kinase within tumor cells before activity occurs. Compared to other purine nucleoside analogues, it has greater affinity for the activating phosphorylating enzyme deoxycytidine kinase. It is differentiated from other purine nucleoside analogues by incorporating 2 halogen atoms (fluorine and chlorine) within its chemical structure.

Clofarabine was first investigated at The University of Texas M.D. Anderson Cancer Center (MDACC); IND 43,275 filed in 1993. The original route of synthesis produced Lot BK-I-48 (June 1993) that was used in preclinical, toxicology, pharmacology, and the early Phase I dose-escalation study. This lot was synthesized at [redacted]. However, the API manufacturer changed to [redacted] and 2 more lots were synthesized, Lot GB-3-63-1 (November 1999) and Lot GB-3-77-1 (December 1999)—both of which were used in Phase I studies and toxicology dose-ranging studies. For ILEX's pivotal Phase II studies (CLO-212 and CLO-222), the API manufacturer was [redacted] and the drug product manufacturer was [redacted]. The lot numbers used in CLO-212 were CTM-02059, ICJ001, CTM-02081, N12008F, CO3E015.

The lot numbers used in CLO-222 were CTM-02059, ICJ001, and CO3E015.

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In March 2001, ILEX acquired licensing rights from [] which previously licensed rights from MDACC and a new IND was filed by ILEX on 07 November 2001 (IND 63,641).

The ILEX IND used API lots manufactured by both [] and later on API lots manufactured by [] but eventually transitioned to lots made only at [] In March 2002, ILEX assumed responsibility for the MDACC IND (43,275).

Clofarabine was granted Orphan Drug Designation for ALL on 07 February 2002 and Orphan Drug Designation for AML on 14 March 2002. The ILEX pre-IND meeting was held on 30 August 2001 and the ILEX IND (63,641) was opened on 07 December 2001. The MDACC studies were transferred to the ILEX IND 11 April 2002.

FDA-Sponsor Discussion

An End-of-Phase 2 meeting was held on 29 April 2002. ILEX requested Fast Track Designation on 08 May 2003, which was approved by the Division on 08 July 2003. A preNDA package was submitted to the Division on 15 July 2003. On 13 August 2003, ILEX and the Division had a preNDA teleconference, as a result of which the following decisions were made:

- The phase 2 study design (CLO-212 and CLO-222) was determined to be acceptable.
- Proportion of responding patients who have a successful transplant was determined to be an important issue.
- The COG Response Criteria could be acceptable after review by the Division.
- CR/CRp/PR can be considered a clinical benefit, depending on response duration, survival, toxicity, and results achievable with other therapy. For transplant patients, clinical benefit depends upon the success of transplant after treatment with clofarabine.
- The rolling NDA submission was determined to be acceptable.
- The analysis plan was determined to be acceptable.
- The ALL approach was determined to be acceptable for AML.

A summary of the regulatory history of clofarabine, provided by Robert White, Jr., M.D. follows (Table 2):

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Table 2: Regulatory review

DATE	MEETING, SUBMISSION, ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
August 30, 2001	Pre-IND meeting	U.S. registration strategy <ul style="list-style-type: none"> • Adult salvage ALL: Two Phase II studies • 20% CR + CRp 	Standard battery of GLO in vitro genotoxicity tests performed concurrently with Phase II trial Randomized, controlled studies for approval; for Phase II studies: high rate of durable CRs Phase III protocol requested
November 11, 2001	Receipt of IND	Protocol No. CLO-221: A Phase II, open-label study of Clofarexin adult patients with refractory or relapsed acute myelogenous leukemia (AML). To demonstrate an overall response (OR) rate > 30% in salvage therapy adults with refractory or relapsed AML.	<ul style="list-style-type: none"> • The pre-clinical development does not support further Phase II development; additional toxicology and genetic toxicology studies should be ongoing • There was cardiac toxicity seen in the rat study • A phase 2 trial is unlikely to be adequate to support accelerated approval for an indication of acute leukemia
January 28th 2002	Receipt of new pediatric protocols	<p>CLO-212 a phase 2 open label study of Clofarex in children with refractory or relapsed acute lymphoblastic leukemia (ALL)</p> <p>Indications: For the induction of remission in patients less than are equal to 21 years of age with ALL who had failed to achieve remission following two or more different regimens</p> <p>CLO-222 a phase 2 open label study of Clofarex in children with refractory or relapsed acute myelogenous leukemia (AML)</p> <p>Indications: For the induction of remission in patients less than are equal to 21 years of age with AML who had failed to achieve remission following</p>	<p>The expansion of the protocol to a larger number of patients with intent to register a marketing claim should be discussed with the FDA prior to the enrollment of patients. Issues to be resolved would include entry criteria, endpoints, stratification, and statistical analysis.</p> <p>This ALL protocol could form one component of a program in pediatric oncology that may be used to qualify for an Exclusivity extension in response to a Written Request from the FDA should the sponsor be interested in qualifying for an exclusivity extension.</p> <p>This protocol may be sufficient to fulfill the requirements of the Pediatric Rule if an adult indication is sought for AML.</p>

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DATE	MEETING, SUBMISSION, ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		two or more different regimens	
March 3, 2002	Written Request for Pediatric studies		Phase 1 and Phase 2 studies in refractory or relapsed pediatric hematologic malignancies and solid tumors
March 21, 2002	Telecon: Sponsor-FDA	Clarification of pediatric protocols	Sponsor: studies were not exploratory but registration studies FDA: request an end-of-Phase 2 meeting
April 29, 2002	End-of-Phase 1 meeting	<p>Pediatric Acute Lymphoblastic Leukemia</p> <p>Pediatric Acute Myelogenous Leukemia</p> <p>ILEX contends that treatment with a single agent (CLOFAREX) administered to Pediatric patients with refractory/ relapsed ALL and AML and demonstrating a ³ 30% overall response rate is clinically significant in this refractory patient population. Do you concur?</p>	<p>Advice to the Sponsor: The FDA views the planned Phase 2 study as exploratory. Plans for a randomized Phase 3 trial should be made. Please be advised that the Agency strongly recommends two Phase 3 trials to support an application. (2 pediatric or 1 adult/1 pediatric, all in leukemia).</p> <p>Response by the FDA: No, not if the Sponsor is asking whether this endpoint and magnitude demonstrated in the proposed single arm trials would be adequate for registration. Although Phase 2 trials may be the next step in the development of this drug, and an overwhelmingly positive result (extremely high rate of durable complete response) in single arm trials might be considered for registration in these diseases, randomized controlled studies are generally required for approval because the clinical relevance of the observed magnitude of response and duration is best evaluated in the presence of a comparator arm. Historical comparisons are fraught with difficulty and conclusions drawn from such comparisons are not generally valid.</p>

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DATE	MEETING, SUBMISSION, ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		<p>Do you concur that the study design of our Phase II pediatric ALL (CLO-212) and/or AML pediatric (CLO-222) protocol as a single pivotal trial (multi-center) would be sufficient for registration approval of CLOFAREX for treatment of pediatric salvage ALL?</p>	<p>(See answers to #7 and #8 above.) Complete response rate observed in a properly designed randomized trial might be accepted as the basis for accelerated approval. The biological rationale to support the clinical significance of a CRp associated with the proposed chemotherapy combination is not evident, and it would not be considered a valid component of the CR-endpoint. (See Oncologic Drug Advisory Committee discussion of the Mylotarg NDA- March 17, 2000)</p> <p>After discussion, the following bullet was added: Two randomized trials in leukemia are strongly recommended.</p>
May 6, 2002	<p>sponsor request that comments be included as part of the official meeting minutes.</p>	<p>In response to the Division's preference for 2 randomized Phase 3 trials to support registration of Clofarex in the pediatric population, with either 2 pediatric trials OR one trial in adults and the second trial in children, ILEX contends that it will be difficult to enroll patients due to the limited number of patients available for the AML and ALL indications.</p> <p>As presented by ILEX, we anticipate great difficulty in gaining consensus from the medical community as to an agreement defining the comparator arm for a randomized Phase 3 pediatric study with Clofarex and to complete these trials in a reasonable time frame.</p>	<p>The Division gave ILEX approval to initiate the Phase 2 pediatric protocols.</p>
May 9, 2003	<p>Request for Fast Track Designation</p>	<p>For the treatment of pediatric primary refractory or relapsed ALL</p>	

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DATE	MEETING, SUBMISSION, ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
May 23, 2003 addendum written by FDA 10/13/03	Request for elimination of the solid tumor component from Pediatric Written Request	Rationale: absence of evidence of activity of clofarabine in pediatric solid tumors and therefore no scientific or ethical basis for performing a formal study.	FDA agreed There was no endpoint stated for the Phase 2 component. The endpoint of complete remission rate for hematologic malignancies was added.
July 8, 2003	Granted Fast Track Designation	Clofarabine for the treatment of pediatric primary refractory or relapsed ALL	
August 13, 2003	Pre-NDA meeting	<p>Pediatric Refractory or Relapsed ALL Nonrandomized, open-label, Phase 2 study of clofarabine in pediatric patients with refractory or relapsed ALL Primary endpoint: CR and/or CRp¹)</p> <p>Supportive: CLO-222² and ID99-383³</p> <p>Sponsor contends that the design of the Phase II pediatric ALL study (CLO-212) is sufficient for registration approval of clofarabine for treatment of relapsed or refractory pediatric patients with ALL.</p>	<p>The design is acceptable</p> <p>The number of patients studied is relatively small and the CR rate is relatively low.</p> <p>The Sponsor was encouraged to increase the size of the study to gain experience.</p> <p>It was strongly suggested that the Sponsor continue to accrue patients regardless of whether you submit the NDA as proposed.</p> <p>If the proposed NDA is approved, it will likely be accelerated approval under subpart H. This requires confirmatory studies. It must be credible that the confirmatory studies will be completed in an acceptable time frame. This means that the protocols for confirmatory studies should be submitted prior to submission of the NDA. If there is concern that the studies will have difficulty accruing patients or that approval will interfere with completion of the confirmatory studies, the studies should have</p>

¹ complete remission in the absence of total platelet recovery

² Phase 2 nonrandomized, open-label, single-arm study of clofarabine in 35 pediatric patients with refractory or relapsed AML

³ Phase 1 study conducted at MD Anderson Cancer Center in 25 pediatric patients with both ALL and AM

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DATE	MEETING, SUBMISSION, ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		<p>The sponsor asked whether 40 patients from CLO-212 would be sufficient to file an NDA.</p> <p>The sponsor asked whether it would be acceptable to submit the data on the first 40 patients, and then submit data on any additional patients at a later date.</p>	<p>completed accrual or accrued a substantial portion of the patients, prior to approval under subpart H.</p> <p>a commitment to a specific number of patients generally cannot be made, but encouraged the sponsor to continue accruing patients.</p> <p>The Division discouraged this approach and stated that in general, it is acceptable to submit additional safety data (i.e., 120-day safety update), but not efficacy data. The Division explained that in the rolling review process, the sponsor must submit complete sections of the NDA. The sponsor has the option of submitting additional information as an amendment, but if the information is substantial and is submitted within 3 months of the due date, it may extend the review clock by 3 months.</p> <p>The Division further explained that 40 patients may not be enough if the drug has a low response rate, however, 40 patients may be enough if the drug has a high response rate. This will be an ongoing discussion and should be addressed again in the future when more data is available.</p> <p>The Division explained that the type of confirmatory study that may be appropriate has not been assessed at this stage, however, the Division encouraged the sponsor to submit any proposed post-marketing commitment protocols with the NDA for review. The Division reminded the sponsor that the NDA is not restricted to Subpart H accelerated approval, because there may be enough data to receive full approval.</p>

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DATE	MEETING, SUBMISSION, ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		<p>The sponsor asked whether the Division would accept a post-marketing commitment to conduct a Phase 2 study in a similar population of patients.</p> <p>ILEX contends that treatment with a single agent (clofarabine) administered to Pediatric patients with relapsed or refractory ALL demonstrating a $\geq 15\%$ overall response rate (CR + CRp) is clinically significant in this heavily pretreated and refractory population.</p> <p>The Sponsor contends that a 1 to 3 month remission is considered durable and a clinical benefit in this population of patients (refractory or in second or</p>	<p>The Oncology Division does not commit to a particular response rate in advance. This will be a review issue. There are many other factors to consider, such as response duration, toxicity and results that can be achieved with other therapy.</p> <p>An important aspect will be the proportion of responding patients that have a successful transplant.</p> <p>This will be a review issue.</p> <p>For transplant patients, it depends on the success of the transplant after treatment with Clofarabine. For non-transplant patients, it depends on response duration, survival, toxicity and results achievable with other therapy.</p> <p>Same answer as above</p> <p>This will be a review issue. The Division noted that only 9 patients were treated with the regimen proposed for marketing and none of these had a CR. In patients treated at other doses, there was disagreement between the independent review board and the investigator regarding CR status. Documentation of Refractory/ relapse history should be provided for each patient. The Division asked the Sponsor to submit for each patient the prior treatment regimens received (including dates) and the response and response</p>

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DATE	MEETING, SUBMISSION, ACTION	INDICATION, PROTOCOL, ISSUES	AGREEMENTS OR FDA RECOMMENDATIONS
		<p>subsequent relapse).</p> <p>The Sponsor contends that a CR or CRp is a clinical benefit, especially for patients who are enabled to undergo a bone marrow, stem cell, or umbilical cord transplant.</p> <p>The Sponsor contends that a PR (>5% to <25% blasts) is of clinical benefit in this group of children, allowing selected patients to receive a bone marrow, stem cell, or umbilical cord transplant.</p> <p>The Sponsor contends that the ID99-383 pediatric ALL efficacy data will be supportive of the registration application by demonstrating additional clinical activity in pediatric leukemia.</p> <p>The Sponsor contends that CRF's for only those patients who died or discontinued from the study be supplied.</p> <p>The Sponsor asked what the age cut-off was for pediatric studies and gave the following Scenario: Suppose a patient is diagnosed at age 17, then relapses at age 18 or 19. Would that patient be treated on the adult protocol and can the data from this patient be included in the pediatric patient dataset?</p>	<p>duration status after each regimen. The date of most recent relapse or documentation of refractoriness should be provided for each patient. For transplanted patients the date of transplant and results of transplant should be submitted.</p> <p>The Division added that a complete electronic database on all patients is submitted. Otherwise, CRFs on all patients should be submitted. We need complete information on each patient. There are relatively few patients in this NDA.</p> <p>The Division said that this is a review issue and would have to be addressed on a case-by-case basis.</p>

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Overview of Clinical Studies

MDACC conducted 2 Phase I studies and 2 Phase II studies with clofarabine in patients with leukemias and solid tumors. In addition, ILEX has conducted a total of 5 clinical studies with clofarabine in patients with leukemias and solid tumors as well as an emergency expanded access program. **Table 3** provides a chronology of the clofarabine studies including the ongoing emergency expanded access patient treatment program (EEAP).

Table 3: Clofarabine studies

Protocol	Sponsor	Date Initiated	Patient Population	Disease Description
DM93-036	MDACC	Feb 1999	Adult	Solid and Hematologic Malignancies
DM99-225	MDACC	Sep 1999	Adult	CLL Refractory to Fludarabine/Alkylators
ID99-383	MDACC	Aug 2000	Pediatric	Hematologic Malignancies
ID00-038	MDACC	May 2001	Adult	Acute Leukemia and MDS, Refractory/Relapsed
CLO-221	ILEX	Nov 2001	Adult	AML
CLO-212	ILEX	Apr 2002	Pediatric	ALL
CLO-222	ILEX	Jan 2002	Pediatric	AML
CLO-151	ILEX	May 2002	Adult	Solid Tumors
CLO-141	ILEX	June 2002	Adult	Clofarabine in Combination with Ara-C in AML, ALL, High-Risk MDS; or CML Blast Phase as First or Second Line Therapy
Expanded Access	ILEX	Jan 2002	Adult/Pediatric	AML and ALL

D. Other Relevant Information

Clofarabine inhibits DNA synthesis by decreasing cellular deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide reductase, and by terminating DNA chain elongation and inhibiting repair through incorporation into the DNA chain by competitive inhibition of DNA polymerases. The affinity of clofarabine triphosphate for these enzymes is similar to or greater than that of deoxyadenosine triphosphate. In preclinical models, clofarabine has demonstrated the ability to inhibit DNA repair by incorporation into the DNA chain during the repair process. Clofarabine 5'-triphosphate also disrupts the integrity of mitochondrial membrane, leading to the release of the pro-apoptotic mitochondrial proteins, cytochrome C and apoptosis-inducing factor, leading to programmed cell death.

E. Important Issues with Pharmacologically Related Agents

The nucleoside analogs are among the most widely used class of drugs for treating acute leukemias. Cytosine nucleoside analogs include cytarabine (ara-C), the most active drug in treating AML, gemcitabine which has broad antitumor activity including hematologic malignancies, and 5-azacytidine and decitabine which have activity in myelodysplastic syndrome. Guanosine analogs, including 6-mercaptopurine and 6-thioguanine, have

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antitumor activity in ALL. Deoxyadenosine nucleoside analogs, including fludarabine, cladribine and deoxycorformycin, have activity against several hematologic malignancies.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Clinical Pharmacology and Biopharmaceutics

See appropriate review.

B. Statistics

See statistical review.

C. Chemistry

See chemistry review.

D. Animal Pharmacology and Toxicology

See pharmacology review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The population pharmacokinetics of clofarabine were studied in 40 pediatric patients ages 2 to 19 years old (21 males/19 females) with relapsed or refractory ALL or AML given multiple doses. Clofarabine pharmacokinetics were weight-dependent, although intravenous infusion (IVI) of 52 mg/m² produced equivalent exposure across a wide range of weights. Clofarabine pharmacokinetics were best described by a 2-compartment model with a systemic clearance of 32.8 L/h (27% between-subject variability) in a 40 kg pediatric patient.

Clofarabine had a beta-half-life of 6.4 hours in a 40 kg person having a WBC count of 10 x 10³/mL. Clofarabine was 47% bound to plasma proteins, predominantly to albumin, and had a volume of distribution at steady-state in a 40 kg person having a WBC count of 10 x 10³/mL of 210 L (72% between-subject variability). Based on noncompartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m² and 172 L/m², respectively. As WBC count was depleted, clofarabine AUC decreased and C_{max} increased, although the change was likely not clinically significant. No apparent difference in pharmacokinetics was observed between patients with ALL and AML or between males and females.

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Hepatic and Renal Impairment: The effects of significant renal or hepatic insufficiency on the disposition of clofarabine have not been assessed.

Special Populations: The studies were performed in pediatric patients. No clofarabine data is available for elderly patients. Results appeared comparable for males and females.

B. Pharmacodynamics

No pharmacodynamic data was reviewed.

IV. Description of Clinical Data and Sources

A. Overall Data

EDR submission of March 29, 2004

B. Table Listing the Clinical Trials

Table 4: Submitted clinical trials (pediatric patients only)

Data Source	ALL n	AML n	ALL/AML n
Total	67	46	113
CLO-212	49		49
CLO-222		35	35
ID99-383 (MDACC)	17	8	25
DM 93-036/CLO-221/CLO-141	1	3	4

C. Postmarketing Experience

None

D. Literature Review

Manuscripts and abstracts relating to the submitted clinical trials. Manuscripts related to the role of stem cell transplantation in the management of acute pediatric leukemias.

V. Clinical Review Methods

A. How the Review was Conducted

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The efficacy review is based primarily on data submitted as SAS transport files for the two pivotal pediatric AML (CLO-222) and ALL (CLO-212) studies. Bone marrow aspirates/biopsy were provided in the Aspirate database, hematology analysis in the ANL_Hema database, hematology in the HEMA database and AE's in the adverse event dataset.

B. Overview of Materials Consulted in Review

See above.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI on-site audit was used to audit sponsor's data quality, integrity and analysis.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes.

E. Evaluation of Financial Disclosure

The sponsor has submitted certification that they have not entered into any financial arrangement with any of the clinical investigators who participated in Protocol CLO-212 "A Phase II, Open-Label Study of Clofarabine in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia" or Protocol CLO-222 "A Phase II, Open-Label Study of Clofarabine in Pediatric Patients With Refractory or Relapsed Acute Myelogenous Leukemia". This certification was signed on 3/29/04 by Mike Bernstein, MPH, Senior Director Regulatory Affairs and Safety.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In pediatric AML there was 1 CRp (2.9%) and 8 PR's among 35 treated patients. Twelve of 35 AML patients went on to transplant including the CRp patient, 6 PR's, 3 not-evaluable patients and 2 treatment failures. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In trial CLO-222 there were no CR's, only one CRp (2.9%) and 8 PR's. The CRp patient and 6 of the PR's went on to have a transplant. Long duration responses and prolonged survival were confined to patients who received a transplant. Four clofarabine plus transplant patients had response durations to that treatment exceeding those of immediate prior therapy. Three of these 4 patients also had longer TTP with clofarabine plus transplant then they had with their preceding transplant.

In Pediatric ALL there were 6 CR's (12.2%), 4 CRp's (8.2%) and 5 PR's among 49 treated patients. Eight ALL patients went on to transplant including 2 CR's, 2 CRp's, 2 PR's, 1 not-evaluable patient and 1 treatment failure. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In study CLO-212 among the 6 CR patients 3 had ongoing responses at the time of data cutoff and 3 had relapsed. Using the

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criteria of longer TTP with clofarabine \pm transplant than to immediate prior therapy 2 of 6 CR patients, 3 of 4 CRp patients and 0 of 5 PR patients demonstrated benefit. With further follow-up benefit may be demonstrated in 3 additional CR patients and 1 PR patient.

B. General Approach to Review of the Efficacy of the Drug

Individual patient data provided by the sponsor were analyzed to confirm sponsor's reported results and analyses.

C. Detailed Review of Trials by Indication

The efficacy review is based primarily on two multicenter trials, one for pediatric ALL and one for pediatric AML

Protocol Review

The initial version of the phase 2 study designs was approved by Ilex on 24 January 2002. There were 6 amendments. Basic protocol elements for studies 212 and 222 are provided in the Appendix.

Amendment 1, 05 March 2002

No patients were enrolled and treated under the original protocol or Amendment 1. This amendment included administrative changes to improve the clarity and consistency of the document such as previous clinical data, treatment regimen, number of patients required to enroll, updated cycle definition to reflect the current practice at MDACC, and any references to the study being performed in Europe, as well as the following specific changes:

- The decision was made to treat all patients at 52 mg/m²/day for a maximum of 12 cycles, thus all references to Induction and Post- induction phases of treatment were deleted. The rationale for selecting the 52 mg/m²/day dose was added and the timing for subsequent cycles was revised.
- The decision was made to limit enrollment to 40 patients, thus all references to a patient population >40 were deleted.
- A decision was made to broaden the inclusion criteria to allow patients in first or subsequent relapse as there are fewer treatment options for pediatric AML patients. Other aspects of the entry criteria were modified for clarification and to reflect recent data and current practice.
- Inclusion laboratory values were revised based on toxicity seen in an ongoing MDACC study and to allow for greater flexibility in enrolling patients.
- The incidence of pediatric AML was updated for 2002, as was information regarding pediatric and adult exposure to clofarabine and timing for repeat cycles to reflect the current practice at MDACC.
- The decision was made to confine this study to the US, thus all references to European sites and regulatory requirements were deleted.

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Amendment 2, 01 April 2002

Three patients were enrolled and treated under Amendment 2. This amendment included administrative changes for clarification and consistency, as well as substantive changes.

The substantive changes are itemized below:

- Cardiac and renal toxicities information was added to "possible Risks/Discomfort" section in response to a request from the FDA.
- A requirement was added to specify that patients with acute promyelocytic leukemia (M3) be treated with at least 2 prior regimens before being considered for this study.
- A clarification was made that both male and female patients were required to use barrier contraception.
- A 25% dose reduction was added in the event a patient experienced a second occurrence of a grade 3 event.

Amendment 3, 08 May 2002

Sixteen patients were enrolled, but only 15 were treated under Amendment 3. This amendment consisted of administrative changes for clarification and consistency, as well as substantive changes, many of them at the request of the FDA following the "End of Phase II" Meeting (29 April 2002), and investigator comments that arose from the Investigator's Meeting (05 April 2002). The substantive changes are itemized below:

- Per FDA request, the significance level was changed from 0.04 to 0.02, which resulted in a change in the power from 94 to 79%, and a change in the confidence level from between 16 to 44% to between 25 to 55%.
- Per FDA request, a requirement was added that cardiac assessments be performed every 4 cycles of treatment.
- Per FDA request, more pharmacokinetic samples were added to provide more reliable pharmacokinetic parameter estimates.
- The targeted remission rate was revised from 30 to 40%.
- Safety and pharmacokinetic data were updated to reflect the first completed clinical study, DM93-036.
- Per FDA request, patients experiencing an NCI CTC grade 2 neurologic or cardiac event were to have their clofarabine dose level re-evaluated by the medical monitor.
- A statement was added to obtain the medical monitor's approval prior to implementing prophylactic use of colony stimulating factor.
- Added a patient assent form to the Informed Consent Document for patients ≥ 7 years old to sign.
- Revised the response criteria for PR to aid in the stratification of patient response.

Amendment 4, 18 July 2002

Two patients were enrolled and treated under Amendment 4; however 1 of these patients (001-0021) had been previously enrolled under Amendment 3, but was not treated. This amendment consisted of administrative changes to reflect the decision to include Europe, thus changes were made throughout the protocol and appendices to be compliant with European regulatory requirements. However, no European patients were enrolled in this study.

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Amendment 5, 01 May 2003

Ten patients were enrolled and treated under this amendment as of the 21 November 2003 data cutoff date. Amendment 5 consisted of administrative changes for clarification and consistency, as well as substantive changes. The substantive changes are itemized below:

- Changes were made throughout the protocol and appendices to reflect the name change from CLOFAREX to clofarabine.
- Information regarding HIPAA was added to the protocol and the informed consent documents.
- The stopping rule was voided to continue enrollment to 40 patients to collect further response and safety data.

Amendment 6, 10 October 2003

No patients were enrolled and treated under Amendment 6 prior to the 21 November 2003 data cutoff. This amendment consisted of administrative changes for clarification and consistency, as well as substantive changes, and patients enrolling in the ongoing study are subject to the terms of this amendment. The substantive changes are itemized below:

- Upon review of all SAEs reported in the CLO-212 and CLO-222 studies, it appears that patients with poor Karnofsky Performance Status (KPS) are at an increased risk of developing hypotension and capillary leak syndrome, which may be attributed to sepsis. Thus, in order to minimize the possibility of these occurrences and more importantly, to reduce the risk to patients, entry criteria were changed to include a KPS of ≥ 70 rather than ≥ 50 , patients with known or suspected fungal infections or febrile neutropenia at study entry were to be excluded.
- Cardiac assessments were increased for all patients with either ECHO or MUGA to be performed prior to every cycle. In select patients, cardiac assessments will be performed on Days 1, 3, and 5 of all cycles and will be reviewed by a pediatric cardiologist.
- A requirement was added that patients who undergo peripheral blood stem cell transplant or bone marrow transplant post-clofarabine treatment be followed for 120 days post-transplant in an effort to gather safety and efficacy data on clofarabine in this subpopulation.
- Patients who achieved a response and did not go on to transplant or who discontinued for reasons other than disease relapse or treatment failure were to be followed until disease relapse, the initiation of alternative therapy, or death, whichever occurred first. All SAEs and drug-related AEs were to be followed until resolution, initiation of alternative treatment, or patient death.
- A statement clarifying that no deletions or major deviations were to be made to the sample ICD/PIS or patient assent document without prior approval from ILEX, and the patient assent document had to be signed by patients ≥ 7 years old according to the local IRB/IEC and institutional requirements.

Table 5 lists the principal investigators and the corresponding participating institutions.

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Table 5: Participating sites

<u>Site</u>	<u>Investigator Name & Address</u>
001	Edythe Albano, MD The Children's Hospital 1056 East 19th Avenue, B115 Denver, Colorado 80218
002	Arnold Altman, MD Connecticut Children's Medical Center 282 Washington Street Hartford, Connecticut 06106
003	Victor M Aquino, MD The University of Texas Southwestern Medical Center 5323 Harry Hines Boulevard Dallas, Texas 75390
004	Paul S Gaynon, MD Children's Hospital Los Angeles 4650 Sunset Boulevard MS#54 Los Angeles, California 90027
005	Stuart Goldman, MD Children's Memorial Hospital 2300 Children's Plaza, Box #30 Chicago, Illinois 60614
006	Sima C Jeha, MD Replaced by Michael Rytting MD The University of Texas MD Anderson Cancer Center 1515 Holcombe Boulevard Box 87 Houston, Texas 77030
007	Richard P Kadota, MD Children's Hospital and Health Center 3020 Children's Way, MC 5035 San Diego, California 92123
008	N/A Site number was assigned, however the investigator was not registered and did not participate in this study.
009	Lori Luchtman-Jones, MD Washington University School of Medicine St Louis Children's Hospital One Children's Place St Louis, Missouri 63110
010	Bassem Razzouk, MD St Jude Children's Research Hospital 332 North Lauderdale Street Memphis, Tennessee 38105
011	Susan Rheingold, MD The Children's Hospital of Philadelphia 34th Street and Civic Center Boulevard 4300 Wood Building Philadelphia, Pennsylvania 19104
012	Arthur Kim Ritchey, MD Pediatric Hematology/Oncology Children's Hospital of Pittsburgh 3705 Fifth Avenue Pittsburgh, Pennsylvania 15213
013	N/A Site number was assigned, however the investigator was not registered and did not participate in this study.
014	Peter Steinherz, MD Memorial Sloan Kettering Cancer Center 1275 York Avenue New York, New York 10021
015	Kimo C Stine, MD Arkansas Children's Hospital 800 Marshall Street Little Rock, Arkansas 72202
016	Timothy C Griffin, MD Cook Children's Medical Center Hematology/Oncology & Research Hematology Laboratory 901 Seventh Avenue, Fort Worth, Texas 76104
017	N/A Site number was assigned, however the investigator was not registered and did not participate in this study.
018	Violet Shen, MD Children's Hospital of Orange County Pediatric Subspecialty Faculty, Inc. 455 South Main Street Orange, California 92868
019	Susan M Blaney, MD Texas Children's Hospital 6621 Fannin Street, MC 3-3320 Houston, Texas 77030
020	N/A Site number was assigned, however the investigator was not registered and did not participate in this study.
021	N/A Site number was assigned, however the investigator was not registered and did not participate in this study.
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Table 6 indicates enrollment by site.

Table 6: Enrollment by site

Site	Investigator	Institution	N =36*	%
001	Edythe Albano, MD	Children's Hospital at Denver	1	2.8
002	Arnold Altman, MD	Connecticut Children's Medical Center	1	2.8
004	Paul Gaynon, MD	Children's Hospital of Los Angeles	1	2.8
006	Sima Jeha, MD	MD Anderson Cancer Center	6	16.7
007	Richard Kadota, MD	Children's Hospital of San Diego	1	2.8
009	Lori Luchtman-Jones, MD	Washington University Medical Center	2	5.6
010	Bassem Razzouk, MD	St. Jude Children's Research Hospital	7	19.4
011	Susan Rheingold, MD	The Children's Hospital of Philadelphia	4	11.1
012	A. Kim Ritchey, MD	Children's Hospital of Pittsburgh	1	2.8
014	Peter Steinherz, MD	Memorial Sloan-Kettering Cancer Center	9	25.0
015	Kimo Stine, MD	Arkansas Children's Hospital	1	2.8
019	Susan Blaney, MD	Texas Children's Cancer Center	1	2.8
023	Robert Arceci, MD	Johns Hopkins, Baltimore, MD	1	2.8

*One patient 014-0006 was enrolled but not treated. One patient was initially enrolled as 001-0012 but not treated at the time due to elevated AST; the patient later re-enrolled as Patient 001-0021.

Reasons for discontinuation of therapy are listed in Table 7. The two most common reasons were failure to achieve response and patient scheduled to receive a transplant.

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Table 7: Reasons for discontinuation

Termination Reason	N=35	%
Investigator decision	2	5.7
Refused further treatment	1	2.9
AE	2	5.7
Failure to achieve response after 2 cycles	13	37.1
Disease Progression	2	5.7
Transplant	9	25.7
Death from AE	5	14.3
Not available	1	2.9

The median age of the 35 treated patients was 12 years. See **Table 8** for patient demographics and Karnofsky performance status.

Table 8: Demographics and Karnofsky Performance Status

Variable	N=35 (%)
Age Category	
0 to 2	2 (5.7)
>2 to ≤ 12	16 (45.7)
>12 to ≤ 16	7 (20.0)
>16 to 22	10 (28.6)
Sex	
Female	13 (37.1)
Male	22 (62.9)
Ethnicity	
Hispanic	7 (20.0)
Caucasian	19 (54.3)
Black	3 (8.6)
Asian	3 (8.6)
Other	3 (8.6)
Karnofsky Performance Status	
100	14 (40.0)
90	9 (25.7)
80	8 (22.9)
70	3 (8.6)
60	1 (2.9)

Each of the patients had received at least 1 prior induction therapy. Most of the patients (18/35 [51%]) had received at least 3 prior induction therapies before study entry (**Table 9**).

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Table 9: Prior Induction Therapies

Number of Prior Induction Regimens	ITT Patients (N=35)	
	n	%
1	5	14.3
2	12	34.3
3	8	22.9
4	4	11.4
5	6	17.1

A total of 18/35 (51%) patients received at least 1 transplant before study entry: 13/35 (37%) received 1 prior transplant and 5/35 (14%) received 2 prior transplants

Table 10 indicates best response, judged by the Independent Review panel, and confirmed by FDA review.

Table 10: Best response - ITT population

Response Category	N=35	%
Complete Remission (CR)	0	0.0
Complete Remission-Absence of Total Platelet Recovery (CRp)	1	2.9
Partial Remission (PR)	8	22.9
Treatment Failure	19	54.3
Not Evaluable*	7	20.0

* 2 patients had early death; 1 patient stopped treatment after 2 doses; 1 patient stopped treatment after 4 doses; 1 patient was enrolled but not treated

Table 11 indicates the FDA reviewer's response summary. This table includes disease history including time to relapse from prior therapies. The asterisk indicates the number of months on the treatment immediately preceding entry into the clofarabine study. As indicated 3 of the responders had a prior stem cell transplant. Only one patient had a confirmed response (second marrow \geq 21 days after the initial response was demonstrated). Response duration (days) and time from initiation of clofarabine treatment to disease progression (TTP) or death are also indicated. Response duration and TTP, for patients with CR, CRp or PR, was censored at the date of the last bone marrow evaluation

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Table 11: CLO-222 FDA Responder Summary

Patient	014-0003	006-0013	009-0018	014-0002	014-0019	014-0027	015-0017	006-0036	014-0031
Time to first relapse (mo)	3	2	4*	26	10*	1	8	14	1
Time to 2nd relapse (mo)	12	1	-	27	-	3*	2*	16	1*
Time to 3 rd or later relapse (mo)	3, 9*	2, 1*	-	7,2,9*	-	-	-	1,1*	-
Stem cell transplant (Y or N)	Y	N	N	Y	Y	N	N	Y (2)	N
Stem cell transplant response duration (mo)	5	-	-	6	6	-	-	12,16	-
Clofarabine response	CRp	PR							
Clofarabine response confirmed Y or N	Y	N	N	N	N	N	N	N	Y
Clofar response duration (d)**	519+	12	34	141	44+	14	410+	82+	53+
Clofarabine TTP or death (d)**	547+	54	67	161	78+	49	465+	130+	93+
Post-clofarabine SCT (Y or N)	Y	N	N	Y	Y	N	Y	Y	Y
Current status (Alive or Dead)	A	D	D	D	D	A	A	A	A
Post-clofarabine OS (w)	93.6+	7.7	24.3	30.3	39.0	29.0+	67.9+	16.4+	24.9+

* response duration for treatment immediately preceding clofarabine treatment

** censored at the time of last bone marrow evaluation

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Reasons for discontinuation of clofarabine treatment for treatment responders are summarized in **Table 12.**

Table 12: CLO-222 Reasons for Discontinuation

Pt ID	IRRP Response	Alive at Last Follow Up	Reason for Discontinuation		
			Progressive Disease	AE	Transplant
006-0013	PR	N		Y	
009-0018	PR	N	Y		
014-0002	PR	N			Y
014-0003	CRp	Y			Y
014-0019	PR	N			Y
014-0027	PR	Y			Y
015-0017	PR	Y			Y
006-0036	PR	Y			Y
014-0031	PR	Y			Y

Clofarabine treated patients who underwent a transplant are listed in **Table 13.** As indicated in the table, transplants were performed in 5 patients who had not responded to clofarabine based on independent committee review (3 patients non-evaluable, 2 patients treatment failures).

Table 13: CLO 222 Patients receiving a transplant

Site-Patient Number	# of Courses of Clofarabine	Clofarabine Response (IRRP)	Survival from Start of Clofarabine (w) (30APR04 Cutoff)
006-0014	2	NE	75.3+
006-0036	3	PR	16.4+
010-0020	2	TF	28.7
010-0022	1	NE	24.4
010-0023	1	TF	20.6+
014-0002	2	PR	30.3
014-0003	5	CRp	93.6+
014-0019	2	PR	39.0
014-0027	4	PR	29.0+
014-0031	2	PR	24.9+
014-0034	4	NE	23.3+
015-0017	1	PR	67.9+

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Patients who were treatment failures or who were non-evaluable and nevertheless, received a transplant are summarized in **Table 14**.

Table 14: CLO-222 Non-responding patients who received a transplant

Patient	010-0020	0010-0023	006-0014 [^]	010-0022	014-0034 [^]
Time to first relapse (mo)	4	2	13*	13*	4
Time to 2nd relapse (mo)	1	1	-	NE	19
Time to 3 rd or later relapse (mo)	1,1,1*	1, 1*	-		14*
Stem cell transplant (Y or N)	N	Y	N	Y	Y
Stem cell transplant response duration (mo)	-	7	-	5	11
Clofarabine response	TF	TF	NE	NE	NE
Clofarabine TTP or death (d)	109	55+	107+	ND	137+
Post-clofarabine SCT (Y or N)	Y	Y	Y	Y	Y
Current status (Alive or Dead)	D	A	A	D	A
Post-clofarabine OS (w)	28.7	20.6+	75.3+	24.4	

[^] Not eligible for enrollment. 20% marrow blasts (010-0022) and 12% blasts (014-0034) at entry; ND=no data; NE=non-evaluable; TF=treatment failure

Survival data for patients enrolled in CLO-222 is summarized in **Table 15**.

Table 15: CLO-222 Survival (weeks)

Response Category	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored
CRp	1	.	.	.	93.6	93.6	100.0
PR	8	30.3	24.3	.	7.7	67.9	50.0
Treatment Failure/Not Evaluable	26	12.4	5.4	22.1	1.6	84.9	15.4
Overall Remission(CR+CRp)	1	.	.	.	93.6	93.6	100.0
Remission(CR+CRp+PR)	9	24.3	24.3	.	7.7	93.6	55.6
All Patients	35	21.0	7.7	30.3	1.6	93.6	25.7

Patients benefiting from clofarabine treatment, using the criteria of longer TTP to clofarabine + transplant compared to the therapy immediately preceding clofarabine, are listed in **Table 16**.

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Table 16: Pediatric AML patients benefiting from clofarabine + transplant treatment

Patient	014-0003	015-0017	006-0036	014-0031
TTP for treatment immediately preceding entry into CLO-222 (mo)	9	2	1	1
Prior Stem cell transplant (Y or N)	Y	N	Y (2)	N
Post-transplant response duration (mo)	5	-	12, 16	-
Number of courses of clofarabine	5	1	3	2
Clofarabine response	CRp	PR	PR	PR
Clofarabine TTP (d)	519+	465+	130+	93+
Post-clofarabine SCT (Y or N)	Y	Y	Y	Y
Current status (Alive or Dead)	A	A	A	A
Post-clofarabine OS (w)	93.6+	67.9+	16.4+	24.9+

Efficacy conclusions

The patient population studied is a difficult population to evaluate. Patients had failed several prior treatment regimens and had often failed one or more bone marrow or stem cell transplants. In this multiply resistant population it is difficult to demonstrate efficacy. Further, depending upon availability of a donor and other clinical considerations, stem cell transplant is an important modality of treatment. Transplants are often performed before blood count recovery from treatment and before additional cycles of treatment can be administered.

The usual definition of efficacy is long duration complete responses or prolonged survival. In trial CLO-222 there were no CR's, only one CRp and 8 PR's. The CRp patient and 6 of the PR's went on to have a transplant. Long duration responses and prolonged survival were confined to patients who received a transplant. Thus patient 014-0003 had a TTP of 74+ weeks after starting clofarabine and an OS of 93.6+ weeks. This patient had had a stem cell transplant prior to starting clofarabine with a post-transplant response duration of 5 months and an overall response duration of 9 months. The clofarabine plus transplant TTP has already exceeded that of prior treatment, including transplant, and the remission is ongoing.

Patients 006-0036 and 014-0031 also seemed to benefit from clofarabine plus transplant. The former patient had received 2 transplants prior to enrollment in CLO-222 and had also failed two consecutive post-transplant regimens administered prior to clofarabine treatment. The TTP following the second transplant was 16 months. Thus if benefit was

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determined based on the two most recently failed chemotherapy regimens then the patient benefited from clofarabine + transplant treatment. If it is based on the remission duration achieved after prior transplant it is too early to tell.

Similarly patient 015-0017 has an ongoing TTP with clofarabine plus transplant treatment that currently just exceeds his prior therapy TTP.

Pediatric ALL (CLO-212)

STUDY PATIENTS

This report summarizes the data for the 49 patients enrolled and treated. Data cutoff for this report is 30 April 2004.

Eighteen study sites participated in CLO-212; however, only 14 sites enrolled patients into the study (**Table 17**). One (patient 005-0001) of the 50 patients enrolled in the study did not receive study drug and was not included in the efficacy or safety analyses.

Table 17: CLO-212 Patient Enrollment by Site

Site	Investigator	Institution	N=50	
			n	%
001	Edythe Albano, MD	Children's Hospital at Denver	2	4.0
002	Arnold Altman, MD	Connecticut Children's Medical Center	1	2.0
004	Paul Gaynon, MD	Children's Hospital of Los Angeles	7	14.0
005	Stewart Goldman, MD	Children's Memorial Hospital, Chicago	2	4.0
006	Sima Jeha, MD	MD Anderson Cancer Center	3	6.0
007	Richard Kadota, MD	Children's Hospital of San Diego	5	10.0
009	Lori Luchtman-Jones, MD	Washington University Medical Center	4	8.0
010	Bassem Razzouk, MD	St. Jude Children's Research Hospital	5	10.0
011	Susan Rheingold, MD	The Children's Hospital of Philadelphia	2	4.0
012	A. Kim Ritchey, MD	Children's Hospital of Pittsburgh	2	4.0
014	Peter Steinherz, MD	Memorial Sloan-Kettering Cancer Center	9	18.0
016	Timothy Griffin, MD	Cook Children's Hematology & Oncology Center, Fort Worth Tx	2	4.0
018	Violet Shen, MD	Children's Hospital of Orange County CA	3	6.0
019	Susan Blaney, MD	Texas Children's Cancer Center, Houston	3	6.0

Patient Disposition

Table 18 summarizes the reasons for discontinuation for the 49 patients who received study drug. A total of 20/49 (41%) patients discontinued because of failure to respond after 2 cycles of treatment and 9/49 (18%) discontinued due to disease progression. Of the 3 patients who were discontinued by the investigator, 2 were to receive a transplant. Therefore a total of 6 (12%) patients were discontinued to receive transplant.

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Table 18: Reason for Discontinuation

Termination Reason	ITT Patients (N=49)	
	n	%
Investigator Decision	3	6.1
Refused Further Treatment	3	6.1
Adverse Event or Treatment Toxicity	1	2.0
Failure to Achieve Response after 2 Courses	20	40.8
Disease Progression	9	18.4
Patient Scheduled to Receive Transplant	4	8.2
Death:		
Malignant Disease	1	2.0
Adverse Event	3	6.1
Other	3	6.1
Not Available	2	4.1

Protocol Deviations

Multiple patients received steroid treatment per investigator decision. The protocol excluded steroid treatment. As these patients likely had received steroids multiple times in the past the FDA disregarded this protocol deviation.

Demographic and Other Baseline Characteristics

Patient demographics and performance status are recorded in **Table 19**.

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Table 19: CLO-212 Demographics and Performance Status

Variable	ITT Patients (N=49)	
Age (years):	Mean	12.18
	Median	12
	Minimum	1
	Maximum	20
Age Category	0 to ≤2	3 (6.1%)
	>2 to ≤12	22 (44.9%)
	>12to<16	11 (22.4%)
	>16 to ≤22	13 (26.5%)
Sex:	Female	20 (40.8%)
	Male	29 (59.2%)
Ethnicity:	Caucasian	20 (40.8%)
	Hispanic	20 (40.8%)
	Other	3 (6.1%)
	Black	6 (12.2%)
Karnofsky Grade	n	%
100	15	30.6
90	12	24.5
80	7	14.3
70	8	16.3
60	4	8.2
50	2	4.1
Not assessed	1	2.0

ALL Subtype

A subtype analysis showed that 20/49 (41%) patients had subtype L1 and 12/49 (25%) had subtype L2. The subtype was not known for 17/49 (35%) patients. Analysis showed that 32/49 (65%) patients had a pre-B cell phenotype; 9/49 (18%) had B cell; 5/49 (10%) had T cell/pre-T cell; and 3 (6%) were unknown.

Each of the patients had received at least 2 prior regimens. The median number of prior regimens (**Table 20**) was 3 (range: 2 to 6).

Table 20: Prior Regimens

Number of Prior Regimens	ITT Patients (N=49)	
	n	%
2	17	34.7
3	17	34.7
4	12	24.5
5	1	2.0

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6	2	4.1
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Prior transplants are shown in **Table 21**.

Table 21: Prior Transplants

Number of Prior Transplants	ITT Patients (N=49)	
	n	%
0	34	69.4
1	13	26.5
2	2	4.1

Efficacy Evaluation

All responses are per IRRP determination and have been confirmed by the FDA. **Table 22** summarizes the best objective response rates.

Table 22: Objective Responses

Response Category	N=49	
	n	%
Complete Remission (CR)	6	12.2
Complete Remission Without Total Platelet Recovery (CRp)	4	8.2
Partial Remission (PR)	5	10.2
Treatment Failure	26	53.1
Not Evaluable	8	16.3
Overall Remission (CR + CRp)*	10	20.4
CR+CRp+PR	15	30.6

*95% Confidence Interval for Independent Panel Response Rate of Overall Remission (CR + CRp): (0.10, 0.34)

Table 23 indicates the FDA reviewer's response summary. This table includes disease history including time to relapse from prior therapies. The single asterisk indicates the number of months on the treatment immediately preceding entry into the clofarabine study. As indicated 3 of the responders had a prior stem cell transplant. Only one clofarabine treated patient had a confirmed response (second marrow \geq 21 days after the initial response was demonstrated). Response duration (days) and time from initiation of clofarabine treatment to disease progression or death are also indicated. Response duration and TTP, for patients with CR, CRp or PR, was censored at the date of the last bone marrow evaluation.

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Table 23: CLO-212 FDA Response Summary

Patient	007-0018	014-0030	006-0047	018-0036	009-0045	014-0049	009-0024	009-0028	012-0014	014-0040	010-0042	004-0025	006-0003	006-0004	014-0007
Time to 1st relapse (mo)	22	86	1	30	53	53	2	25	31	3	50	11	19	8	28
Time to 2nd relapse (mo)	2	35	3	10	48*	31	4*	25*	1	3	4*	6	1	4*	1
Time to 3 rd or later relapse (mo)	1*	18*	1, 1*	2, 31*	-	68*	-	-	1, 1, 2, 1*	1*	-	2, 1*	1, 1*	-	8*
Stem cell transplant (Yes or No)	N	Y (2)	N	Y (2)	N	N	Y	Y	N	N	N	Y	N	Y	Y
Stem cell transplant resp dur (mo)	-	27, 10	-	6, 29	-	-	2	20	-	-	-	4	-	2	3
Clofarabine response	CR	CR	CR	CR	CR	CR	CRp	CRp	CRp	CRp	PR	PR	PR	PR	PR
Clofar response confirmed (Y or N)	N	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y
Clofar response duration (days)**	43	160+	50	82	57+	93+	237	77	142+	32	55+	21	16	7	56+
Clofarabine TTP or death (days)**	143	216+	76	108	82+	110+	259	96	168+	64	68+	46	44	21	77+
Post-clofarabine SCT (Y or N)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	N	Y
Current status (Alive or Dead)	D	A	A	A	A	A	A	A	D	D	A	D	D	D	D
Post-clofarabine OS (w)	58.6	32.7+	10.4+	28.3+	17.6+	16.3+	63.1+	44.0+	42.0	9.1	22.9+	18.1	36.3	7.0	29.7

* response duration for treatment immediately preceding clofarabine treatment

** censored at the time of the last bone marrow evaluation

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Table 24 summarizes the Kaplan-Meier medians for survival.

Table 24: CLO 212 Survival (weeks)

Response Category	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored
CR	6	58.6	.	.	10.4	58.6	83.3
CRp	4	42.0	9.1	.	9.1	63.1	50.0
PR	5	29.7	7.0	36.3	7.0	36.3	20.0
Treatment Failure/Not Evaluable	34	7.4	6.3	11.7	0.9	40.1	8.8
Overall Remission(CR+CRp)	10	58.6	42.0	.	9.1	63.1	70.0
Remission(CR+CRp+PR)	15	42.0	29.7	.	7.0	63.1	53.3
All Patients	49	11.7	7.1	18.4	0.9	63.1	22.4

Reasons for discontinuation of clofarabine treatment are summarized in Table 25.

Table 25: CLO-212 Responder reasons for discontinuation

Patient	IRRP Determination of Response	Alive at Last Follow-Up	Reason for Discontinuation		
			Progressive Disease	AE	Transplant
007-0018	CR	N		X	
014-0030	CR	Y			
018-0036	CR	Y	X		
009-0045	CR	Y			X
006-0047	CR	Y	X		
014-0049	CR	Y			
012-0014	CRp	N			X
009-0024	CRp	Y			X
009-0028	CRp	Y	X		X
014-0040	CRp	N		X	
006-0003	PR	N	X		
006-0004	PR	N		X	
014-0007	PR	N			X
004-0025	PR	N	X		
010-0042	PR	Y			X

Post-Treatment Transplant

Table 26 summarizes the 7/49 (14%) patients who went on to receive a bone marrow transplant or PBSCT after treatment with clofarabine. As indicated all patients except one was a CR, CRp or PR. Patient 014-0029 was non-evaluable because of a poor quality bone marrow. He had received 3 prior induction chemotherapy regimens and 1 prior

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transplant. While having failed his initial treatment and achieving only a short duration PR (1 month) on his second treatment he subsequently had a 12 month remission with chemotherapy plus transplant. He started clofarabine on 16 June 2003 with 93% blasts and received 2 cycles of clofarabine. On 24 July 2003 to receive a transplant. His TTP post-transplant was 5.4 weeks. His post-transplant survival was 29.7+ weeks, and his overall survival was 40.1+ weeks.

Table 26: CLO 212 Bone Marrow or Stem Cell Transplant

Site-Patient Number	Total Cycles	Response (IRRP)	Survival (weeks)
009-0024	3	CRp	63.1+
009-0028	3	CR	44.0+
012-0014	2	CRp	42.0
014-0007	2	PR	29.7
014-0029	2	NE	16.0+
009-0045	2	CR	17.6+
010-0042	2	PR	22.9+

D. Efficacy Conclusions

The patient population studied is a difficult population to evaluate. Patients had failed several prior treatment regimens and had often failed one or more bone marrow or stem cell transplants. In this multiply resistant population it is difficult to demonstrate efficacy. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In the present study (CLO-212) there were 6 CR's, 4 CRp's and 5 PR's among 49 treated patients. Among the 6 CR patients 3 had ongoing responses at the time of data cutoff and 3 had relapsed. Two of the relapsing patients appeared to benefit from clofarabine treatment. Patient 007-0018 had a longer TTP with clofarabine than to her 2 prior regimens (146 days versus 30 and 60 days, respectively). Patient 006-0047 also had a longer TTP with clofarabine than to his 2 prior regimens (76 days versus 30 and 30 days, respectively). Neither of these patients had a pre-clofarabine transplant. Clofarabine TTP was shorter than was TTP with the treatment immediately preceding entry into study CLO-212 (~ 3.6 months for clofarabine versus 31 months for prior therapy) for patient 018-0036.

The 3 CR's with ongoing responses have too short a follow-up to evaluate benefit from clofarabine treatment.

Three of the 4 of the CRp patients (009-0024, 012-0014 and 014-0040) have longer TTP to clofarabine treatment than they had to their prior chemotherapy regimens. One of these patients (009-0024) had a pre-clofarabine transplant with a TTP of 4 months and two (009-0024 and 012-0014) had post-clofarabine transplants.

Among the 5 PR's one patient (010-0042) is alive and has an ongoing response which, to-date, is briefer in duration than his pre-clofarabine response duration. This patient has

also received a transplant. Three PR's who were not transplanted had relatively brief TTP (21, 44 and 48 days) and a fifth PR, who received a transplant has died with a TTP of 77+ days (based on last bone marrow examination).

Using the above evaluation criteria benefit was demonstrated in 2 of 6 CR patients, 3 of 4 CRp patients and 0 of 5 PR patients. With further follow-up benefit may be demonstrated in 3 additional CR patients and 1 PR patient.

Expert advice is being sought as to the meaningfulness of these results.

Summary of Other Clinical Studies

ID99-383, Phase I Study of CL-F-Ara-A (Clofarabine) in Pediatric Patients with Hematologic Malignancies

This Phase I study was conducted at MDACC from 23 August 2000 to 22 June 2002. The primary objective of this study was to determine the MTD and toxicity profile of clofarabine administered by IVI over 1 to 3 hours each day for 5 consecutive days in pediatric patients with hematologic malignancies. Secondary objectives were to analyze the pharmacologic profile, including metabolism of clofarabine in circulating leukemic cells and mononuclear cells during therapy; to quantitate the effects of treatment on deoxynucleotide levels, rate of DNA synthesis, and stability of DNA in these cells; and to seek correlation between these parameters and clinical response. Initially, clofarabine was administered by IVI over approximately 1 hour for 5 consecutive days; however, infusion times were increased to 2 hours and up to 3 hours if necessary to control infusion-related adverse events including agitation, chest tightness, depressed level of consciousness, dermatitis NOS, diarrhea NOS, dyspnea NOS, dystonia, fatigue, feeling abnormal, irritability, muscle twitching, maculopapular rash, nausea, palmar-plantar erythrodysesthesia syndrome, pruritus NOS, somnolence, skin disorder NOS, and vomiting NOS. Similarly, the time between cycles was increased from 2 to 4 weeks to 2 to 6 weeks depending on toxicity and response. Patients were to receive up to 2 cycles of therapy beyond the best response or a maximum of 12 cycles. Patients who failed to achieve a response after 2 cycles were to be discontinued from the study. Patients 21 years or younger diagnosed with refractory leukemia or lymphoma who were not candidates for treatment of higher efficacy or priority were eligible for enrollment. Patients were not to have received chemotherapy, immunotherapy, or radiotherapy for 2 weeks before entering this study and were to have recovered from the toxic effects of that therapy, except for patients with leukemia who were allowed to start treatment with the study drug if life-threatening increases in leukemia cell burden occurred during the 2-week period. All patients were to have a Zubrod performance status no greater than 2 and must have had adequate liver function (bilirubin ≤ 2 mg%) and renal function (creatinine ≤ 1.5 mg%). Pregnant and lactating females were not eligible. Although up to 50 patients were planned, the study was closed after 25 patients were treated because the investigator determined the DLT (grade 4 hyperbilirubinemia and grade 3 maculopapular rash) and the MTD (52 mg/m²/day) for this patient population. Of the 25 patients, 15 (60%) were male, 10 (40%) were female, most were either Caucasian (13/25 [52%]) or Hispanic

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(9/25 [36%]), the median age was 12 years (range: 1 to 19 years), and 17 were diagnosed with ALL, and 8 were diagnosed with AML. All patients received at least 1 cycle (range: 1 to 8 cycles) of clofarabine at doses of 11.25, 30, 40, 52, or 70 mg/m². More than half of the patients received 52 mg/m². One patient received an escalated dose due to improvement and no toxicity, and 11 patients required dose reductions or dose delays, and/or increased infusion times.

Using MDACC response criteria 8/25 (32%) of the patients achieved either a CR (5/25 [20%]) or PR (3/25 [12%]). Of the 5 patients who had CR, 4 were diagnosed with ALL and received doses of 30 mg/m² (n=1), 40 mg/m² (n=2), and 70 mg/m² (n=1); 1 patient was diagnosed with AML and received 52 mg/m². Among the 3 patients who achieved a PR, 2 were diagnosed with AML and received 40 mg/m² and 1 was diagnosed with ALL and received 52 mg/m².

ILEX convened an Independent Response Review Panel (IRRP) on 10 March 2003 to perform a separate analysis of the 5 patients who achieved a CR. The IRRP applied modified Children's Oncology Group (COG) response criteria for this analysis, the same criteria used in CLO-212 and CLO-222. Of the 4 ALL patients categorized by MDACC as CRs, 2 were categorized as CRs and 2 were categorized as PRs by the IRRP. All 4 patients proceeded to receive a transplant. The 1 AML patient categorized by MDACC as a CR was assessed as a CRp by the IRRP.

Of the 25 patients, 10 (40%) discontinued due to disease progression. Six (24%) discontinued to receive a bone marrow transplant, 3 (12%) died due to an adverse event secondary to their disease, 2 (8%) patients refused further treatment, 1/25 (4%) patient each discontinued due to investigator decision, an adverse event, failure to achieve a response after 2 courses of treatment, and "other" (failure to achieve a response after 3 courses of treatment).

Adverse events and laboratory toxicities were graded according to the NCI CTC, version 2.0 (30 April 1999). Drug-related adverse events reported for >20% of the patients included vomiting NOS, nausea, pruritus NOS, diarrhea NOS, and mucosal inflammation NOS. Drug-related grade 3 or 4 adverse events included nausea, vomiting NOS, diarrhea NOS, febrile neutropenia, bone marrow depression NOS, convulsions NOS, dyspnea NOS, feeling abnormal, headache NOS, Herpes zoster, hyperbilirubinemia, increased ALT and AST, maculopapular rash, post procedural hemorrhage, and skin disorder NOS; none of which were reported by more than 10% of the patients overall. The most frequently reported drug-related SAEs were nausea and vomiting. One patient with ALL discontinued due to an adverse event of grade 4 hyperbilirubinemia. Five patients died within 30 days of the last dose of clofarabine due to progressive disease or adverse events secondary to the patients' disease. Although infections were prevalent among the patients in this study, only 1 was considered to be drug related. As expected, significant myelosuppression, defined as grade 3 or 4 anemia, neutropenia, and thrombocytopenia was observed during the study in all patients. Occurrences of grade 3 or 4 hyperbilirubinemia, hypercalcemia, elevated creatinine, elevated SGPT, hypoalbuminemia, and hypocalcemia were reported in the higher dose groups (40, 52, or

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70 mg/m²). Occurrences of grade 3 hyperuricemia and hyperglycemia and grade 3 or 4 hypophosphatemia did not appear to be dose related. Two patients treated with clofarabine 70 mg/m², experienced a DLT. One patient with ALL discontinued from the study due to grade 4 hyperbilirubinemia that started within 2 days of starting treatment and lasted more than 30 days. One patient with ALL experienced grade 3 maculopapular rash during the first cycle that resulted in a dose reduction from 70 mg/m² to 52 mg/m².

Pharmacokinetic data were available for 12/25 (48%) patients. Plasma clofarabine concentrations increased with increasing dose. Maximal concentrations were observed at the end of infusion and remained quantifiable 24 hours after the start of the infusion. Intracellular clofarabine triphosphate concentrations were correlated with plasma clofarabine concentrations but were many- fold higher on a per mL basis. Intracellular clofarabine triphosphate concentrations increased with increasing dose, were highest at the end of infusion, and remained quantifiable 24 hours after the start of infusion.

Emergency Expanded Access Program

Patients were offered clofarabine as part of an emergency expanded access program (EEAP) if they were not eligible for the studies approved by the FDA under ILEX IND 63,641. Treating physicians were required to obtain an Investigator IND before clinical trial material was supplied to the individual clinical sites. No protocols were written for this program; however, copies of the FDA-approved clofarabine protocols and the clofarabine Investigator's Brochure were provided to the treating physician as a reference for treatment. Case report forms were not required for this program; however, treating physicians were asked to provide ILEX with response and safety information for each patient who was treated in this program.

As of 30 April 2004, 11 pediatric patients had been enrolled and 10 had been treated in this program. Of the 10 pediatric patients treated in the EEAP, 4 had ALL (3 females, 1 male, ages 9 to 19 years) and 6 had AML (2 females, 4 males, ages 4 to 21 years). The pediatric patients were treated in accordance with ILEX's CLO-212 and CLO-222 protocols.

Response information has been received for 4 of the 10 treated pediatric patients. Of the 4 ALL patients, 1 achieved a CR and proceeded to transplant, 1 achieved a PR, and 1 has experienced some benefit as indicated by a reduced blast count. Of the 6 AML patients, 2 patients responded, however, specific information regarding the level of response has not yet been submitted.

VII. Integrated Review of Safety

The ISS includes new and updated data from pediatric clinical trial patients and updated adult SAE data through 30 April 2004. All clinical trials were conducted in the United States. As of 30 April 2004, a total of 113 unique pediatric patients with ALL or AML participated in clinical trials (Table 4).

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A. Brief Statement of Conclusions

The principal clofarabine toxicities were nausea and vomiting, hematologic toxicity, fever and febrile neutropenia, hepatobiliary toxicity, infections and renal toxicity. Clofarabine can produce systemic inflammatory response syndrome/ capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. With attentive patient care, however, clofarabine was tolerable.

B. Description of Patient Exposure Per Sponsor

Maximum Daily Dose of Clofarabine

The majority of pediatric patients (85%, 96/113) received a maximum daily dose of clofarabine 52 mg/m². Fourteen patients overall (7 ALL, 7 AML, received a maximum daily dose of clofarabine less than 52 mg/m² (ie, a maximum daily dose ranging from 11.25 mg/m² to 40 mg/m²). Three patients received a maximum daily dose greater than 52 mg/m² (1 AML patient received 56 mg/m²/day, and 2 ALL patients received 70 mg/m²/day).

Number of Cycles of Treatment

Most of the pediatric patients (60% overall; 64% ALL, 54% AML) received at least 2 cycles of treatment with clofarabine (Table 27).

Total Exposure to Clofarabine

The median total exposure to clofarabine for one treatment cycle was 300 mg (292 mg for ALL patients and 300 mg for AML patients). The median total exposure to clofarabine (ie, total median milligrams administered) by cycle is presented in Table 27.

Table 27: Median Total Exposure to Clofarabine by Cycle

Cycle	ALL		AML		ALL/AML	
	N	Median Total mg Clofarabine	N	Median Total mg Clofarabine	N	Median Total mg Clofarabine
1	67	350.0	46	309.0	113	340.0
2	43	275.5	25	328.0	68	282.5
3	15	250.0	9	275.0	24	255.0
4	3	185.0	4	180.0	7	185.0
5	2	222.5	2	195.0	4	222.5
6	1	185.0	1	380.0	2	282.5
7	1	185.0	1	300.0	2	242.5
8	1	180.0	1	225.0	2	202.5

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C. Methods and Specific Findings of Safety Review

Concurrent Conditions

Concurrent conditions at baseline in at least 10% of the 113 pediatric patient database overall are shown in **Table 28**. A total of 98% of pediatric patients overall (99% ALL, 100% AML) had at least one concurrent condition at baseline.

Table 28: Concurrent Conditions at Baseline

Concurrent Conditions	Overall ALL/AML (N=113)									
	Total		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%	n	%
Total Patients with Concurrent Conditions at Baseline	111	98.2	13	11.5	43	38.1	42	37.2	13	11.5
Alopecia	60	53.1	12	10.6	48	42.5				
Tachycardia NOS	31	27.4	24	21.2	3	2.7	3	2.7	1	0.9
Fatigue	28	24.8	21	18.6	7	6.2				
Pyrexia	25	22.1	12	10.6	8	7.1	5	4.4		
Nausea	25	22.1	10	8.8	14	12.4	1	0.9		
Anorexia	23	20.4	8	7.1	7	6.2	3	2.7	5	4.4
Vomiting NOS	22	19.5	14	12.4	8	7.1				
Headache NOS	19	16.8	10	8.8	9	8.0				
Anxiety NEC	19	16.8	6	5.3	13	11.5				
Cough	16	14.2	12	10.6	4	3.5				
Diarrhea NOS	15	13.3	12	10.6	3	2.7				
Constipation	15	13.3	10	8.8	5	4.4				
Depression NEC	15	13.3	8	7.1	7	6.2				
Abdominal Pain NOS	14	12.4	8	7.1	5	4.4	1	0.9		
Bone Pain	14	12.4	3	2.7	9	8.0	2	1.8		
Hypertension NOS	12	10.6	2	1.8	1	0.9	9	8.0		

Concurrent Infections

In the updated database a total of 47% of pediatric patients overall (48% ALL, 46% AML) had 1 or more concurrent infections at baseline. The most frequent concurrent infection of any grade was sinusitis NOS (8% overall; 6% ALL, 11% AML).

In the distribution of concurrent infections according to grade (where a patient with multiple events is counted only once and for the event with the highest grade), 20% of pediatric patients overall (24% ALL, 15% AML) had at least one grade 1 infection, 16% (10% ALL, 24% AML) had at least one grade 2 infection, 10% (12% ALL, 7% AML) had at least one grade 3 infection, and 1% (2% ALL, 0% AML) had at least one grade 4 infection. In the ALL and AML subgroups each of the grade 3 concurrent infections were reported for 1 patient each, and the only grade 3 concurrent infection present in both subgroups was staphylococcal infection NOS. Grade 3 concurrent infections in ALL patients included fungal infection NOS, pneumonia NOS, pneumonia Aspergilla,

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bacteremia, enterococcal bacteremia, infection NOS, osteomyelitis salmonella, pneumonia bacterial NOS, pseudomonas infection NOS, sepsis NOS, septicemia staphylococcal, and staphylococcal infection NOS. Grade 3 concurrent infections in AML patients included bacterial infection NOS, staphylococcal infection NOS, and streptococcal infection NOS.

Only 1 patient (with ALL) had a grade 4 concurrent infection at baseline (pneumonia NOS).

AE's

An overall summary of AEs is presented in **Table 29**. 112 of 113 pediatric patients experienced at least one AE during treatment with clofarabine.

Table 29: Adverse Events Summary

Adverse Event Reports	ALL (N=67)		AML (N=46)		ALL/AML (N=113)	
	0	%	0	%	0	%
Patients with at least one AE	66	98.5	46	100.0	112	99.1
Patients with drug-related AEs	65	97.0	46	100.0	111	98.2
Patients with at least one SAE	51	76.1	43	93.5	94	83.2
Patients with drug-related SAEs	37	55.2	30	65.2	67	59.3
Patients discontinued due to AEs	2	3.0	2	4.3	4	3.5
Patients discontinued due to drug-related AEs	2	3.0	2	4.3	4	3.5
Patients who died within 30 days of last dose	16	23.9	10	21.7	26	23.0
Patients who died due to drug-related AEs	3	4.5	1	2.2	4	3.5
Severity of AEs according to NCI CTC grade:	66	98.5	46	100.0	112	99.1
Grade 1
Grade 2	3	4.5	1	2.2	4	3.5
Grade 3	35	52.2	25	54.3	60	53.1
Grade 4	16	23.9	10	21.7	26	23.0
Grade 5	12	17.9	10	21.7	22	19.5

Table 30 presents AEs by MedDRA preferred term that were reported by at least $\geq 5\%$ of pediatric patients overall by NCI CTC grade.

*Appears This Way
On Original*

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Table 30: AE's in ≥ 5% of Pediatric Patients by CTC Toxicity Grade

Preferred Term	ALL/AML (N=113)											
	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	%	n	%	n	%	n	%	n	%	n	%
Total Patients with Adverse Events	112	99.1			4	3.5	60	53.1	26	23.0	22	19.5
Vomiting NOS	94	83.2	24	21.2	59	52.2	10	8.8	1	0.9		
Nausea	82	72.6	10	8.8	54	47.8	17	15.0	1	0.9		
Febrile Neutropenia	67	59.3			1	0.9	61	54.0	5	4.4		
Diarrhea NOS	59	52.2	31	27.4	17	15.0	11	9.7				
Headache NOS	54	47.8	25	22.1	23	20.4	6	5.3				
Pruritis NOS	54	47.8	21	18.6	32	28.3	1	0.9				
Pyrexia	45	39.8	11	9.7	17	15.0	17	15.0				
Dermatitis NOS	43	38.1	15	13.3	21	18.6	7	6.2				
Fatigue	42	37.2	22	19.5	16	14.2	3	2.7	1	0.9		
Rigors	42	37.2	25	22.1	14	12.4	3	2.7				
Abdominal Pain NOS	41	36.3	19	16.8	14	12.4	8	7.1				
Tachycardia NOS	36	31.9	19	16.8	11	9.7	6	5.3				
Anorexia	34	30.1	11	9.7	11	9.7	5	4.4	7	6.2		
Petechiae	34	30.1	17	15.0	10	8.8	7	6.2				
Epistaxis	33	29.2	16	14.2	1	0.9	16	14.2				
Pain In Limb	33	29.2	12	10.6	15	13.3	6	5.3				
Hypotension NOS	31	27.4	2	1.8	9	8.0	12	10.6	8	7.1		
Anxiety NEC	26	23.0	10	8.8	14	12.4	2	1.8				
Cough	25	22.1	20	17.7	5	4.4						
Constipation	24	21.2	11	9.7	13	11.5						
Erythema NEC	21	18.6	16	14.2	5	4.4						
Mucosal Inflammation NOS	21	18.6	10	8.8	8	7.1	3	2.7				
Pain NOS	20	17.7	3	2.7	9	8.0	7	6.2	1	0.9		
Flushing	19	16.8	19	16.8								
Edema NOS	19	16.8	3	2.7	13	11.5	1	0.9	2	1.8		
Hematuria	17	15.0	11	9.7	4	3.5	2	1.8				
Depression NEC	16	14.2	7	6.2	8	7.1	1	0.9				
Gingival Bleeding	16	14.2	6	5.3	2	1.8	7	6.2	1	0.9		
Appetite Decreased NOS	15	13.3	10	8.8	5	4.4						
Arthralgia	15	13.3	3	2.7	9	8.0	3	2.7				
Dizziness (Exc Vertigo)	15	13.3	12	10.6	3	2.7						
Dyspnea NOS	15	13.3	3	2.7	3	2.7	5	4.4	4	3.5		
Herpes Simplex	15	13.3	3	2.7	6	5.3	6	5.3				
Hypertension NOS	15	13.3	4	3.5	5	4.4	6	5.3				
Jaundice NOS	15	13.3	8	7.1	5	4.4	2	1.8				

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**Table 30 AE's in $\geq 5\%$ of Pediatric Patients Overall by CTC Toxicity Grade
(continued)**

Preferred Term	ALL/AML (N=113)											
	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	%	n	%	n	%	n	%	n	%	n	%
Myalgia	15	13.3	7	6.2	7	6.2	1	0.9				
Sepsis NOS	15	13.3					7	6.2	3	2.7	5	4.4
Sore Throat NOS	15	13.3	13	11.5	2	1.8						
Back Pain	14	12.4	4	3.5	7	6.2	3	2.7				
Contusion	14	12.4	10	8.8	3	2.7	1	0.9				
Hepatomegaly	14	12.4	6	5.3			8	7.1				
Injection Site Pain	14	12.4	7	6.2	6	5.3	1	0.9				
Irritability	14	12.4	10	8.8	3	2.7	1	0.9				
Weight Increased	14	12.4	7	6.2	6	5.3	1	0.9				
Cellulitis	13	11.5	1	0.9	2	1.8	10	8.8				
Insomnia NEC	13	11.5	9	8.0	4	3.5						
Oral Candidiasis	13	11.5	5	4.4	6	5.3	2	1.8				
Respiratory Distress	13	11.5			2	1.8	6	5.3	4	3.5	1	0.9
Transfusion Reaction	13	11.5	4	3.5	5	4.4	4	3.5				
Palmar-Plantar Erythro- dysesthesia Syndrome	12	10.6	3	2.7	5	4.4	4	3.5				
Pleural Effusion	12	10.6	4	3.5	3	2.7	3	2.7	2	1.8		
Staphylococcal Infection NOS	12	10.6			2	1.8	10	8.8				
Bone Pain	11	9.7	2	1.8	5	4.4	4	3.5				
Dry Skin	11	9.7	6	5.3	4	3.5	1	0.9				
Lethargy	11	9.7	8	7.1	3	2.7						
Pneumonia NOS	11	9.7	3	2.7			5	4.4	2	1.8	1	0.9
Rash Pruritic	11	9.7	2	1.8	7	6.2	2	1.8				
Somnolence	11	9.7	8	7.1	2	1.8	1	0.9				
Weakness	11	9.7	3	2.7	5	4.4	2	1.8	1	0.9		
Abdominal Distension	10	8.8	5	4.4	2	1.8	3	2.7				
Bacteremia	10	8.8					10	8.8				
Dehydration	10	8.8	2	1.8	7	6.2	1	0.9				
Neutropenia	10	8.8					3	2.7	7	6.2		
Tremor NEC	10	8.8	9	8.0	1	0.9						
Cardiac Murmur NOS	9	8.0	9	8.0								
Face Edema	9	8.0	5	4.4	4	3.5						
Hematoma NOS	9	8.0	8	7.1			1	0.9				
Rash Maculo-Papular	9	8.0	3	2.7	3	2.7	2	1.8	1	0.9		
Septic Shock	9	8.0					1	0.9	5	4.4	3	2.7
Tachypnea	9	8.0	2	1.8	2	1.8	4	3.5	1	0.9		
Abdominal Pain Upper	8	7.1	5	4.4	2	1.8	1	0.9				
Chest Pain NEC	8	7.1	3	2.7	4	3.5	1	0.9				
Conjunctival Hemorrhage	8	7.1	5	4.4	2	1.8	1	0.9				

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**Table 30 AE's in $\geq 5\%$ of Pediatric Patients Overall by CTC Toxicity Grade
(continued)**

Preferred Term	ALL/ AML (N=113)											
	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	%	n	%	n	%	n	%	n	%	n	%
Ecchymosis	8	7.1	4	3.5	1	0.9	2	1.8	1	0.9		
Hallucination NOS	8	7.1	3	2.7			5	4.4				
Lip Dry	8	7.1	8	7.1								
Splenomegaly	8	7.1	3	2.7	1	0.9	4	3.5				
Abdominal Tenderness	7	6.2	4	3.5	2	1.8			1	0.9		
Agitation	7	6.2	1	0.9	4	3.5	2	1.8				
Colitis Pseudomembranous	7	6.2			3	2.7	4	3.5				
Dyspepsia	7	6.2	6	5.3	1	0.9						
Fungal Infection NOS	7	6.2	1	0.9			5	4.4	1	0.9		
Hematemesis	7	6.2	2	1.8	1	0.9	4	3.5				
Herpes Zoster	7	6.2			2	1.8	5	4.4				
Hypersensitivity NOS	7	6.2	2	1.8	1	0.9	4	3.5				
Implant Infection	7	6.2	1	0.9	2	1.8	3	2.7	1	0.9		
Loose Stools	7	6.2	5	4.4	2	1.8						
Mouth Ulceration	7	6.2	4	3.5	2	1.8	1	0.9				
Nasal Congestion	7	6.2	6	5.3	1	0.9						
Neck Pain	7	6.2	4	3.5	3	2.7						
Pericardial Effusion	7	6.2	4	3.5	2	1.8			1	0.9		
Proteinuria Present	7	6.2	3	2.7	2	1.8	2	1.8				
Renal Failure Acute	7	6.2	1	0.9	3	2.7	2	1.8	1	0.9		
Skin Disorder NOS	7	6.2	2	1.8	3	2.7	2	1.8				
Skin Hyperpigmentation	7	6.2	6	5.3	1	0.9						
Staphylococcal Bacteremia	7	6.2					6	5.3	1	0.9		
Candidal Infection NOS	6	5.3	2	1.8	3	2.7	1	0.9				
Malaise	6	5.3	4	3.5	1	0.9	1	0.9				
Multi-Organ Failure	6	5.3									6	5.3
Edema Peripheral	6	5.3	3	2.7	3	2.7						
Rhinorrhea	6	5.3	6	5.3								
Tumor Lysis Syndrome	6	5.3					6	5.3				
Vision Blurred	6	5.3	4	3.5	2	1.8						

As summarized in Table 31 the majority of pediatric patients (96% overall; 94% ALL and 98% AML) had at least one AE with a maximum severity of $>$ grade 3 according to the investigator. A total of 60/113 (53%) of the pediatric population overall (52% ALL, 54% AML) had at least 1 grade 3 AE and 23% overall (24% ALL, 22% AML) had at least 1 grade 4 AE. A total of 20% of pediatric patients overall (18% ALL, 22% AML) had at least 1 AE that contributed to death,

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Table 31: Adverse Events in Pediatric Patients by Maximum CTC Grade

Maximum NCI Toxicity Grade	ALL N=67		AML (N=46)		ALL/AML (N=113)	
	n	%	n	%	n	%
Grade 1
Grade 2	3	4.5	1	2.2	4	3.5
Total grade 3, 4, and 5	63	94.0	45	97.8	108	95.6
Grade 3	35	52.2	25	54.3	60	53.1
Grade 4	16	23.9	10	21.7	26	23.0
Grade 5	12	17.9	10	21.7	22	19.5

Grades were assigned by the investigator according to the NCI Common Toxicity Criteria Version 2.0. For AEs not included in this rating system, the investigator was asked to judge the severity of the AE according to the following scale: 1 =mild, 2=moderate, 3=severe, 4=life threatening or disabling, 5=death. Grade was missing for 1 AE for 1 AML patient. Patients with multiple AEs are counted once, for the AE with the highest grade reported.

All but 2 pediatric patients (98% of the total population) experienced at least 1 AE the investigator considered related to study drug. The drug-related AEs most frequently reported by pediatric patients overall during treatment with clofarabine were vomiting NOS (66% ALL, 65% AML) and nausea (58% ALL, 70% AML). In addition to vomiting and nausea, drug- related AEs reported by at least 10% of pediatric patients overall included:

- Febrile neutropenia (31% ALL, 28% AML);
- Pyrexia (21% ALL, 26% AML);
- Pruritis NOS (24% ALL, 20% AML);
- Dermatitis NOS (24% ALL, 17% AML);
- Headache NOS (18% ALL, 35% AML);
- Diarrhea NOS (21% ALL, 22% AML);
- Anxiety NEC (16% ALL, 7% AML);
- Fatigue (15% ALL, 13% AML);
- Mucosal inflammation NOS (16% ALL, 15% AML);
- Flushing (12% ALL, 11% AML);
- Anorexia (12% ALL, 9% AML);
- Palmar-plantar erythrodysesthesia syndrome (12% ALL, 9% AML).

Grade 3 Adverse Events

A total of 53% of the pediatric population overall (52% ALL, 54% AML) had at least 1 grade 3 (severe) AE, regardless of relationship to study drug. Grade 3 AEs reported by at least 10% of pediatric patients overall included:

- Febrile neutropenia (51% ALL, 59% AML);
- Pyrexia (13% ALL, 17% AML);
- Epistaxis (10% ALL, 20% AML);

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- Nausea (15% ALL, 15% AML); and
- Hypotension NOS (10% ALL, 11% AML); and
- Diarrhea (9% ALL, 11% AML).

Approximately 80% of all reports of grade 3 diarrhea (9/11), 60% of all reports of grade 3 nausea (10/17), 50% of all reports of grade 3 febrile neutropenia (32/61) or pyrexia (9/17), 30% of all reports of grade 3 hypotension NOS (4/12), and 20% of all reports of grade 3 epistaxis (3/16) were considered by the investigator to be related to study drug.

Grade 4 Adverse Events

A total of 23% of pediatric patients overall (24% ALL, 22% AML) experienced at least 1 grade 4 (life threatening or disabling) AE, regardless of relationship to study drug. Grade 4 AEs reported by at least 2 pediatric patients overall included:

- Hypotension NOS (6% ALL, 9% AML);
- Febrile neutropenia (5% ALL, 4% AML);
- Anorexia (9% ALL, 2% AML);
- Septic shock (6% ALL, 2% AML);
- Neutropenia NOS (8% ALL, 4% AML);
- Sepsis NOS (3% ALL, 2% AML);
- Respiratory distress (6% ALL, 0% AML);
- Dyspnea NOS (2% ALL, 7% AML);
- Hyperbilirubinemia (3% ALL, 2% AML);
- Pleural effusion (3% ALL, 0% AML);
- Capillary leak syndrome (3% ALL, 0% AML);
- Metabolic acidosis (2% ALL, 2% AML);
- Hypokalemia (2% ALL, 2% AML);
- Disseminated intravascular coagulation (3% ALL, 0% AML);
- Respiratory failure (except neonatal) (3% ALL, 0% AML);
- Edema NOS (2% ALL, 2% AML);
- Pneumonia NOS (0% ALL, 4% AML).

The drug- related grade 4 AEs reported by at least 2 patients included neutropenia (6% overall, 8% ALL, 4% AML), anorexia (3% overall, 3% ALL, 0% AML), edema NOS (2% overall, 2% ALL, 2% AML), capillary leak syndrome (2% overall, 2% ALL, 0% AML), and hyperbilirubinaemia (3% overall, 3% ALL, 0% AML).

Grade 5 Adverse Events

A total of 20% of pediatric patients overall (16% ALL, 22% AML) had at least one grade 5 AE, regardless of relationship to study drug. These AEs included:

- Sepsis (5% ALL, 4% AML);

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- Multi- organ failure (8% ALL, 2% AML);
- Septic shock (0% ALL, 7% AML);
- Disease progression NOS (2% ALL, 2% AML);
- Pulmonary hemorrhage (2% ALL, 2% AML);
- Respiratory distress (2% ALL, 0% AML);
- Pneumonia NOS (2% ALL, 0% AML);
- Renal failure NOS (0% ALL, 2% AML);
- Cardiac arrest (2% ALL, 0% AML);
- Hepatocellular damage (2% ALL, 0% AML);
- Leukemia NOS (0% ALL, 2% AML);
- Respiratory failure (exc neonatal) (0% ALL, 2% AML);
- Acute myeloid leukemia NOS (0% ALL, 2% AML); and
- Cardio- respiratory arrest (0% ALL, 2% AML).

Only 3 patients (2% of pediatric patients overall) had a drug- related grade 5 AE. These AEs were hepatocellular damage and respiratory distress in 1 ALL patient, multi- organ failure and septic shock in 1 AML patient, and multi- organ failure in 1 ALL patient.

Other toxicities: Capillary Leak Syndrome, Systemic Inflammatory Response Syndrome, and Tumor Lysis Syndrome, Hypotension

A SIRS/capillary leak- like syndrome, manifested by the rapid onset of respiratory distress, hypotension, and multi- organ failure, has been associated with many oncolytics including cytarabine, and possibly cladribine. The pathophysiology of SIRS/capillary leak syndrome is not entirely understood. It may result from the release of cytokines and may also reflect either direct or indirect damage to endothelial cells. In addition, it is believed that patients with rapid tumor lysis may be at particular risk for SIRS/capillary leak syndrome.

Capillary leak syndrome, SIRS, or tumor lysis syndrome occurred in 10 pediatric patients overall (6 ALL, 4 AML). Patient 212- 004- 0031 (12- year- old male Hispanic, ALL) and Patient 212- 001- 0034 (15- year- old male Hispanic, ALL) died secondary to grade 4 capillary leak syndrome, and Patient 212-005- 0037 (17- year- old male Caucasian, ALL) experienced hepatic toxicities in addition to grade 3 capillary leak syndrome.

Tumor Lysis Syndrome Grade 3 tumor lysis syndrome was reported as an AE in 6 patients (3 ALL, 3 AML). Five of the events were considered by the investigator to be related to treatment with clofarabine.

Hypotension: Hypotension is a component of SIRS but it also may occur with other conditions such as sepsis, dehydration, etc. In the integrated database, 27% of patients overall; 25% ALL, 30% AML) experienced hypotension, and 18% overall (16% ALL, 20% AML had a grade 3 or grade 4 event of hypotension.

Deaths, Serious Adverse Events, and Other Significant Adverse Events

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Deaths

During the clofarabine pediatric development program, 26 patients (23%; 16 ALL, 10 AML) died on- study or within 30 days of the last dose of clofarabine. None of these patients died during or immediately after the infusion of clofarabine.

Twelve patients died from progressive disease, 4 of whom also experienced at least one AE that contributed to death: 383-001-004 (multi-organ failure), 212-014-0013 (hepatic disorder NOS and renal impairment NOS), 222-011-0028 (septic shock), and 212- 014-0050 (sepsis NOS).

Sepsis or septic shock contributed to the death of 7 patients, and renal impairment (reported as renal impairment NOS, renal failure NOS, or increased creatinine) was present in 3 patients who died (Patient 383-001-0016, Patient 212-014-0013 and Patient 212-006-0004). Multi-organ failure contributed to the death of 6 patients. Pulmonary hemorrhage, liver impairment (reported as hepatic disorder NOS or hepatocellular damage), or cardiac arrest each contributed to the death of 2 patients. Other causes of death in individual patients included acute vascular leak syndrome, hypotension, pulmonary edema, respiratory distress, and worsening pneumonia.

Four of the deaths were considered by the investigator to be related to treatment with clofarabine; 212-004 0031 died from drug-related acute vascular leak syndrome that contributed to cardiac arrest, 212-005-0037 died from drug- related respiratory failure and liver damage, 222-014-0029 died from septic shock and multi-organ failure, and 212-014-0040 died from multi-organ failure.

Serious Adverse Events

A total of 83% of pediatric patients overall (76% ALL, 94% AML) experienced at least one SAE. The majority of these SAEs were hospitalizations and/ or life- threatening conditions, which were not unexpected in this study population. Most (91 of 94 events) were grade 3 or higher, with 23% (22/ 94) of patients having at least one SAE that contributed to death.

The distribution of SAEs across the MedDRA SOCs was as expected for this study population. The most frequently affected MedDRA SOCs were Blood and Lymphatic System Disorders (60% overall; 55% ALL, 67% AML) and Infections and Infestations (55 % overall; 57% ALL, 52% AML). In addition, at least 5% of pediatric patients overall had an SAE in the following SOCs:

- General Disorders and Administration Site Conditions (21% ALL, 17% AML);
- Gastrointestinal Disorders (13% ALL, 28% AML);
- Respiratory, Thoracic, and Mediastinal Disorders (12% ALL, 17% AML);
- Vascular Disorders (9% ALL, 17% AML);
- Renal and Urinary Disorders (5% ALL, 9% AML);
- Hepato- Biliary Disorders (8% ALL, 4% AML); and

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- Nervous System Disorders (5% ALL, 11% AML).

Table 32 presents the SAEs that occurred in more than 1 pediatric patient overall by preferred term and severity grade. Serious adverse events occurring in at least 10% of patients overall included febrile neutropenia (46% ALL, 57% AML, pyrexia (10% ALL, 13% AML), hypotension NOS (9% ALL, 15% AML), and sepsis NOS (13% ALL, 13% AML).

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Table 32: SAE's in 2 or More Pediatric Patients Overall by NCI CTC Grade

Preferred Term	ALL/AML (N=113)											
	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	%	n	%	n	%	n	%	n	%	n	%
Total Patients with Serious Adverse Events	94	83.2			3	2.7	50	44.2	19	16.8	22	19.5
Febrile Neutropenia	57	50.4			1	0.9	53	46.9	3	2.7		
Sepsis NOS	15	13.3					7	6.2	3	2.7	5	4.4
Hypotension NOS	13	11.5			1	0.9	7	6.2	5	4.4		
Pyrexia	13	11.5	2	1.8	5	4.4	6	5.3				
Neutropenia	10	8.8					3	2.7	7	6.2		
Nausea	9	8.0			2	1.8	7	6.2				
Septic Shock	9	8.0					1	0.9	5	4.4	3	2.7
Vomiting NOS	9	8.0	1	0.9	2	1.8	6	5.3				
Bacteremia	7	6.2					7	6.2				
Pneumonia NOS	7	6.2	1	0.9			4	3.5	1	0.9	1	0.9
Staphylococcal Bacteremia	7	6.2					6	5.3	1	0.9		
Multi-Organ Failure	6	5.3									6	5.3
Respiratory Distress	6	5.3					3	2.7	2	1.8	1	0.9
Staphylococcal Infection	6	5.3					6	5.3				
Cellulitis	4	3.5					4	3.5				
Herpes Simplex	4	3.5			2	1.8	2	1.8				
Herpes Zoster	4	3.5			1	0.9	3	2.7				
Capillary Leak Syndrome	3	2.7					1	0.9	2	1.8		
Diarrhea NOS	3	2.7			1	0.9	2	1.8				
Disseminated Intravascular Coagulation	3	2.7					2	1.8	1	0.9		
Hyperbilirubinemia	3	2.7							3	2.7		
Infection NOS	3	2.7					2	1.8	1	0.9		
Proctalgia	3	2.7			1	0.9	2	1.8				
Renal Failure NOS	3	2.7					1	0.9	1	0.9	1	0.9
Tumor Lysis Syndrome	3	2.7					3	2.7				
Abdominal Pain NOS	2	1.8					2	1.8				
Alanine Aminotransferase Increased	2	1.8					2	1.8				
Aspartate Aminotransferase Increased	2	1.8					2	1.8				
Colitis Pseudomembranous	2	1.8					2	1.8				
Dehydration	2	1.8			1	0.9	1	0.9				
Disease Progression NOS	2	1.8									2	1.8
Dyspnea NOS	2	1.8							2	1.8		
Fungal Infection NOS	2	1.8					1	0.9	1	0.9		
Headache NOS	2	1.8					2	1.8				
Hypersensitivity NOS	2	1.8					2	1.8				
Pneumonia Fungal NOS	2	1.8					1	0.9	1	0.9		
Pulmonary Hemorrhage	2	1.8									2	1.8

Clinical Laboratory Evaluations.

Hematology

The majority of pediatric patients entered into the current studies were red blood cell- and/ or platelet transfusion-dependent. Also treatment was aimed at complete suppression of both normal and abnormal cellular elements. Therefore bone marrow toxicity is not considered in this review.

Biochemistry

Hepato-Biliary Toxicities

The liver is a known target organ of clofarabine toxicity, and hepato biliary toxicities were frequently observed in pediatric patients during treatment with clofarabine (**Table 32**).

Most patients experienced the onset or worsening of elevated AST (75% overall; 74% ALL, 77% AML) or ALT (76% overall; 79% ALL, 70% AML). The incidence of grade 3 or 4 AST shifted from 0% overall at baseline to 38% overall (37% ALL, 40% AML) post-baseline, and the incidence of grade 3 or 4 ALT shifted from 2% overall (2% ALL, 2% AML) at baseline to 44% overall (43% ALL, 44% AML) post- baseline.

A total of 46% of patients overall (46% ALL, 47% AML) experienced the onset or worsening of elevated total bilirubin during treatment with clofarabine. No patient had a grade 3 or 4 total bilirubin at baseline, while 15% overall (15% ALL , 16% AML) had a grade 3 or 4 total bilirubin post-baseline. The remainder of the post-baseline shifts to elevated levels (34 of 51) were to grade 1 or grade 2. Two patients discontinued treatment with clofarabine due to the onset of grade 4 hyperbilirubinemia.

A total of 23% of patients overall (28% ALL, 15% AML) experienced the onset or worsening of elevated alkaline phosphatase. No patient had grade 3 or 4 alkaline phosphatase at baseline, and only 1 patient (ALL) had post- baseline grade 3 or 4 alkaline phosphatase (specifically, grade 3 [Table 4.1.3]). The remainder of the post- baseline shifts to elevated levels (22 of 23) were to grade 1 or 2.

Elevations in AST and ALT were transient and typically of < 2 weeks duration. The majority of AST and ALT elevations occurred within 1 week of clofarabine administration and returned to baseline or \leq grade 2 within several days. Although less common, elevations in bilirubin appeared to be more persistent. Where follow- up data are available, bilirubin elevations took from 4 days to 32 days to return to baseline or \leq grade 2.

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Table 33: Hepato-biliary toxicities

Toxicity	Baseline				Post-Baseline								
	Class	n	%	n	%	Low	Normal	Grade					
								1	2	3	4		
Elevated SGOT (AST) (N=84)	Low"	1	1.2	1	1.2								
	Normal"	44	52.4	8	9.5	1	7	14	9	12	1		
	Grade 1	34	40.5	26	31.0		1	9	8	14	2		
	Grade 2	5	6.0	17	20.2			3		1	1		
	Grade 3			28	33.3								
	Grade 4			4	4.8								
Elevated SGPT (ALT) (N=110)	Low"												
	Normal"	56	50.9	13	11.8		11	15	12	16	2		
	Grade 1	43	39.1	26	23.6		2	11	10	17	3		
	Grade 2	9	8.2	23	20.9				1	6	2		
	Grade 3	2	1.8	41	37.3					2			
	Grade 4			7	6.4								
Elevated Alkaline Phosphatase (N=102)	Low"	6	5.9	13	12.7	5	1						
	Normal"	85	83.3	58	56.9	8	55	20	1	1			
	Grade 1	10	9.8	27	26.5		2	7	1				
	Grade 2	1	1.0	3	2.9				1				
	Grade 3			1	1.0								
	Grade 4												
Elevated Total Bilirubin (N=112)	Low"	6	5.4	9	8.0	3	1	1	1				
	Normal"	102	91.1	50	44.6	6	48	17	15	12	4		
	Grade 1	3	2.7	20	17.9			2		1			
	Grade 2	1	0.9	16	14.3		1						
	Grade 3			13	11.6								
	Grade 4			4	3.6								

Cardiac evaluation

Significant cardiac toxicity was observed in rat toxicology studies. Because of possible cardiac toxicity of clofarabine in humans cardiac evaluations included multiple gated acquisition (MUGA) scans and echocardiograms (ECHOs).

Only 7 of the 113 patients (6%) in the integrated database had a MUGA scan at baseline and only 2 of these patients had a MUGA scan performed at the end of the study (2 AML patients). All MUGA scans for these patients were normal.

A pediatric cardiologist reviewed all ECHOs. A total of 47 of 113 patients (42% [28/67] ALL, 41% [19/46] AML) had both a baseline and a post- baseline ECHO. Most patients overall 55%, 26/47 had no adverse post- baseline change. A total of 21% (10/47; 4 ALL, 6 AML) had a shift from a normal ECHO at baseline to an abnormal ECHO post-baseline. Additionally, 1 ALL patient had a normal MUGA scan at study entry and an abnormal ECHO result at the end of study.

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Pericardial effusion was a frequent finding in these patients, but it was almost always minimal to small and never had any hemodynamic significance. Left Ventricular Systolic Dysfunction (LVSD) was also noted. Six of 32 (19%) patients on CLO- 212 and 9/ 23 (39%) on CLO- 222 had some evidence of LVSD after study entry. The exact etiology for the LVSD is not clear but likely reflects multiple factors. In nearly all of the cases of LVSD, patients were being treated for other serious concurrent illnesses such as culture-positive bacterial or fungal sepsis around the time of follow- up echocardiograms. Several patients also came on study with either a history of serious concurrent illness (eg, sickle cell disease), recent episodes of sepsis, or a history of hypotension, all factors that could also have negatively impacted cardiac function. In addition, all patients had already received significant amounts of anthracyclines before study entry. In this regard, clofarabine treatment in several patients was initiated close enough to the last anthracycline dose for the LVSD to have possibly been due to the anthracycline. Others had received high- dose cyclophosphamide and total body irradiation (TBI) as part of conditioning regimen for bone marrow transplant (BMT). While direct cardiotoxicity of clofarabine cannot be completely ruled out, the patients in this study who had mild- to- moderate LVSD also had other factors that were possibly responsible for the LVSD. In addition, it should be noted that in at least 1 patient (222- 023- 0033) with severely reduced cardiac function, clofarabine was tolerated with no significant further reduction in cardiac function. In some cases, LVSD could also be a transient effect secondary to cytokine release resulting from tumor lysis. It should also be noted that in many cases where follow-up data were available, the LVSD appeared to improve or resolve. This issue requires additional investigation.

Renal and Electrolyte Toxicities

The most prevalent renal toxicities observed in pediatric patients exposed to clofarabine were hypokalemia and elevated creatinine. A total of 42% of patients overall (40% ALL, 44% AML) experienced the onset of or worsening of elevated creatinine. The incidence of grade 3 or 4 elevated creatinine shifted from 0% overall at baseline to 5% overall. The remainder of the post-baseline shifts to elevated levels (35 of 40 shifts) were to grade 1 or 2.

The occurrence of renal toxicity was likely influenced by the use of concurrent medications with known nephrotoxicity, such as amphotericin B and vancomycin. In addition, tumor lysis with concurrent hyperuricemia may have also contributed to the development of renal insufficiency, as well as hypovolemia and hypotension.

Infections

Infections were an important AE because of prolonged immunosuppression and myelosuppression from current and prior therapies.

A total of 83% of pediatric patients overall (86% ALL, 80% AML) experienced at least one post-baseline infection. Post-baseline infections reported by at least 5% of pediatric patients overall included:

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Cellulitis (12% ALL, 13% AML);
Oral candidiasis (14% ALL, 10% AML);
Staphylococcal infection NOS (14% ALL, 10% AML);
Herpes simplex (11% ALL, 13% AML);
Sepsis NOS (11 % ALL, 13% AML);
Bacteraemia (7% ALL; 13% AML);
Pneumonia NOS (11% ALL; 5% AML);
Septic shock (7% ALL; 10% AML);
Colitis pseudomembranous (9% ALL; 5% AML);
Herpes zoster (5% ALL; 10% AML);
Candidal infection NOS (7% ALL; 5% AML);
Fungal infection NOS (5% ALL; 8% AML);
Implant infection NOS (7% ALL; 5% AML);
and Staphylococcal bacteremia (9% ALL; 3% AML).

D. Adequacy of Safety Testing

Safety evaluation was adequate.

E. Summary of Critical Safety Findings and Limitations of Data

As expected in this relatively sick pediatric population all patients suffered AE's. The principal toxicities were nausea and vomiting, hematologic toxicity, fever and febrile neutropenia, hepatobiliary toxicity, infections and renal toxicity. Systemic inflammatory response syndrome/capillary leak syndrome (SIRS) manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure occurred in 10 patients. Cardiac toxicity most often manifest as left ventricular systolic dysfunction with accompanying tachycardia may also occur.

VIII. Dosing, Regimen, and Administration Issues

The recommended clofarabine pediatric dose and schedule is 52 mg/m² administered by intravenous infusion (IVI) over 1 to 2 hours daily for 5 consecutive days. Treatment cycles are repeated every 2 to 6 weeks following recovery or return to baseline organ function. The dosage is based on the patient's body surface area (BSA), calculated using the actual height and weight before the start of each cycle.

IX. Use in Special Populations

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A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Most of the frequently occurring AEs were reported by similar percentages of male and female patients. This finding is consistent with pharmacokinetic analyses that showed no pharmacokinetic differences between the sexes.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age

The small number of patients in each age group makes it difficult to evaluate the data for age.

2. Race/Ethnicity

The small number of patients in each ethnic group makes it difficult to evaluate the data for race/ethnicity.

C. Evaluation of Pediatric Program

Only pediatric patients were evaluated.

D. Comments on Data Available or Needed in Other Populations

1. Renal or Hepatic Impairment

Clofarabine should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Clofarabine has not been evaluated in patients with significant renal or hepatic impairment.

2. Pregnancy

Category D - Pregnancy studies have not been done in humans. Female patients with childbearing potential must have a negative serum pregnancy test before starting each cycle of clofarabine therapy. Men and women with reproductive potential must use an effective contraceptive method while taking the drug. If a patient becomes pregnant while taking clofarabine, she should be apprised of the potential hazard to the fetus. Because impairment of fertility is unknown, reproductive planning should be discussed with the patient, as appropriate.

X. Conclusions and Recommendations

A. Conclusions

Sufficient data were submitted to allow the independent evaluation of CLO-222 (pediatric AML) and CLO-212 (pediatric ALL) study results.

In pediatric AML (CLO-222) there was 1 CRp and 8 PR's among 35 treated patients. Twelve of 35 AML patients went on to transplant including the CRp patient, 6 PR's, 3 not-evaluable patients and 2 treatment failures. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In trial CLO-222 there were no CR's, only one CRp (2.9%) and 8 PR's. The CRp patient and 6 of the PR's went on to have a transplant. Long duration responses and prolonged survival were confined to patients who received a transplant. Four clofarabine plus transplant patients had longer time to progression (TTP) with that treatment than they had with the therapy that immediately preceded clofarabine. Three of these 4 patients also had longer TTP with clofarabine plus transplant than they had with their preceding transplant.

In Pediatric ALL (CLO-212) there were 6 CR's (12.2%), 4 CRp's (8.2%) and 5 PR's among 49 treated patients. Eight ALL patients went on to transplant including 2 CR's, 2 CRp's, 2 PR's, 1 not-evaluable patient and 1 treatment failure. The usual definition of efficacy is long duration complete responses or prolonged overall survival. In study CLO-212 among the 7 CR patients 3 had ongoing responses at the time of data cutoff and 4 had relapsed. Using the criteria of longer TTP with clofarabine \pm transplant than to immediate prior therapy 2 of 6 CR patients, 2 of 4 CRp patients and 0 of 5 PR patients demonstrated benefit. With further follow-up benefit may be demonstrated in 3 additional CR patients and 1 PR patient.

The principal toxicities of clofarabine were nausea and vomiting, hematologic toxicity, fever and febrile neutropenia, hepatobiliary toxicity, infections and renal toxicity. Clofarabine can produce systemic inflammatory response syndrome/ capillary leak syndrome (SIRS), manifested by the rapid development of tachypnea, tachycardia, hypotension, shock, and multi-organ failure. Cardiac toxicity most often manifest as left ventricular systolic dysfunction with accompanying tachycardia may also occur. With attentive patient care, however, the drug was tolerable.

The significance of these results will be discussed with pediatric leukemia experts.

B. Recommendations

The Medical Reviewer Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA, while awaiting the comments of our outside consultants and the Oncologic Drugs Advisory Committee (ODAC), believes that accelerated approval should be given for both the pediatric AML and ALL indications. The reviewer believes that a favorable outcome (prolonged TTP of clofarabine \pm transplant compared to treatment regimens administered prior to the start of clofarabine treatment) has been

demonstrated. This endpoint is not a traditional endpoint for acute leukemia studies, however. Clofarabine toxicity, while considerable, is what one might expect in a heavily pretreated population of pediatric acute leukemia.

C. Binding phase 4 commitments

Phase 3 trials, conducted in less refractory pediatric ALL and AML populations, comparing a clofarabine containing regimen \pm transplant to an appropriate control regimen \pm transplant should be submitted in timely fashion as a Special Protocol Assessment.

XI. Appendix 1- Inspection Results

Institution 14

1. Two subjects did not meet the inclusion criteria

CLO 212 007 MDH

The subject met the exclusion criteria and the subject was not excluded from the study:

Exclusion criteria 5 (Protocol page 27) states: Are receiving any other chemotherapy. Patients must have been off previous therapy for at least 2 weeks (with the exception of intrathecal therapy) and must have recovered from acute toxicity of all previous therapy) prior to enrollment.

The subject had retuximab treatment before the study drug. The last dose was August 20. On August 29, the subject started cycle 1 treatment for the study drug, which is within two weeks before study drug.

Exclusion criteria 2 (Protocol page 27) states: Have an active, uncontrolled systemic infection considered opportunistic, life threatening, or clinically significant at the time of treatment.

Protocol: Table 5-1 at page 31 also states: if a patient develops a clinically significant infection (including, but not limited to, bacteremia, systemic fungal infections, cytomegalovirus (CMV) infection, Pneumocystis carinii pneumonia (PCP), disseminated Varicella, etc.) Treatment will be withheld until the infection is clinically controlled (ie. Afebrile and without signs of active infection).

The subject: the subject had fever on August 25 (T max 39.7), August 26 (T max 40.2), August 27 (T max 39.7), August 28 (T max 38.9), August 29 (T max 40.0), August 30 (T max 39.7) and August 31 (T max 39.5).

Patient was admitted for r/o Bacteremia, febrile with chills. Patient was started Vancomycin and Ciprofloxacin on August 25, 2002. Amikacin and Acyclovir were added on August 27. Patient had fever even with Tylenol T max 40 on August 29 when the patient was received cycle 1 of the study drug.

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Comment - Protocol violation but probably of insufficient magnitude to exclude the patient from efficacy and safety analysis.

CLO 222 0034 DG

Protocol 4.2 Inclusion Criteria (1) Have a diagnosis of ALL according FAB classification with > or = 25% blasts in the bone marrow.

Subject did not meet inclusion criteria Baseline with BM blast 12%. The patient was later classified as Complete Remission (CR).

Comment -Not classified as a CR. Classified as NE because of not meeting the inclusion criteria

2. Clinical Investigator did not follow study protocol, resulted deaths of study subjects.

Subject CLO 212 0013 CTP

Table 5-1 at page 31 also states: if a patient develops a clinically significant infection (including, but not limited to, bacteremia, systemic fungal infections, cytomegalovirus (CMV) infection, Pneumocystis carinii pneumonia (PCP), disseminated Varicella, etc.) CLOFAREX treatment will be withheld until the infection is clinically controlled (ie. Afebrile and without signs of active infection).

Subject had fever (T max 40.3) on October 21 and patient was started cycle 2 study drug on this day.

Subject CLO 212 0019 LVS

The subject was admitted on November 11, 2002 for Febrile Neutropenia. The PI reported this as Serious Adverse Event, the SAE resolved on November 21, 2002. The causality was rated 1, related to study drug. On November 19, the subject was started study drug cycle 2. At the same date, the patient's had fever, T max 38.3 (with meds for fever). The subject was on multiple antibiotics. According to protocol, the treatment should be withheld.

Subject CLO 212 0023 MAA

Subject was admitted for neutropenia fever (t 39.4), on 12/18/2004 and was discharged on 12/24/02 with multiple antibiotics and Tylenol. On December 21, subject's blood culture had a gram positive rod in anaerobic bottle. On 12/30/02 subject developed hypotension. Pt was given one dose of study drug on 12/30/02. Subject developed septic shock, fever, respiratory distress and died on January 1, 2003. Study medicine should be withheld.

Subject CLO 212 0029 MB

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6/22/02 Blood Culture positive for coagulase negative staph. Subject was treated with IV Cefepime, IV Cipro and IV Vancomycin. On 7/3/02, Subject's T max 38.7. The subject was given study drug cycle 2 on 7/3/02.

Subject CLO 212 0040 MG

The subject developed VRE Infection grade 4, Respiratory distress (10/9/03 to 10/31/03) Fever and Neutropenia grade 3, Hypotension grade 3 and respiratory distress grade 3 on 10/9/03. Protocol 4.5 (2, 3, 4). Table 5.1. Subject should be discontinued from study drug or reduced dose.

Patient developed septic shock and this was reported as a SAE started on November 16 and stopped on December 5, 2003. Subject died on December 5, 2003. Cause of death was VRE sepsis, complicating renal failure caused by prolonged hypotension.

3. Study end point assessments highly questionable/false.

Protocol Criteria for CR:

- no evidence of circulating blasts or extramedullary disease.
- an M1 bone marrow (<5% blasts); and
- Recovery of peripheral counts (platelets $\geq 100 \times 10^9/L$ and ANC $\geq 1 \times 10^9/L$).

CRp:

Complete Remission in the absence of Total Platelets Recovery (CRp):

- Patients who have met all criteria for CR except for recovery of platelet counts to $> 100 \times 10^9/L$

Partial Remission (PR): Patient who have

- complete disappearance of circulating blasts;
- an M2 bone marrow ($\geq 5\%$ and $< 25\%$ blasts); and appearance of normal progenitor cells;
- an M1 marrow that does not qualify for CR or CRp.

All other responses will be considered as treatment failures.

Subject CLO 212 0030 FR

On 8/27/03 the patient was classified as complete remission (CR)

8/27/03

M1 marrow

ANC 3.9

Platelets 55

Based on the CBC and BM on this date, the subject should be classified as CRp.

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The CI used the BM from 8/27/03 and CBC from 9/3/03: platelets 138 to classify the subject as CR. The subject had been transfused platelets during the study period.

Cycle 3, 9/8 to 9/12/03 No bone marrow aspirate for the cycle 3 . Protocol requires BM at Day 1 each cycle for the first 6 cycles.

Cycle 4 10/6 to 10/10/03 CR 11/3/03

BM Blast 1

Platelets: 77

ANC 2.5

Should be CRp based on the BM and CBC.

Cycle 5: No bone marrow CI signed the CR form. The form has no date.

Cycle 6. CI Classified as CR

Blast 1

ANC: 15.9

Platelets: 17

Should be CRp

Cycle 7. CI classified as CR

Blast 1

ANC: 6.4

Platelets: 42

Should be CRp

Cycle 8. CI classified as CR 3/2/04

Blast 0

ANC: 0.2

Platelets 57

Should be PR. ANC <1

Subject CLO 212 0040 MG

11/3/02 CI classified as CRp.

M1: Blast 3%

ANC: 6.2

Platelets: 10

CLINICAL REVIEW

However, patient was transfused white blood cell almost everyday during this cycle. Is the ANC real reading? Or just the white cell from the transfusion?

Subject CLO 222 0027 HC

Cycle 3 11/3 to 11/7/03

11/17/03 CI classified as PR

Bone Marrow : Non-Diagnostic bone marrow aspirate
Progenitor cell: not reported
How did the CI derive the classification of PR?

Cycle 4 11/17 to 11/21/03

11/28/03 CI classified as PR

Bone Marrow : bone marrow aspirate 28 blasts 11/28/03 32 blasts 11/03/03
Progenitor cell: not reported
How did the CI derive the classification of PR? This should be treatment failure.

Subject CLO 222 002 A-F

Cycle 2 7/19 to 7/13

8/21/02 CI classified as PR

8/21/02 Bone Marrow : Non-Diagnostic bone marrow aspirate
Progenitor cell: not reported
Blast: not reported
How did derive the classification of PR?

Subject CLO 222 003 JVM

Cycle 1 7/15 to 7/19/02

8/8/02 CRp

ANC 7/15 0.7 7/17 0.8 7/19 1.0 7/22 0 7/26 0 7/29 0 8/2 0.3 8/5 0.4 8/8 0.4

How did the CI derive CRp while ANC < 1.0

Subject CLO 222 0019 RB

CLINICAL REVIEW

Cycle 2 3/5/03 to 3/9/03
3/24/03 CI classified as PR
BM 3/24/03 blast 5
No progenitor cell
How did you derive the PR when there is no progenitor cell?

Subject CLO 222 0031 P-S

Cycle 2 11/2/03 to 11/8/03
311/4/03 PR
BM 3/24/03 blast: Not reported
progenitor cell : not reported

How did the CI derive the PR when there was no report of blast and progenitor cell?

Subject CLO 222 0034 D-G

This patient classified as CR while the Subject did not meet inclusion criteria Baseline BM blast 12%.

Subject CLO 212 007 MH

This patient was classified as PR while the subject did not meet the inclusion criteria.

Reviewer comment

Many of the observations documented above represent single evaluations occurring during the course of treatment. The patient's best response is used for the classification of CR, CRp or PR. As long as the patient does not progress they maintain their best classification. This accounts for a CR at times being recorded as a CRp or a CRp at times being recorded as a PR.

XII. Appendix 2 - Basic protocol elements

Primary Objective

- To determine the overall remission (CR plus CRp) rate in children with refractory or relapsed ALL (Protocol CLO-212) or AML (Protocol CLO-222).

Secondary Objectives

-To document the rate of complete remissions (CR) in the study population;
-To document the rate of CRps in the study population;
- To document the rate of partial remissions (PR) in the study population;
-To document time- to- event parameters including duration of remission and overall survival (OS);

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- To document the safety profile and tolerability of Clofarex for this population and dosing regimen;
- To determine the pharmacokinetic profile and intracellular pharmacology and metabolism of Clofarex in selected patients.

INVESTIGATIONAL PLAN

Phase II, open label, single arm study of Clofarex administered by intravenous infusion (IVI) over 60 minutes daily for 5 consecutive days and repeated every 21 days (1 cycle) at the following doses:

- Induction phase: 52 mg/ m². Cycles may be repeated every 21 days, for up to a maximum of 2 cycles or until a CR or PR is documented, whichever comes first. If a patient does not achieve a CR or PR after a maximum of 2 cycles, they will be discontinued from the study. Patients may be discontinued after only 1 cycle if the bone marrow aspirate and/ or biopsy taken between days 14 and 21 indicate no clinical effect. If a patient achieves a CR or PR following Induction therapy, they may go on to receive subsequent cycles of Clofarex. Patients achieving a PR following the first Induction cycle at 52 mg/ m² will receive a second Induction cycle at 52 mg/m². If the patient is still in PR following the second Induction cycle at 52 mg/ m², the investigator must consult with the ILEX Medical Monitor to discuss whether continued treatment with Clofarex would be in the best interest of the patient.
- Post- induction phase: 52 mg/ m². Cycles are repeated every 21 days in patients demonstrating CR or PR within 2 cycles. Patients may continue to receive cycles of treatment as long as they are benefiting from treatment.

Dosages may be decreased after the Induction phase of therapy according to the criteria in Table 5.3. For patients achieving CR, bone marrow transplant or peripheral blood stem cell transplant (PBSCT) may be applicable. Patients who opt for these procedures will be discontinued from Clofarex therapy (Induction phase or Post- induction phase).

The primary objective of this study is to establish the efficacy of Clofarex in children with refractory or relapsed AML. A Fleming two- stage design 21 will be employed in which 20 qualified patients (ie, those patients who meet the inclusion criteria for the diagnosis of AML as confirmed by the IRRP and who receive Clofarex) will be enrolled into the first stage. If = 1 patient of the first 20 patients achieves a CR or CRp following Clofarex therapy, the accrual will be stopped. If = 2 patients achieve a CR or CRp following Clofarex therapy, another 20 qualified patients will be enrolled into the second stage of the study. An independent response review panel (IRRP) will confirm response to therapy for each patient. The investigator will also determine the date of progression for each patient based on the definitions provided in section 8.1 of this protocol. Procedures governing the convening and execution of the IRRP are specified separately in an IRRP Charter document. Safety will be evaluated based on incidence, severity, and type of adverse events and changes in the patient's physical examination, vital signs, and clinical laboratory results. Particular attention will be paid to the incidence of infection

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and bone marrow toxicity. Investigators will grade adverse events using the NCI CTC, version 2.0 (published 30 April 1999).

Disease Diagnostic and Staging Criteria

All patients must have pathologic confirmation of AML or ALL by the IRRP. For the purpose of this protocol, AML is defined by the French American British (FAB) classification. If a patient has $\geq 25\%$ blasts in the bone marrow, they may be enrolled without further consult; however, if the patient has $>10\%$ but $< 25\%$ blasts, they must have a repeat bone marrow aspiration/ biopsy 1 week later. If the repeat aspiration/ biopsy reveals $\geq 25\%$ blasts, the patient may be enrolled in the study. If the repeat aspiration/ biopsy shows $< 25\%$ blasts, the investigator must consult the ILEX Medical Monitor before enrolling the patient in the study. The original bone marrow aspirate slide that will be used for diagnosis at study start will be retained and archived by the Sponsor for future reference. This will also be true for the bone marrow aspirate slide that confirms the response. Should the patient's diagnosis be unclear, please consult with the ILEX Medical Monitor.

4.2 Inclusion Criteria

For Inclusion and Exclusion criteria, a regimen is defined as including Induction, Consolidation, and Maintenance therapies. Patients must meet all of the following criteria for admission in the study:

- (1) Have a diagnosis of Acute lymphocytic or myelocytic leukemia with $\geq 25\%$ blasts in the bone marrow.
- (2) Be aged ≤ 21 years at time of initial diagnosis.
- (3) Must not be eligible for therapy of higher curative potential, and must be in second or subsequent relapse and/ or refractory, ie, failed to achieve remission following 2 or more different regimens. Where an alternative therapy has been shown to prolong survival in an analogous population, this should be offered to the patient prior to discussing this study.
- (4) Children aged < 10 years must have a Lansky Play-Performance Status of ≥ 50 . Children aged ≥ 10 years must have a Karnofsky Performance Status of ≥ 50 or a World Health Organization Performance Status of ≤ 2 .
- (5) Provide signed, written informed consent according to local IRB and institutional requirements.
- (6) Be able to comply with study procedures and follow- up examinations.
- (7) Have adequate organ function as indicated by the following laboratory values, obtained within 2 weeks prior to registration:

Table 4.2: Inclusion Laboratory Values

Parameter ^a	Required Value
Renal	
Age-adjusted serum creatinine	Normal
Creatinine clearance	≥ 60 mL/min/1.73 m ²
Hepatic	
Serum bilirubin	$\leq 1.5 \times$ ULN

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AST and ALT	≤ 2.5 × ULN without liver involvement
Other	
Chest radiograph	Within normal limits

ULN = Institutional Upper Limit of Normal.

Exclusion Criteria

- (1) Received previous treatment with Clofarex.
- (2) Have a known hypersensitivity to any of the nucleoside analogues, eg, fludarabine, cladribine, pentostatin.
- (3) Have an active, uncontrolled systemic infection considered opportunistic, life threatening, or clinically significant at the time of treatment.
- (4) Must not be pregnant or lactating. Patients who are fertile must agree to use an effective means of birth control, including abstinence, to avoid becoming pregnant.
- (5) Have psychiatric disorders that would interfere with consent, study participation, or follow-up.
- (6) Are receiving any other chemotherapy. Patients must have been off previous therapy for at least 2 weeks (with the exception of intrathecal therapy) and must have recovered from acute toxicity of all previous therapy prior to enrollment. Treatment may start earlier if there is evidence of disease progression prior to that time.
- (7) Have any other severe concurrent disease, which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
- (8) Have positive CNS leukemia. Patients with a history of effectively treated CNS disease are allowed to enroll as long as they meet all other criteria.

Patient Registration

Qualified patients will be enrolled in the study by faxing the completed entry criteria checklist to ILEX. Patients must begin treatment within 7 days of study enrollment. Patients will be considered to be "enrolled" and therefore, "on study" once a study number has been assigned. Slides of the bone marrow aspirate and/ or biopsies must be submitted to the IRRP for confirmation of diagnosis and remission.

Patient Discontinuation

Patients may be discontinued from the study for the following reasons:

- (1) Patient (or parent(s)/ guardian) requests discontinuation.
- (2) There is unacceptable toxicity (ie, grade 4 nonhematologic toxicity).
- (3) Patient becomes pregnant or fails to use adequate birth control (for those patients who are fertile).
- (4) There is a need for any treatment not allowed by the protocol.
- (5) Drug shows lack of efficacy by either a lack of response following 2 cycles or disease progression.

STUDY TREATMENT

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Formulation

Clofarex is formulated at a concentration of 1 mg/ mL in sodium chloride, USP, 9 mg/ mL and water for injection, USP qs to 1 mL. Clofarex is supplied in 2 vial sizes: a 10 mL flint vial and 20 mL flint vial. The 10 mL flint vials contain 5 mL (5 mg) of solution and the 20 mL flint vials contain 20 mL (20 mg) of solution. For both vial types, the pH range of the solution is 4.0 to 7.0. The solution is clear with color ranging from colorless to yellow and is free from visible particulate matter.

Dosage, Administration, and Storage

Vials containing undiluted Clofarex for injection should be stored at controlled room temperature (15 to 30 ° C). Shelf- life studies of intact vials are currently ongoing. Clofarex for injection should be further diluted with 5% dextrose injection USP (D5W) or 0.9% sodium chloride injection USP (normal saline [NS]) prior to IVI. The resulting admixture must be stored at 2 to 8 ° C and used within 24 hours of preparation.

Clofarex will be administered by IVI over 60 minutes daily for 5 consecutive days and repeated every 21 days. To prevent drug incompatibilities, no other medications should be administered through the same IV line. Doses are as follows:

- Induction phase: 52 mg/ m². Cycles may be repeated every 21 days, for up to a maximum of 2 cycles or until a CR, CRp, or PR is documented, whichever comes first. If a patient does not achieve a CR, CRp, or PR after a maximum of 2 cycles, they will be discontinued from the study. Patients may be discontinued after only 1 cycle if the bone marrow aspirate and/ or biopsy taken between days 14 and 21 indicate no clinical effect. If a patient achieves a CR, CRp, or PR following Induction therapy, they may go on to receive subsequent cycles of Clofarex. Patients achieving a PR following the first Induction cycle at 52 mg/ m² will receive a second Induction cycle at 52 mg/ m². If the patient is still in PR following the second Induction cycle at 52 mg/ m², the investigator must consult with the ILEX Medical Monitor to discuss whether continued treatment with Clofarex would be in the best interest of the patient.
- Post- induction phase: 52 mg/ m². Cycles are repeated every 21 days in patients demonstrating CR, CRp, or PR within 2 cycles. Patients may continue to receive cycles of treatment as long as they are benefiting from treatment.

Body Surface Area Calculation

. In calculating the BSA, actual height and weight should be used; that is, there will be no downward adjustment to “ ideal” weight. BSA will be calculated before each cycle based on the actual weight of the patient.

Dose Modification

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There will be no dose modification during the Induction phase of treatment. Doses may be modified (reduced/delayed) during the Post- induction phase according to the criteria in Table 5.3. If clinically indicated, the investigator may further reduce the dose. In no circumstances will a dose be reduced less than that indicated in Table 5.3. There will be no escalation of the dose during the study.

Patients should begin the Post- induction phase of treatment once a CR or PR is confirmed, but no later than 4 weeks after documentation of CR or PR.

In the event of non-hematologic toxicities, the dose should be modified according to Table 5.3. Dose modification based on hematologic toxicities experienced during the Post- induction phase is as follows:

Post-induction cycles should be given no less than every 21 days from the starting day of the previous Post- induction cycle provided recovery of ANC $> 1.0 \times 10^9/L$. If the ANC does not recover by day 21, a bone marrow aspirate/ biopsy should be performed between days 21 to 28 to assess possible relapse. If relapse is not evident, the next cycle of Post-induction therapy may be delayed until recovery of the ANC to $> 1.0 \times 10^9/L$ for up to a maximum of 35 days from the start of the previous cycle. For patients with delayed recovery (ie, after day 28) of their ANC, the dosage for the next cycle of Post-induction therapy should be reduced by 25% of the previous dose.

Should patients experience NCI CTC grade 4 hematologic toxicity (ie, ANC $< 0.5 \times 10^9/L$, platelet count $< 100 \times 10^9/L$) during Post- induction therapy, the dose for the next cycle should be reduced by 25%.

Table 5.3: Criteria for Dose Reduction in Patients Experiencing Nonhematologic Toxicities During Post- induction Phase

Nonhematologic Toxicity

If a patient develops a clinically significant infection^a, Clofarex treatment will be withheld until the infection is completely resolved (ie, afebrile, no longer requiring antibiotics, and without signs of active infection). At this time, treatment may be reinitiated at the full dose. Prophylactic therapy to prevent recurrence of a diagnosed infection should be instituted as clinically indicated. If an infection recurs a second time, Clofarex treatment will be withheld until the infection is completely resolved and may be reinitiated at a 25% reduction.

Description of Event	Dose Modification
1 st Occurrence of a non-infectious event: Grade 3 toxicity ^b	If toxicity recovers within 14 days: Delay treatment until resolution of Grade 3 toxicity to baseline or to the point where it is no longer life threatening and the potential benefit of continued Clofarex outweighs the risk of such continuation; then administer Clofarex at a 25% reduction. If toxicity DOES NOT recover within 14 days: Withdraw patient from study.

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1st Occurrence of a non-infectious event: Grade 4

Withdraw patient from study.

2nd Occurrence of a non-infectious event: Grade 3 toxicity^b

If toxicity recovers within 14 days:

Delay treatment until resolution of Grade 3 toxicity to baseline or to the point where it is no longer life threatening and the potential benefit of continued Clofarex outweighs the risk of such continuation; then administer Clofarex at a further 25% reduction.

If toxicity DOES NOT recover within 14 days:

Withdraw patient from study.

3rd Occurrence of a non-infectious event: Grade 3 toxicity

Withdraw patient from study.

^a Including, but not limited to, bacteremia, systemic fungal infections, cytomegalovirus (CMV) infection, *Pneumocystis carinii* pneumonia (PCP), disseminated *Varicella*, etc.

^b Excluding NCI CTC grade 3 transient elevations in liver function tests (based on institutional normals for age) that occur without clinical significance.

Concomitant Therapy

Necessary supportive measures for optimal medical care will be given throughout the study, including IV antibiotics to treat infections, blood components, granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) for neutropenic fever or infection, and allopurinol for hyperuricemia. Additional care will be administered as indicated by the treating physician and the patient's medical need. No concomitant cytotoxic therapy will be allowed during this study.

Routine prophylactic use of a colony-stimulating factor (G-CSF or GM-CSF) is not permitted. Therapeutic use may be considered at the treating physician's discretion in patients with serious neutropenic complications such as grade 4 neutropenia, \geq grade 3 febrile neutropenia, or obvious sepsis.

Prophylactic antibiotics, antifungals, and antiviral agents (eg, co-trimoxazole, levofloxacin, fluconazole, acyclovir, etc) may be administered at the investigator's discretion according to institutional guidelines.

Each institution must utilize standard precautions when patients receive treatment with a nucleoside analog, ie, irradiation of blood components to be used for blood transfusions.

STUDY ASSESSMENTS

If at any time during the course of the study there is clinical suspicion of relapse, (ie, hematology tests reveal blasts in the peripheral blood, deteriorating clinical status, etc), a bone marrow aspiration and/or biopsy must be performed.

Laboratory Assessments

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All hematology, blood chemistries, and bone marrow aspirations and/ or biopsies will be performed by the local laboratory at each investigational site. An IRRP will be used for confirming diagnoses and responses. Pharmacokinetic and intracellular pharmacologic and metabolic assessments will be performed in a subset of patients from sponsor-selected sites. Instructions for the processing, handling, and shipment of all samples will be provided in the study manual.

Screening and Pretreatment Assessments

Prior to study enrollment each patient will have the following assessments:

Within 14 Days Prior to First Dose

- (1) Signed, written informed consent from parent or guardian and assent from patient, if applicable.
- (2) Bone marrow aspiration and/ or biopsy must be performed for morphology, flow cytometry, and cytogenetic analyses.
- (3) Lumbar puncture.

Within 7 Days Prior to First Dose

- (1) A complete physical examination and medical history including concurrent baseline conditions and detailed documentation of failure on prior induction regimen(s).
- (2) Measurements of height (cm) and weight (kg) for BSA calculation.
- (3) Lansky Play- Performance Status (Lansky PPS), Karnofsky Performance Status (KPS), or World Health Organization Performance Status (WHO).
- (4) Vital signs (blood pressure, pulse rate, respiratory rate, and temperature).
- (5) Complete/ full blood count (CBC/FBC) with differential and platelet count.
- (6) Serum chemistries (for liver and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, lactic dehydrogenase (LDH), creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), electrolytes (chloride, sodium, potassium, and bicarbonate).
- (7) Echocardiogram (ECHO) or multigated acquisition scan (MUGA).
- (8) Imaging studies as appropriate. (9) Concomitant medication notation.

Assessments During Treatment

All tests need to be done within the specified time window for each parameter.

Induction Phase

During the study, the following tests and procedures will be performed during Cycle 1 and Cycle 2 (if needed to achieve a CR, CRp, or PR) as noted below:

Each Treatment Week

- (1) Clofarex administration (52 mg/ m² daily for 5 consecutive days).

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(2) Hematology: CBC/FBC with differential and platelet count. Samples will be collected immediately prior to dosing on every other day that Clofarex is administered, ie, days 1, 3, and 5).

(3) Serum chemistries. Samples will be collected immediately prior to dosing on every other day that Clofarex is administered (ie, days 1, 3, and 5).

Day 1 of Each Cycle (Every 21 Days)

(1) Physical examination.

(2) Measurements of height (cm) and weight (kg).

(3) BSA calculation prior to dosing on day 1 of cycle 2 (if a second cycle is needed to induce a CR, CRp, or PR).

(4) Lansky PPS, KPS, or WHO PS.

(5) Vital signs.

(6) AEs using the NCI CTC.

(7) Concomitant medication notation.

Days 1 and 5 of Cycle 1 Only

(1) Blood and urine samples will be collected during Cycle 1 for pharmacokinetic and intracellular pharmacologic and metabolic evaluations.

(2) Baseline cardiac assessments (ie, ECHO or MUGA) will be repeated as clinically indicated.

Weekly

(1) Hematology: CBC/ FBC with differential and platelet count. Samples will be collected weekly as long as the ANC remains $\geq 0.5 \times 10^9/L$. If the ANC drops to $< 0.5 \times 10^9/L$, a CBC/ FBC with platelet count must be performed every other day until the ANC is $\geq 0.5 \times 10^9/L$. Once recovery is documented, a differential must be performed and the full hematology testing will resume on a weekly basis.

(2) Serum chemistries. If any grade 3 or 4 chemistry toxicity occurs, retest every other day to document the duration.

Days 14 and 21 of Each Induction Cycle

(1) Hematology worksheet to be faxed to the Sponsor on a weekly basis.

Day 14 to 21 of Each Induction Cycle

(1) Bone marrow aspiration and/ or biopsy obtained between days 14 to 21 of each induction cycle. If the bone marrow has not recovered and there is no evidence of leukemia, a bone marrow aspiration and/ or biopsy should be repeated within 14 days.

Confirmation of Remission

(1) Bone marrow aspiration and/ or biopsy obtained to confirm remission 21 days after initial response (CR, CRp, or PR) is reported. If a patient has a PR and the confirmatory bone marrow aspiration and/ or biopsy performed 21 days later shows the patient to be in CR or CRp, the patient should have a repeat bone marrow aspiration and/ or biopsy done

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21 days later to confirm the CR or CRp. Slides must be submitted to the IRRP for confirmation.

Post- induction Phase

Each Dose Day

(1) Clofarex administration (52 mg/ m² daily for 5 consecutive days).

Day 1 of Each Cycle (Every 21 Days)

(1) Physical examination.

(2) Weight measurement (kg) and BSA calculation.

(3) Lansky PPS, KPS, or WHO PS (see Appendix B).

(4) Vital signs (see section 6.2.2).

(5) Hematology: CBC/ FBC with differential and platelet counts (prior to dosing). If the ANC is $< 0.5 \times 10^9/ L$, a CBC/ FBC with platelet count must be performed 3 times a week (ie, days 1, 3, and 5) until the ANC is $\geq 0.5 \times 10^9/ L$. Once recovery is documented, a differential must be performed and the full hematology testing will resume on a weekly basis.

(6) Serum chemistries: If any grade 3 or 4 chemistry toxicity occurs, retest 3 times a week (ie, days 1, 3, and 5) to document the duration.

(7) Imaging studies, as clinically indicated.

(8) Baseline cardiac assessments (ie, ECHO or MUGA) will be repeated as clinically indicated.

(9) AEs using the NCI CTC.

(10) Concomitant medication notation.

(11) Confirmation of continued remission will be based on a CBC/ FBC with differential and platelet count and the clinical status of the patient. Bone marrow aspiration and/ or biopsy will be repeated when there is clinical suspicion of relapse.

Weekly

(1) Hematology: CBC/ FBC with differential and platelet counts. If the ANC drops to $< 0.5 \times 10^9/ L$, a CBC/ FBC with platelet count must be performed 3 times a week (ie, days 1, 3, and 5) until the ANC is $\geq 0.5 \times 10^9/ L$. Once recovery is documented, a differential must be performed and the full hematology testing will resume on a weekly basis.

(2) Serum chemistries: (see section 6.2.2). If any grade 3 or 4 chemistry toxicity occurs, retest 3 times a week to document the duration.

Days 14 and 21 of Each Post- induction Cycle

(1) Hematology worksheet to be faxed to the Sponsor on a weekly basis.

Three Months After Response is Confirmed

The following will be performed 3 months after the first documentation of response:

(1) Bone marrow aspiration and/ or biopsy must be performed for morphology, cytogenetic analyses, and immunophenotyping.

6.4 Off- Study

When the patient goes off study, the following assessments will be performed:

- (1) Physical examination.
- (2) Weight (kg).
- (3) Lansky PPS, KPS, or WHO PS.
- (4) Vital signs.
- (5) Hematology: CBC/ FBC with differential and platelet count.
- (6) Serum chemistries.
- (7) In patients achieving a CR, CRp, or PR, repeat bone marrow aspiration at discontinuation of therapy.
- (8) Bone marrow aspiration and/ or biopsy performed for morphology and cytogenetic analyses. If samples were collected within 7 days prior to going off study, they do not have to be repeated.
- (9) AEs using the NCI CTC.
- (10) Concomitant medication notation.

Follow- Up Assessments

During the follow- up period, all patients will be evaluated for AEs, concomitant medications, leukemic status, alternative treatment, and survival as outlined below. All patients will be followed for a date of disease progression and a date and cause of death. Patients who progress on study will be followed every 3 months for a date and cause of death. Patients who progress after withdrawal from study will be seen every other month until disease progression or death, whichever occurs soonest. Once a date of disease progression is obtained, patients will be followed every 3 months for a date and cause of death only.

Assessments to be performed every month for the first year and then every 2 months thereafter include:

- (1) Assessment of leukemic status:
 - Physical examination.
 - Weight (kg).
 - Hematology: CBC/FBC with differential and platelet count.
 - Serum chemistries.
- (2) Lansky PPS, KPS, or WHO PS.
- (3) Vital signs.
- (4) Confirmation of continued remission will be based on a CBC/FBC with differential and platelet count and the clinical status of the patient. Bone marrow aspiration and/ or biopsy will be repeated when there is clinical suspicion of relapse.
- (5) Assessment of AEs and concomitant medications for 1 month following the end of treatment or until the patient begins alternative treatment.

7. STATISTICAL METHODS

7.1 General Considerations

The primary objective of this clinical trial is to establish the efficacy of Clofarex in children with refractory or relapsed AML. The safety and tolerability of Clofarex when administered on this schedule will also be assessed. This is a Phase II, open-label study.

7.2 Determination of Sample Size

Forty qualified patients will be enrolled in a two- stage sequential study. The sample size of this study is based on overall remission (CR or CRp). The targeted remission rate is 30%. By enrolling 40 qualified patients, an observed remission rate of 30% would have a 95% confidence interval of 16% to 44%. By expanding enrollment to 100 patients, the 95% confidence interval would be from 21% to 39%.

Twenty qualified patients will be enrolled into the first stage of the study. If ≤ 1 patient achieves a CR or CRp following Clofarex therapy, the accrual will be stopped. If ≥ 2 patients achieve a CR or CRp following Clofarex therapy, another 20 qualified patients will be enrolled into the second stage of the study. If fewer than 8 patients achieve a CR or CRp following Clofarex therapy by the end of the second accrual stage, by which time 40 qualified patients will have enrolled in the study, the conclusion will be drawn that a 30% remission rate is not likely in this indication. If at least 8 of 40 patients achieve a CR or CRp after the second accrual stage, the conclusion will be drawn that the treatment is promising

The procedure described above tests (for 40 patients) the null hypothesis (H0) that the true remission rate is = 10% versus the alternative hypothesis (HA) that the true remission rate is at least 30%. The significance level (ie, the probability of rejecting the H0 when it is true) is 0.04. The power (ie, the probability of rejecting H0 when the alternative hypothesis is true) is 94%. The expected sample size under the H0 is 32 patients while the expected sample size under the HA is 40 patients.

7.6 Efficacy Analysis

The primary efficacy endpoint is the overall remission rate. A 95% confidence interval will be used to characterize the OR rate. All patients with centrally confirmed diagnosis of AML who receive any amount of Clofarex will qualify for the estimate of the OR rate (ie, the sum of the number of patients with CR and CRp divided by the total number of qualified patients). An IRRP will confirm eligibility and response to therapy for each patient.

Secondary endpoints will include CR, CRp, and PR rates, duration of remission, and OS. Kaplan- Meier plots will be utilized to characterize time- to- event parameters. Kaplan- Meier analysis will be done utilizing PROC LIFETEST in Statistical Application Software (SAS).

7.7 Safety Analysis

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All patients who receive any amount of Clofarex will be included in the safety analyses. Safety analyses will include the following: (1) The incidence, severity, and type of adverse events and changes in the patient's physical examination, vitals signs, clinical laboratory results, and cytokine assessments. (2) Particular attention will be paid to the incidence of infection and bone marrow toxicity. (3) In addition, deaths and other SAEs will be tabulated.

7.8 Pharmacokinetic Analysis

Bioanalytical analysis will be conducted at a centralized laboratory on samples collected from patients at sponsor- selected sites using a GLP validated assay. Plasma concentrations will be summarized by descriptive statistics, including mean, n, standard deviation, coefficient of variation, minimum, maximum, and median.

Nonlinear mixed effect models will be used to characterize the population pharmacokinetics of Clofarex in the patient population. Plasma and urine kinetics will be analyzed simultaneously. Method development will proceed as follows: First, a base model without population covariates will be developed. Once the base model is established, the empirical Bayes estimates for the individual pharmacokinetic parameters will be estimated. Second, population covariates will be either screened directly using Nonlinear Mixed Effects Modeling (NONMEM) or by regression techniques, such as linear regression or generalized additive models. Covariates will be entered one at a time into the model in a forward- selection process using the likelihood ratio test as the test criteria. A change in $-2 * \log$ likelihood ($-2LL$) between the full and reduced model significant at $p < 0.05$ will allow entry of the covariate into the model. Once all covariates are entered into the model these will be challenged by backwards- stepwise selection one covariate at a time. The change in $-2LL$ between the full and reduced model must be significant at the 0.001 level for the covariate to remain in the model. Lastly, once the model is final, goodness of fit will be examined by graphical analysis. From the population estimates, the following parameters will be reported or calculated: area under the curve (AUC(0-8)), half- life, clearance, renal clearance, and accumulation ratio. Pharmacokinetic- pharmacodynamic correlations will be developed at the discretion of the Sponsor.

Interim Analysis

An analysis of efficacy and safety will be performed after 40 patients have completed induction therapy. A final analysis will be performed after all patients have completed induction therapy.

7.10 Replacement of Patients

Forty qualified patients will be enrolled in this study. To qualify for the efficacy analysis, patients must meet the inclusion criteria for the diagnosis of AML and must have received any amount of Clofarex. If a patient is enrolled in the study without meeting the

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efficacy qualification criteria, the patient may be replaced. All patients (qualified or not) who receive any amount of Clofarex will be included in the safety analysis.

Local laboratories will be utilized to review bone marrow aspirate slides and to perform the cytogenetic analysis and flow cytometry. An IRRP will be utilized to confirm the patient's eligibility and response to treatment. Procedures governing the convening and execution of the responsibilities of the IRRP will be specified separately in a prospectively written IRRP Charter document.

EFFICACY

Study Definitions

- Time to Remission: Time from date of initial treatment until first objective documentation of complete remission (CR) or partial remission (PR).
- Duration of Remission: Time from first objective documentation of CR or PR to first objective documentation of disease relapse or death due to any cause, whichever occurs first.
- Survival: Time from date of initial treatment to date of death.

Response Criteria

The criteria used for responses (CR and PR) are based on the current Children's Oncology Group response criteria with the following modification: CRp is included in the determination of OR since all of the criteria used to define CR is met with the exception of platelet recovery. It is believed that lack of platelet recovery likely reflects bone marrow toxicity from prior therapy, or potentially Clofarex. It is not felt that lack of platelet recovery in this patient population reflects lack of efficacy, therefore CRp is included in determination of OR.

- Complete Remission (CR): Patients who have:
 - no evidence of circulating blasts or extramedullary disease;
 - an M1 bone marrow (< 5% blasts); and
 - recovery of peripheral counts (platelets $\geq 100 \times 10^9/L$ and absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$).
- Complete Remission in the Absence of Total Platelet Recovery (CRp): Patients who have met all criteria for CR except for recovery of platelet counts to $> 100 \times 10^9/L$.
- Partial Remission (PR): Patient who have:
 - complete disappearance of circulating blasts;
 - an M2 bone marrow ($\geq 5\%$ and $< 25\%$ blasts); and appearance of normal progenitor cells
 - An M1 marrow that does not qualify for CR or CRp.
- All other responses will be considered as treatment failures.

9. SAFETY

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The investigator is responsible for monitoring the safety of subjects who have enrolled in the study. All adverse events (AEs) occurring after any administration of the study drug will be followed to the end of the study including the 30- day follow up period or until resolution of drug- related AEs only. AEs will be evaluated using the revised NCI CTC, Version 2.0, published 30 April 1999.

Investigators are required to report to ILEX or its representative all adverse events occurring during the clinical trial, commencing with the first dose of study drug and including the protocol- defined post- treatment follow- up period (21 CFR § 312.64[b]). Serious adverse events, as defined below, must be reported to ILEX or its representative within 24 hours of knowledge of their occurrence. It is also important to report all adverse events that result in permanent discontinuation of the investigational product being studied, whether serious or nonserious.

9.1 Nonserious Adverse Events

An AE is any unfavorable medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the CRF. Each adverse event is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Full laboratory data are to be collected in this study, and toxicity trends will be analyzed utilizing objective toxicity criteria. Consequently, abnormal laboratory findings will not be defined as AEs for the purpose of the current protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus instead of hyperglycemia) on the AE CRF. Do not enter laboratory value changes from baseline on the AE CRF.

Progression of disease is considered an efficacy outcome parameter, and for AE reporting purposes, is excluded from the definition an AE.

A nonserious AE is any untoward medical occurrence that does not meet any of the criteria for serious adverse events (SAEs).

Patients should be instructed to report any AE that they experience to the investigator. Investigators should assess for AEs at each visit. AEs occurring during the clinical trial, including the 30- day follow- up period, should be recorded on the appropriate AE CRF. To capture the most potentially relevant safety information during a clinical trial, it is important that investigators record accurate AE terms on CRFs. Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an

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observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

Serious Adverse Events

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect, or precaution. This includes any experience that:

- Results in death.
- Is a life- threatening adverse drug experience.
- Requires inpatient hospitalization or prolongation of existing hospitalization. - For the purpose of this study, hospitalizations for protocol- scheduled procedures, blood product transfusions, or for social reasons (ie, awaiting transport home) will not be considered SAEs.
- Results in persistent or significant disability/ incapacity.
- Is a congenital anomaly/ birth defect.
- Requires medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Serious Adverse Events

All SAEs occurring during the course of the study or within 30 days of the last administration of study drug must be reported to ILEX or its representative within 24 hours of the knowledge of the occurrence

The investigator will be requested to supply detailed information regarding the event at the time of the initial contact. All serious and/ or unexpected AEs must also be reported to the reviewing IRB/ IEC and a copy of that report must be forwarded to ILEX.

SAE Follow- Up

For all SAEs occurring during the study or within 30 days of the last administration of study drug, the investigator must submit follow- up reports to the sponsor regarding the patient's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient dies, or receives alternative treatment.

For additional details see appropriate protocol.

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this page is the manifestation of the electronic signature.**

/s/

Martin Cohen
10/25/04 02:53:01 PM
MEDICAL OFFICER

John Johnson
12/8/04 11:50:37 AM
MEDICAL OFFICER
Do not fully concur with recommendation. See my Clinical
Team Leader Review.