Briefing Package for
Pediatric Oncology Subcommittee for the
Oncologic Drug Advisory Committee (ODAC) Meeting
20 October 2005

PRODUCT:	**Clofarabine, Clolar™**
NDA:	**21-673**
IND:	**63,641**
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BACKGROUND AND EXECUTIVE SUMMARY

On 22 July 2005, the Division of Oncology Drug Products sent notice to the Sponsor, Genzyme Corporation (Genzyme), inviting participation in an open session at the 20 October 2005 meeting of the Pediatric Subcommittee of the Oncologic Drug Advisory Committee (ODAC). Genzyme was asked to provide an update on the status of 21 CFR 314.500 Subpart H post-marketing commitments for Clolar™.

The Sponsor of record in 2004, ILEX Products, Inc. (ILEX), completed a step-wise submission of a New Drug Application (NDA) for Clolar (clofarabine) in March 2004. ILEX accelerated the pediatric development program in advance of an ongoing adult development program because of the impressive activity demonstrated by clofarabine in the Phase I pediatric study of highly refractory ALL and AML patients. The sponsor then initiated two parallel Phase II studies (in pediatric ALL and AML) following discussion with the U.S. Food and Drug Administration (FDA) and external pediatric oncologists. While the development program of clofarabine in pediatric and adult patients continued, the data from these two Phase II pediatric studies provided the pivotal support for the filing of this NDA. On 28 December 2004 the FDA granted Clolar marketing approval under 21 CFR Subpart H for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory ALL after at least two prior regimens (see approval letter with approved package insert, Appendix A). The accelerated approval required further adequate and well-controlled post-marketing studies to verify and describe the clinical benefit of clofarabine in pediatric ALL. The post-marketing commitments are described herein. The current sponsor, Genzyme, acquired ILEX in December 2004. Background summaries on clofarabine and pediatric acute leukemia populations, treatment options and disease management are provided in Appendix B.

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ACCELERATED APPROVAL PHASE IV COMMITMENTS

1. GENERAL INFORMATION

1.1 Sponsor Name:

Genzyme Corporation

1.2 Drug Name:

Clolar® (clofarabine)

1.3 Indication:

Intravenous Infusion for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia (ALL) after at least two prior regimens

1.4 Accelerated Approval Date:

28 December 2004

2. DESCRIPTION OF COMMITMENT, INCLUDING TITLES OF INDIVIDUAL STUDIES:

2.1 Post-marketing Commitment (PMC) No. 1:

Completion of study CLO-216 titled a "Phase I/II Study of Clofarabine Plus Cytarabine and L-Asparaginase in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia", 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 Phase 2 components fail to identify a useful and tolerated regimen, you have agreed to promptly develop an alternative plan to verify and describe clinical benefit.

2.2 Post-marketing Commitment (PMC) No. 2:

Completion of a controlled clinical study to verify and describe the clinical benefit of clofarabine in pediatric ALL. Your proposed Phase 3 study (CLO-316) to be possibly conducted by the COG does not appear to have a realistic chance of showing clinical benefit of clofarabine in children with ALL in first relapse. Please submit a new protocol for a study to show clofarabine clinical benefit in children with ALL within 2 months of the date of this letter. Timelines or study start, completion and submission of the study report will also be submitted. Please request a meeting to discuss this protocol within 30 days of the receipt of this letter (approval letter of 28 December 2004), so that a meeting can be scheduled to occur about one month after receipt of the protocol.

3. REVISED POST-MARKETING COMMITMENTS

Please note that these PMCs were refined as a result of a meeting held with the Division of Oncology Drug Products on 19 April 2005.

As a first step toward our proposed clinical benefit study, the sponsor had originally submitted a single Phase I/II trial (CLO-216) of clofarabine plus Cytarabine and L-Asparaginase in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia (ALL). However, in detailed discussions with investigators, we received feedback that the proposed Phase I/II trial, designed to incorporate Clolar into the Capizzi II regimen[1] (a well recognized re-induction regimen in pediatric ALL), comprised of high dose Cytarabine (Ara-C) and L-asparaginase, may not be feasible due to potential toxicity concerns. Thus, at the 19 April 2005 meeting, Genzyme proposed the following combination studies:

Genzyme will initiate two Phase I/II trials (CLO21700105 and CLO21800205)[*] in parallel. Both trials are designed to determine the maximum tolerated dose (MTD) and activity of

[*] The studies CLO21700105 and CLO21800205 will be referenced as CLO-217 and CLO-218 throughout the remainder of this document.

Clolar in combination with either Cytarabine (Ara-C) alone, or in combination with etoposide plus cyclophosphamide, in a defined population of patients with relapsed or refractory ALL. These trials would be initiated at approximately the same time. This approach provides more options if, for some reason, the safety or risk/benefit profile, or both, in either of these studies do not warrant further investigation.

Genzyme's proposed alternative post approval clinical development plan intersected with the Children's Oncology Group (COG) development plans, where a proposed study synopsis of a Phase I/II trial of Clolar in combination with Ara-C (Protocol No. AAML0523) was being considered concurrently with Genzyme's. The patient population in this trial includes patients with both ALL and acute myelogenous leukemia (AML). Following discussions with COG with regard to details around trial design, execution, and sponsor access to data in a timely manner, Genzyme determined that this study will supplant the need to initiate CLO-217. Clinical trial data from CLO-218 and COG AAML0523 will support an appropriate comparator and combination regimen for a Phase III post-marketing commitment study. In this circumstance, Phase III development will be restricted to patients with ALL only.

Specifically, the next step would be a randomized Phase III Trial (CLO31700305)[*] where Clolar plus Etoposide and Cyclophosphamide vs. Etoposide and Cyclophosphamide alone, or Clolar plus Ara-C vs. Ara-C alone would be studied in pediatric patients with Acute Lymphoblastic Leukemia (ALL) who fail re-induction in first relapse or are in second or third relapse. The former would be the best option in first relapse patients based on potential concerns with using single agent Ara-C alone in this population.

The Division noted that the potential timelines for a proposed Phase III confirmatory trial were long, and that this could confound the ability to successfully complete the trial as designed. The FDA stressed that it is too early to commit to a detailed Phase III study design and stated that this should be revisited in the future. Of note, the Division stated a

[*] Study CLO31700305 will be referenced as CLO-317 throughout the remainder of this document.

proposed Phase III endpoint of 4-month event-free survival (EFS) is not ideal and that a longer follow-up would be preferred (i.e., 1 year). Genzyme explained that this patient population relapses early and that 4-month EFS should be considered an appropriate measure of clinical benefit.

4. POST-MARKETING STUDIES

4.1 Essentials of Study Design: CLO-218

A Phase 1/2 Dose-Escalation Study of Clofarabine in Combination with Etoposide and Cyclophosphamide in Pediatric Patients with Refractory or Relapsed Acute Leukemias

The final CLO-218 protocol was submitted to FDA as Serial No. 293 on 10 August 2005, (a draft was submitted as Serial No. 260 on 14 March 2005 for review and comment). Please note: CLO-218 replaced the CLO-216 study which was originally submitted for review and approval as the post-marketing commitment study.

4.1.1 Summary of Study Sites (geography, number)

Enrollment is planned for multiple U.S. sites. It is estimated that 7 initial sites will be utilized for the Phase I portion and an additional 20 sites for the Phase II portion.

4.1.2 Patient Population (Inclusion/Exclusion Criteria)

Approximately 39 eligible patients are to be enrolled; 15 patients in the Phase I portion and 24 in the Phase II portion.

4.1.2.1 Inclusion Criteria:

Phase I Inclusion Criteria:

- All patients must have a diagnosis of relapsed or refractory ALL or AML for the Phase I part of the study
- Patients with ALL must be in second or third relapse or refractory to re-induction in first relapse
- Patients with AML must be in first or second relapse

Phase II Inclusion Criteria:

- All patients must have a diagnosis of relapsed or refractory ALL for the Phase II part of the study
- The Phase II portion of the study is limited to only ALL patients

Both Phase I and Phase II Inclusion Criteria:

- Be ≥ 1 year of age with a body weight of >10 kg and be ≤21 years of age at time of enrollment
- Have a Karnofsky Performance Status (KPS) of ≥70 for patients >10 years of age and a Lansky Performance Status (LPS) of ≥70 for patients ≤10 years of age
- Have adequate liver, renal, pancreatic, and cardiac function as indicated by laboratory values and cardiac assessments
- Have received no more than 1 prior hematopoietic stem cell transplant (HSCT). HSCT will not be considered an induction regimen for this study
- Have no evidence of active CNS involvement
- Patients with AML have received no more than 2 prior induction regimens (i.e., patients in first or second relapse) and no more than 1 HSCT
- Patients with ALL have received no more than 3 prior induction regimens (i.e., patients in second or third relapse or refractory to re-induction in first relapse) and no more than 1 HSCT

4.1.2.2 Exclusion Criteria:

Both Phase I and Phase II Exclusion Criteria:

- Received previous treatment with clofarabine
- Have a systemic fungal, bacterial, or other infection requiring ongoing antibiotic treatment
- Pregnant or lactating
- Are receiving any other chemotherapy or investigational therapy
- Must have been off previous therapy for at least two weeks and recovered to ≤ grade 2 from acute toxicity of all previous therapy prior to enrollment
- Have any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart, kidney, liver, or pancreas
- Have received a hematopoietic stem cell transplant (HSCT) within the previous 3 months or have active graft versus host disease (GVHD) requiring immunosuppressive therapy (grade ≥ 2)

4.1.3 Endpoints

4.1.3.1 Phase I Endpoints:

Phase I Primary Endpoint

- To determine the Maximum Tolerated Dose (MTD), Dose Limiting Toxicities (DLTs) and the recommended Phase II dose (RP2D) of clofarabine when used in combination with etoposide and cyclophosphamide in pediatric patients with relapsed or refractory ALL or AML

Phase I Secondary Endpoints

- To determine the safety and tolerability of clofarabine when used in combination with etoposide and cyclophosphamide
- To determine the duration, seriousness, and relationship of adverse events that occur during treatment and follow-up periods
- To determine the overall remission (OR) rate [complete remission (CR) + complete remission in the absence of platelet recovery (CRp)] of clofarabine when used in combination with etoposide and cyclophosphamide
- To document the rate of partial remission (PRs) in the study population
- To document time to remission, duration of remission, event-free survival (EFS), 4-month EFS, and overall survival (OS)
- To characterize the pharmacodynamics of intracellular clofarabine triphosphate in combination with etoposide and cyclophosphamide in a subset of patients

4.1.3.2 Phase II Endpoints:

Phase II Primary Endpoint

- To determine the overall remission (OR) rate [complete remission (CR) + complete remission in the absence of platelet recovery (CRp)] of clofarabine when used in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed ALL at the established clofarabine RP2D

  Note: The Phase II portion is open to pediatric ALL patients (excludes AML patients).

Phase II Secondary Endpoints

- To determine the safety and tolerability of clofarabine when used in combination with etoposide and cyclophosphamide including the frequency, duration, seriousness, and relationship to study treatment
- To document the rate of partial remission (PRs) in the study population
- To document time to remission, duration of remission, event-free survival (EFS), 4-month EFS, and overall survival (OS)
- To characterize the pharmacodynamics of intracellular clofarabine triphosphate in combination with etoposide and cyclophosphamide in a subset of patients

4.1.4 Treatment Schema

Table 4.1.4-1: Clofarabine in Combination with Etoposide and Cyclophosphamide Treatment Regimen

Dose-Escalation Scheme				
Phase I				
Cohort	**No. of Pts**	**Etoposide**	**Cyclophosphamide**	**Clofarabine**
1	3 to 6	75 mg/m^2	340 mg/m²	20 mg/m^2
2	3 to 6	75 mg/m^2	440 mg/m²	20 mg/m^2
3	3 to 6	100 mg/m^2	440 mg/m²	20 mg/m^2
4	3 to 6	100 mg/m^2	440 mg/m²	30 mg/m^2
5[a]	3 to 6	100 mg/m^2	440 mg/m²	40 mg/m^2
Phase II[b]				
No. of Pts		**Etoposide**	**Cyclophosphamide**	**Clofarabine**
24		TBD	TBD	TBD

[a] In the event an MTD is not identified earlier, Cohort 5 will be the RP2D.

[b] Patients in the Phase II portion of the study will be treated at the RP2D of clofarabine in combination with etoposide and cyclophosphamide as determined in the Phase 1 portion of the study.

TBD=to be determined.

- Clofarabine induction therapy will be administered as a 2-hour IV infusion on consecutive days (days 1 through 5) at an initial dose of 20 mg/m^2/day.
- Etoposide will be administered at an initial dose of 75 mg/m^2/day, daily for 5 days as a 2-hour IV infusion.
- Cyclophosphamide will be administered at an initial dose of 340 mg/m^2/day, daily for 5 days as approximately a 30 to 60 minute IV infusion
- When etoposide and cyclophosphamide have been escalated to their target dose (ie, cohort 3), clofarabine will be increased to its target dose in combination with the other two agents.
- There will be no intra-patient dose escalation

The study is divided into two phases:

- In Phase I, the MTD and the recommended Phase II dose (RP2D) of clofarabine in combination with etoposide and cyclophosphamide is to be identified. Doses are to be escalated in cohorts of 3 to 6 patients until the designated number of DLTs are observed
- Once the MTD of clofarabine in combination with etoposide and cyclophosphamide has been established in the Phase I portion, approximately 24 patients are to be treated at the recommended Phase II dose

- In either the Phase I or Phase II portion of the study, multiple cycles of treatment may be administered until a maximum of 8 cycles have been completed
  - Treatment cycles are to consist of 2 induction cycles plus 6 consolidation cycles or 1 induction cycle plus 7 consolidation cycles.

4.1.5 Efficacy and Safety Monitoring

- All adverse events occurring after the patient signs the informed consent (ICD) through 45 days after the last administration of study drug will be captured on the AE CRF (AEs/SAEs defined in detail within the protocol)
- Any study drug-related AE or any SAE is to be followed until resolution
- Full laboratory data are to be collected in the CLO-218 study, and toxicity trends will be analyzed utilizing objective toxicity criteria
  - Abnormal laboratory findings will not be defined as AEs, unless the laboratory abnormality meets the criteria for a DLT, SAE, causes a dose modification and/or delay, or is the reason a patient goes off study
- Periodic review of the safety data will be conducted by an independent data safety monitoring board
- An Independent Response Review Panel (IRRP) will oversee the study
  - The IRRP will assess disease response, including confirmation of the initial diagnosis, for each patient
  - The IRRP-determined response will be used for the efficacy analysis

4.1.6 Statistical Design

- CLO-218 is an open-label, nonrandomized study with the identity of the treatments known to the investigator, patient, and Genzyme
- Safety analysis will be performed on all patient who have received study drug at any dose level regardless of treatment in the Phase I or Phase II part of the study
- Efficacy analysis will be based on all patients with relapsed or refractory ALL who have been treated with clofarabine in combination with etoposide and cyclophosphamide at the RP2D (ITT [Intent-to-Treat population]) (AML patients will not be included in this analysis)
- Sample size will based in the expectation that 15 patients will be enrolled in the Phase I portion of the study (total number of patients will depend on the number of dose levels tested before MTD is established); 24 patients will be treated in the Phase II portion of the study
- An interim efficacy analysis will be performed after 12 patients are treated and evaluated at the MTD or RP2D
- Stopping Rule: Considerations for stopping the trial will occur if there is very low (zero patients achieve OR) or substantial (≥ 3 patients achieve OR) evidence of efficacy. A 25% OR rate at N=12 (3 of 12 patients achieve OR) provides 80% confidence (one-sided) that the true OR rate is ≥ 13%)

4.1.7 Date of Initiation

First patient expected to be enrolled by end of October 2005

4.1.8 Accrual

Approximately 39 eligible patients will be enrolled in the study

4.1.9 Estimated Timeline for Study Completion

Table 4.1.9-1: Original Timeline (from approval letter, based on the CLO-216 study):

	Phase I:	Phase II:
Protocol Submission:	Completed	Completed
Study Start:	1 June 2005	1 June 2006
Trial Completion:	1 March 2006	1 October 2006
Final Report Submission:	1 June 2006(*interim report)	13 April 2007

Table 4.1.9-2: Updated Timeline (based on the CLO-218 study):

	Phase I/II:
Protocol Submission:	Completed (10 August 2005)
Study Start (first patient enrolled:	October 2005
Trial Completion:	August 2008
Final Report Submission:	December 2008

4.1.10 Estimated Timeline for Submission of Study Results

- An interim clinical study report for the Phase I portion of the study is expected to be completed in July 2006.
- The final clinical study report, to include both Phase I and Phase II is expected to be completed in December 2008

In parallel to the CLO-218 study, a second combination study will be conducted by the Children's Oncology Group (COG) in support of the PMC No. 1. The results from these two studies will determine the comparator arm and design of the Phase III study for PMC. No. 2.

4.2 Essentials of Study Design: COG study AAML0523

A Phase II Study of Clolar (Clofarabine) in Combination with Cytarabine in Pediatric Patients with Refractory/Relapsed Leukemia

The final protocol is pending submission to the Agency. Genzyme has provided COG a cross-reference authorization letter for an Investigator Sponsored Trial (IST): COG (Gregory Reaman, M.D.)

4.2.1 Summary of Study Sites (geography, number)

Enrollment is planned for multiple U.S. Sites. It is estimated that 21 initial Phase I sites will be utilized for the dose-finding portion and the remaining group-wide sites (~240) utilized for the remainder study portion.

4.2.2 Patient Population (Inclusion/Exclusion Criteria)

- Patients must be no greater than 21 years of age inclusively when originally diagnosed with the malignancy to be treated on this protocol
- Patients must have a diagnosis of acute myelogenous leukemia (AML) or acute lymphocytic leukemia (ALL) according to FAB classification
- Patients must have disease that is recurrent following or refractory to induction therapy
- Patients with AML must be in 1st relapse (no more than one prior induction regimen)
- Patients with ALL must be in 2nd or 3rd relapse (no more than 3 prior induction regimens) or refractory to reinduction in 1st relapse
- Patients can not have active CNS involvement as evidenced by negative cytology on lumbar puncture and absence of clinical symptoms
- Patients must have a performance status of 0, 1 or 2. For patients >16 years of age, Karnofsky will be utilized and Lansky for patients ≤16 years of age
- Patients must have fully recovered from acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study
- Adequate renal, liver, cardiac and pulmonary function

4.2.3

Endpoints

4.2.3.1 Primary Objectives:

To determine the overall response rate, comprising patients attaining a complete remission (CR) or remission without platelet recovery (CRp) as a measure of efficacy, in patients ≤21 years with relapsed and refractory AML and ALL treated with Clofarabine and Ara-C combination

4.2.3.2 Secondary Objectives:

- To determine the safety profile and tolerability of Clofarabine when given in combination with Ara-C in patients ≤21 years of age with and without prior stem cell transplant
- To determine the plasma and intracellular pharmacokinetic profile of Ara-C alone and in combination with Clofarabine in children with relapsed AML and ALL
- To identify apoptosis specific genes in children with relapsed AML and ALL important in mediating resistance or sensitivity after initiation of therapy with Ara-C and after the addition of Clofarabine
- To quantitate the level of human equilabrative nucleoside transporter (hENT1) protein in blasts of children with relapsed AML and ALL and correlate with intracellular accumulation of Ara-CTP and Clofarabine triphosphate and with clinical outcomes

4.2.4 Treatment Schema

4.2.4.1 Induction Chemotherapy:

- Cycle 1 – clofarabine will be administered as a 2-hour intravenous infusion at a starting dose of 40 mg/m^2/day, daily for 5 days (days 2 through 6)
- Cycle 1 – Ara-C will be administered as a 2-hour IV infusion at a dose of 1 gram/m^2/day on days 1 through 5
- Cycles will be repeated once on weeks 3-6 as indicated by leukemia recurrence or recovery of normal hematopoiesis, but at least 14 days after the first cycle. Both drugs will be administered days 1-5 during induction cycle 2.

4.2.4.2 Maintenance Therapy:

- Patients who achieve a CR or CRp after a maximum of 2 induction cycles and who do not have a donor for SCT, have the option to receive up to 10 additional cycles of maintenance therapy
- Clofarabine will be administered at a 2-hour intravenous infusion at a dose of 40 mg/m^2/day (or the MTD dose determined in the dose escalation/de-escalation phase), daily for consecutive 5 days (days 1 through 5)

- Ara-C will be administered as a 2-hour IV infusion at a dose of 1 gram/m^2/day on days 1 through 5 (same as induction cycle)
- Cycles will be repeated no less than every 21 days, and no more than 42 days from the starting day of the previous cycle, provided count recovery

4.2.5 Efficacy and Safety Monitoring

- Adverse events will be reported in a routine manner at scheduled times and will be further outlined in the data collection packet for this protocol
- Expedited adverse event reporting for AEs experienced by patients receiving the investigational agent will be completed using the NCI's AdEERS (Adverse Event Expedited Reporting System) guidelines
- Secondary AML/MDS reporting – All cases of AML and MDS that occur in patients on NCI-sponsored trials following their chemotherapy for cancer will be reported to the Investigational Drug Branch (IDB) of the NCI CTEP.

4.2.6 Statistical Design

- Both ALL and AML patients can be enrolled in the study phase assessing safety and determining the MTD
- After the MTD has been determined, additional patients can be enrolled group wide at all COG institutions. Patients who received the MTD in the dose finding phase will be included in the efficacy phase
- AML Patients – two-stage design will be used to test the null hypothesis that the response rate is $\leq 50\%$ versus the alternative hypothesis that the response rate is $\geq 70\%$ (based upon the results of the COG CCG 2951 combination study)
- ALL Patients – two-stage design will be used to test the null hypothesis that the response rate is $\leq 30\%$ versus the alternative hypothesis that the response rate is $\geq 55\%$ (based upon the results of the previous multi-agent regimens in ALL patients in 2nd relapse)
- Methods of analysis – response rates and confidence intervals will be constructed according to the method of Change and O'Brien. The response rate will be calculated as the ratio of the number of patients who demonstrate response after the 1st two courses of therapy divided by the number of patients evaluable for response.

4.2.7 Date of Initiation

First patient expected to be enrolled by end of October 2005.

4.2.8 Accrual

It is anticipated that about 50 (30 AML and 20 ALL) patients will be enrolled annually. To accrue a maximum of 86 patients, it is expected to take approximately 2 years, allowing for

a gradual initiation and stopping for evaluation of toxicities. Initially, 10 patients (both ALL and AML) will be enrolled to assess the safety of the combination with Ara-C.

4.2.9 Estimated Timeline for Study Completion

Table 4.2.9-1: Estimated Timeline for Study Completion (AAML0523)

	Phase II:
Protocol Submission:	Pending – targeted for end of September 2005
Study Start (first patient enrolled:	October 2005
Trial Completion:	June 2008
Final Report Submission:	October 2008

4.2.10 Estimated Timeline for Submission of Study Results

- An interim analysis is planned for July 2006.
- The final clinical study report is expected to be completed in October 2008

4.3 Essentials of Study Design: Proposed CLO-317 (PMC No. 2):

A Randomized Phase III Trial of Clofarabine in a Combination Regimen[*] in Pediatric Patients with Refractory or relapsed Acute Lymphoblastic Leukemia (ALL)

4.3.1 Summary of Study Sites (geography, number)

This study will be conducted at multiple centers in the U.S.

4.3.2 Patient Population (Inclusion/Exclusion Criteria)

Planned enrollment is 302 pediatric patients with refractory or relapsed ALL (151 patients per treatment arm)

[*] The combination regimen for the Phase III study will be determined by the results of the Phase I/II study(s).

4.3.2.1 Inclusion Criteria:

- Have a diagnosis of ALL according to French American British (FAB) classification with >25% blasts in the bone marrow.
- Are ≤21 years old at time of enrollment.
- Are in first relapse and refractory to reinduction, or in second or third relapse.
- Had no more than 1 prior hematopoietic stem cell transplant (HSCT).
- Have a Karnofsky Performance Status (KPS) of ≥70 for patients ≥10 years of age and a Lansky Performance Status (LPS) of ≥70 for patients <10 years of age.
- Have adequate liver, renal, and pancreatic function as indicated by the following laboratory values: serum creatinine and serum bilirubin ≤ upper limit normal (ULN) for age; serum amylase and serum lipase ≤ ULN for age; AST and ALT ≤2.5 × ULN
- Have adequate cardiac function: either echocardiogram shortening fraction ≥28% or ejection fraction by gated radionuclide study ≥50%.
- Have no active CNS involvement as evidenced by cytology and absence of clinical symptoms.

4.3.2.2 Exclusion Criteria :

- Have a documented recent (<30 days) history of fungal, bacterial, or other serious infection.
- Are receiving any other chemotherapy.
  - Patients must have been off previous therapy for at least 2 weeks (with the exception of prophylactic intrathecal therapy or hydroxyurea which are allowed up to 24 hours prior to the first dose) and must have recovered from acute toxicity of all previous therapy prior to enrollment.
  - Treatment may start earlier, following consultation with the Genzyme Medical Monitor, if there is evidence of rapid disease progression.
- Have any other severe concurrent disease, or have a history of serious organ dysfunction or known, underlying disease involving the heart, kidney, liver, or pancreas.
- Have received a hematopoietic stem cell transplant (HSCT) within the previous 6 months or have active graft versus host disease (GVHD) (grade ≥2)

4.3.3 Endpoints

The primary objective of this study is to demonstrate that clofarabine in combination is superior to the combination without clofarabine in pediatric patients with relapsed or refractory ALL as measured by 4-month event-free survival (EFS)

- 4-month EFS
- Duration of response
- Overall survival

- Post-transplant engraftment with successful post-transplant engraftment defined as absolute neutrophil counts (ANC) >0.5 × 109/L, with <5% blasts in bone marrow, and platelets >50 × 109/L
- The determination of the safety profile and tolerability of clofarabine in combination with other chemotherapeutic agents
- Response Rates (OR, CR, CRp, PR)

4.3.4 Treatment Schema (possible regimens to be determined by the results of the Phase I/II studies)

4.3.4.1 Proposed regimen containing Clofarabine and Cytarabine (Ara-C):

- The recommended Phase II dose for clofarabine in combination with cytarabine will be determined in the proposed Phase I/II study.
- Patients will be randomized to either the control arm or the experimental arm of the study.
- Clofarabine will be administered to patients in the experimental arm as a 2-hour intravenous infusion (IVI) daily for 5 consecutive days (Days 2 through 6) followed 4 hours later by cytarabine, which will be administered as a 2-hour IVI twice daily for 5 consecutive days (Days 1 through 5).
- On Day 1, patients will receive cytarabine alone, followed by the combination therapy on Days 2 through 5.
- On Day 6, clofarabine will be infused alone. Patients in the control arm of the study will receive cytarabine alone.
- There will be no changes to the cytarabine dosing schedule for the control patients.
- To prevent drug incompatibilities, no other medications should be administered through the same IV lines

Induction Therapy

- Induction therapy may be repeated once, up to 6 weeks after day 1, cycle 1 as indicated by persistent leukemia following Cycle 1.
- A bone marrow aspirate will be performed on Day 14. If >5% blasts are present in the bone marrow and the marrow is in recovery, Cycle 2 should be administered. If marrow is aplastic or there is evidence of normal hematopoiesis with <5% blasts, repeat bone marrow aspirate in 10-14 days.
- Cycle 2 induction therapy may be administered at that time if persistent leukemia (>5% blasts) is present.
- Patients may receive a maximum of 2 cycles of induction therapy or until a CR or CRp is documented, whichever occurs first. If a patient in the control arm does not achieve a CR, CRp, or PR during induction, then the clofarabine regimen may be administered.

Consolidation Therapy

- Patients who achieve a CR, CRp, or PR during induction may receive up to 6 cycles of consolidation therapy.
- The clofarabine dose level and the cytarabine dose level will be reduced during the consolidation phase of the study.
- Patients may receive up to 2 cycles of induction and 6 cycles of consolidation therapy.

4.3.4.2 Proposed regimen containing Clofarabine and Etoposide and Cyclophosphamide:

- The recommended Phase II dose (RP2D) for clofarabine in combination with etoposide and cyclophosphamide will be determined in the proposed Phase I/II study.
- Patients will be randomized to either the control arm or the experimental arm of the study.
- Patients in the experimental arm will receive a 2-hour IVI of clofarabine followed immediately by etoposide (2-hr IVI) and cyclophosphamide (30 min IVI) for Days 1 through 5 every 28 days. Patients in the control arm will receive the combination therapy excluding clofarabine.

Induction Therapy

- Induction therapy may be repeated once, up to 6 weeks after Day 1, Cycle 1 as indicated by persistent leukemia following Cycle 1. A bone marrow aspirate will be performed on Day 14. If >5% blasts are present in the bone marrow and the marrow is in recovery, Cycle 2 should be administered. If the marrow is aplastic or there is evidence of normal hematopoiesis with <5% blasts repeat bone marrow aspirate in 10-14 days.
- Cycle 2 induction therapy may be administered at that time if persistent leukemia (>5% blasts) is present.
- Patients may receive a maximum of 2 cycles of induction therapy or until a CR or CRp is documented, whichever occurs first. If a patient does not achieve a CR, CRp, or PR during Induction, then the clofarabine regimen may be administered.
- Patients who achieve a CR, CRp, or PR during induction therapy may receive up to 6 cycles of consolidation therapy

Consolidation Therapy

- During consolidation therapy the clofarabine dose will be reduced to the next lower dose cohort. The etoposide and cyclophosphamide consolidation dose will be reduced 25% for all cohorts.
- Patients may receive up to 2 induction cycles and 6 consolidation cycles of treatment.

4.3.5 Efficacy and Safety Monitoring:

4.3.5.1 Safety Monitoring

- Toxicities will be graded according to the NCI CTCAE Version 3.0 (published 12 December 2003).
- Safety will be evaluated by analyzing the incidence, severity, relationship, and type of adverse events in addition to changes in physical examination results, vital signs, and clinical laboratory results that occur during the treatment and follow-up period.
- The evaluation period will extend until recovery from all acute toxicities associated with study drug administration.
- The interim monitoring of study results will be provided by a Data and Safety Monitoring Board (DSMB)

4.3.5.2 Efficacy Monitoring

- An independent pathologist will confirm the diagnosis for all patients.
- In order to ensure an unbiased assessment of the primary endpoint, an independent review panel [IRRP] will assess 4-month EFS for all patients
- Clinical and statistical experts from the sponsor will be responsible for the conduct of an internal review process for both the final study report and any study-related material to be authorized for publication

4.3.6 Statistical Design:

4.3.6.1 Safety Analysis

All patients who receive at least 1 dose of study treatment will be included in the safety analysis.

4.3.6.2 Efficacy Analysis

- Efficacy analyses will be performed on the intent-to treat (ITT) population using models that adjust for important prognostic factors, such as, age, cytogenetic abnormalities [eg, t(9;22)], number of prior regimens, bone marrow transplant, and duration of first remission.
- The planned sample size of this study is 302 patients (151 per treatment arm)
- This sample size assumes EFS of 29% in clofarabine plus TBD treatment arm vs EFS of 15% in the nonclofarabine TBD treatment arm with 80% power and $\alpha = 0.05$ (two-sided)
- The primary endpoint (4-month EFS) will be assessed using logistic regression
- The secondary endpoints are OS, OR rate, duration of remission, and successful transplant rate
- The response rates for OR and transplant will be assessed using logistic regression

- OS and duration of remission will be assessed using the Cox proportional hazards model.
  - Kaplan-Meier curves will summarize the distributions of OS and duration of remission
- The analysis of duration of remission will include all patients regardless of whether response was obtained. Patients who failed to obtain response will be assigned a duration of response of value 0 (worst rank analysis)
- Sensitivity analyses of time-to-event endpoints will include fitting Cox proportional hazards models where patients are censored at the time of transplant and time of alternate therapy where applicable

4.3.7 Date of Initiation

Based upon the outcome and timelines of the parallel Phase 1/2 studies, it is estimated that the 1st patient may be enrolled in Quarter 2 of 2008.

4.3.8 Accrual

It is estimated that 302 eligible patients will be enrolled (151 per treatment arm) in the study.

4.3.9 Estimated Timeline for Study Completion

Table 4.3.9-1: Estimated Timeline for Study Completion (CLO-317)

	Phase III:
Protocol Submission:	Q4 2007
Study Start (first patient enrolled:	Q2 2008
Trial Completion:	Q1 2012
Final Report Submission:	Q3 2012

4.3.10 Estimated Timeline for Submission of Study Results

A final clinical study report is expected to be completed in Quarter 3 of 2012.

5. CHALLENGES ANTICIPATED IN CONDUCT, ACCRUAL, OR COMPLETION

The detailed design of a Phase III randomized controlled trial to confirm clinical benefit in a patient population with pediatric ALL will be informed by the results of the two

previously summarized Phase I/II combination trials. The Sponsor recognizes a number of challenges in the design and timely execution of such a study.

5.1 Limited Patient Population

The annual incidence of relapsed or refractory ALL in pediatric patients is quite small. According to SEER data, of the 2470 pediatric patients diagnosed in the US with ALL each year, 124 will be refractory to initial therapy, and 375 will relapse after achieving complete remission Furthermore, many of these patients will participate in clinical trials of other investigational therapies or novel combinations of existing therapies. Thus, even if 25% of the entire population of interest were studied, only 125 patients per year (approximately 10 per month) would be available to enroll in the study. A more realistic, yet still challenging, accrual rate of 5 patients per month would likely be easier to attain.

5.2 Appropriate Primary Endpoint

Selection of a primary endpoint that provides evidence of clinical benefit in this indication poses some important practical, statistical and ethical considerations.

Improvement in overall survival is the gold standard as a primary endpoint for clinical benefit in oncology trials. As noted in FDA's Draft Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, "an improvement in survival is of unquestioned clinical benefit. The endpoint is precise and easy to measure, documented by the date of death. Bias is not a factor in endpoint measurement."

However, demonstration of overall survival may be confounded in this patient population due to the high probability of pediatric ALL patients with relapsed disease receiving alternative therapies following remission, most notably HSCT, or upon relapse. Undergoing HSCT introduces a host of complex clinical factors beyond what additional chemotherapies would be expected to do that could affect survival independent of the effect of clofarabine. Therefore, as patients are offered new interventions, a controlled demonstration of a benefit in overall survival could potentially be confounded in the intent-to-treat setting due to patients receiving alternative therapies, such as HSCT. Although

these therapy changes should, in theory, occur with equal likelihood between the two groups, marked differences between the groups in the proportion of patients who undergo a particular type of therapy could call results into question.

In addition, the sample size needed to show clinical benefit in this setting may not be realistically achievable given the limited number of available patients as discussed above. To illustrate, as outlined in the table below, assuming a control arm median survival of 5 months, a patient accrual of 10 patients per month, and an experimental arm median survival of 7 months, in order to show a statistically significant difference (two-sided α= .05) powered at 80%, the anticipated study duration would be 42 months with a sample size of 300 patients. This sample size is also sensitive to small variations in assumptions. For example, if the control group median survival is 5.5 months (while the median for the experimental arm remained 7 months) we would need to enroll 560 patients in a 70 month study. An even longer study period would be required if accrual did not proceed at this rate, which is aggressive given the factors outlined above, and would require a large number of actively enrolling sites that are often involved in competing trials. FDA has expressed concerns that, under these circumstances, investigators may not maintain interest in entering patients over such a long time period, particularly if additional promising new agents become available for investigation.

Table 5.2-1: Sample Size Calculation (Group Media Survival)

Control Group Median Survival (months)	Clofarabine Group Median Survival (months)	Accrual Rate (pts/mo)	Sample Size	Study Duration (months)
5	7	5	290	69
5	7	10	300	42
5.5	7	5	555	121
5.5	7	10	560	70

Due to the issues discussed above, the Sponsor has proposed that event free survival (EFS, where an event can be defined as relapse, treatment failure, or death from any cause) is a meaningful clinical benefit endpoint in this population. Four-month EFS is currently used by COG in controlled trials of relapsed patients, in part to accommodate the expectation of

alternative therapy (e.g. HSCT) in this patient population. This endpoint also allows for shorter follow up, and thus the potential for shorter study duration, allowing for more rapid assessment of meaningful clinical events. For instance, as defined in the table below, assuming a control arm 4-month EFS of 15% and an experimental arm 4-month EFS of 29%, the Phase III trial could include approximately 270 patients and the study duration could be 31 months based on an accrual rate of 10 patients per month, or 58 months if the accrual rate were 5 patients per month (assuming α=0.05, power=0.80). Though an improvement due to shorter patient follow up, this still represents a trial of substantially long duration, during which additional therapeutic options could become available and challenge the success of continuing accrual.

Table 5.2-2: Sample Size Calculation (EFS)

Control Arm 4 mo. EFS	Experimental Arm 4 mo. EFS	Accrual Rate (pts/mo)	Sample Size	Study Duration (months)
15%	29%	5	270	58
15%	29%	10	270	31

Finally, Genzyme is actively considering the value of additional endpoints that have a high likelihood of representing or predicting clinical benefit, including assessment of minimum residual disease (MRD) and response duration. In addition, Genzyme is also implementing a comprehensive clinical development program in adult acute leukemia that should provide the potential for substantial insights into the safety and efficacy of clofarabine in this biologically similar disease.

6. CONCLUSIONS

Genzyme is fully committed to completing a post-marketing clinical development plan designed to demonstrate the clinical benefit of Clolar in pediatric ALL in the shortest time possible. The sponsor is supporting two parallel Phase I/II trials of clofarabine in combination with existing drugs active in pediatric ALL to enhance our opportunity for identifying an appropriate combination regimen for confirming clinical benefit in a randomized controlled Phase III trial.

Genzyme is prepared to address the shared concerns of the FDA that the potential timelines for the proposed Phase III confirmatory trial are long, and that this could confound the ability to successfully complete the trial as currently conceived. Recognizing several challenges that may be encountered in completing a Phase III trial as discussed here, Genzyme looks forward to ongoing discussions with the Division to reach a mutual agreement regarding appropriate study design and operational plans that will maximize the opportunity for success in meeting the post-marketing commitments for Clolar.

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Appendix A

Clolar™ Approval Letter and Package Insert

(Pages 1 – 23 attached)

Appendix B

Background Summaries:

Clofarabine, Pediatric Acute Leukemia,

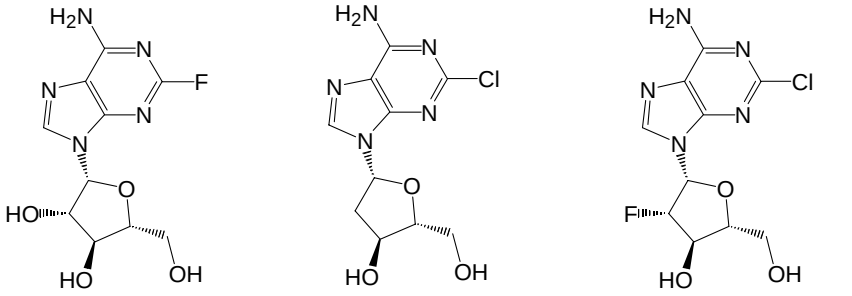
Regulatory History and Development

(Pages 1 – 13 attached)

1. CLOFARABINE

Clofarabine is a second generation purine nucleoside antimetabolite. Originally synthesized at the Southern Research Institute, clofarabine was designed as a hybrid molecule to overcome the limitations and incorporate the best qualities of both fludarabine (Fludara®) and cladribine (Leustatin®). It is differentiated from other purine nucleoside analogues by incorporating 2 halogen atoms (fluorine and chlorine) within its chemical structure. See Figure 1 below.

Figure 1: Structure of Deoxyadenosine Analogues and Clofarabine



Fludarabine (2-fluoro Ara A) | 2-CdA (2-chloro-2'-deoxyadenosine) | Clofarabine (2-chloro-2'-fluoro Ara A)

Clofarabine is a nucleoside pro-drug that must be metabolized to its monophosphate conjugate by deoxycytidine kinase followed by phosphorylation to triphosphate within tumor cells before activity occurs. Compared to other purine nucleoside analogues, it has greater affinity for the activating phosphorylating enzyme deoxycytidine kinase and other kinases.

Clofarabine has demonstrated potent cytotoxic activity in a wide range of cell lines, including leukemia, non-small cell lung, colon, melanoma, ovarian, renal, prostate, and breast cancer cell lines.[1,2] Therapeutic activity has also been shown in murine tumor models (P388 leukemia, colon 36, and mammary 16/c).[3] Curative activity was shown in solid tumor models including early and advanced stages of HT-29 and colon 36 xenograft tumor

models.[3,4] Clofarabine is active against a wide range of in vivo and in vitro human tumor models, including solid tumor and hematologic tumor types. [3,5,6,7,8,9,10,11,12,13,14,15,16,17,18]

2. PEDIATRIC ACUTE LEUKEMIA

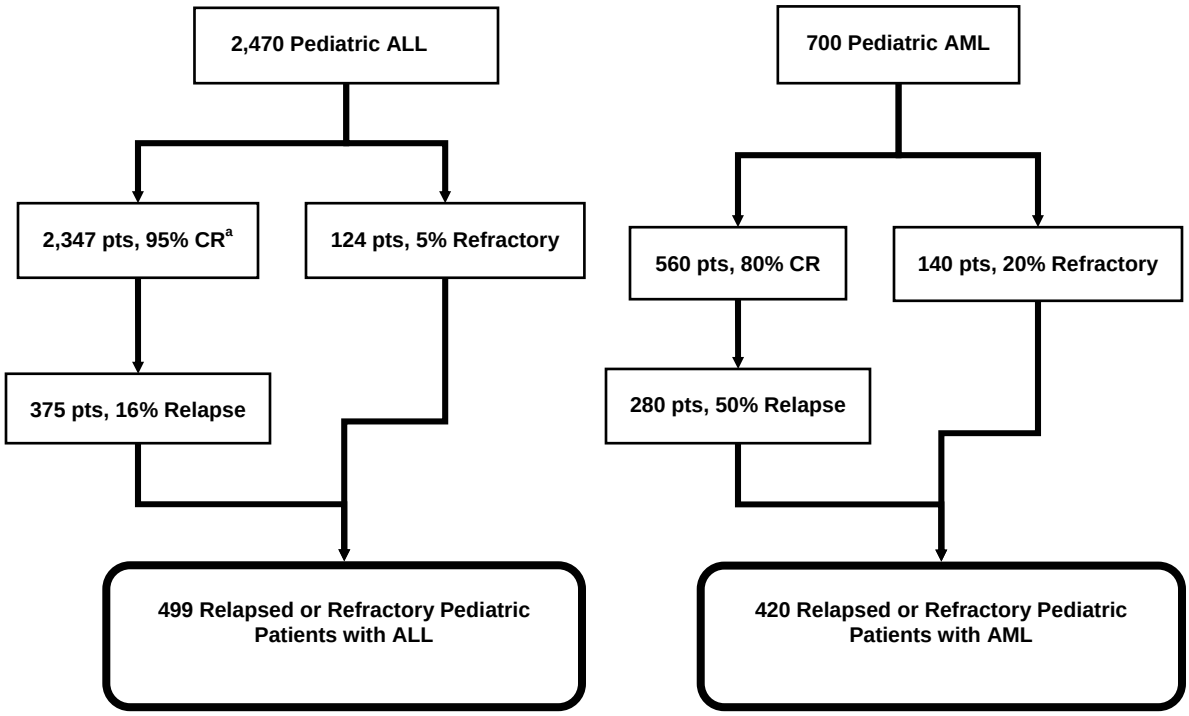
2.1 Disease and Treatment Options

Leukemia is the most common cancer in the pediatric population; acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) are the two most common types of leukemia in pediatric patients. Each year in the United States, approximately 2000 children are diagnosed with ALL, 500 with AML, and <100 with chronic myeloid leukemia (CML).[19] Current therapeutic regimens cure as many as 70% of pediatric patients with ALL and 50% of pediatric patients with AML.[20,21] Unless they are candidates for hematopoietic stem cell transplant (HSCT), the remaining patients do not achieve long-term remission or cure with currently available therapies. In newly diagnosed patients with AML, there are several approaches to dose intensification and combination therapy based upon an Ara-C backbone is usually employed. In newly diagnosed patients with ALL, treatment is more complex, and—for example—may include alkylating agents, antimetabolites, and anthracyclines.

The following figure illustrates the pediatric acute leukemia population as estimated by a cancer surveillance program, SEER*.

* (Surveillance Epidemiology and End Results; NCIs cancer statistics database of incidence and population date)

US Incidence of Pediatric Acute Leukemias



[a]CR = Complete Response
Source: Cancermetric/SEER

Today's pediatric patients with recurrent or refractory acute leukemia are heavily pretreated and, typically, their disease has become cross-resistant to available therapies. Many have already undergone HSCT. As a consequence of their prior therapies, these patients usually have substantial co-morbid conditions. Due to advances in therapy, this modern-day population of children with relapsed or refractory acute leukemia is strikingly different from the published literature of clinical studies targeting the relapsed pediatric acute leukemia population. Thus, this population represents a group of patients with an unmet medical need that has not been addressed in previous controlled clinical studies. Therefore, comparison of the results of the Phase II studies supporting the NDA with other therapies is extremely difficult. Key differences between the population in the Phase II trials and the pediatric population in the literature are as follows:

- Many published results are from small studies (<20 patients) and were investigator studies conducted at a single site.
- Earlier Phase II studies imposed strict limits on the number of prior regimens that patients could have received, often treating patients in first relapse. In addition, these studies rarely included patients who had undergone prior transplant.
- Almost all published results are based exclusively on investigator assessment of response and did not involve an independent review of efficacy.
- Definitions of response terms (complete, partial, etc) varied from study to study and were not often defined in detail. In many studies, complete remission (CR) was defined as <5% bone marrow blasts, but without any reference to recovery of peripheral blood counts.
- Many of the studies conducted were not well controlled with rigorous data collection, monitoring, and reporting.
- "Death on study" was not always clearly defined.

Unfortunately, the underlying leukemogenic disease process–whether in myeloid or lymphoid clonality–is not permanently eliminated in the 30% of patients with ALL and the 50% of patients with AML who are not cured.[22,23,24] Refractory patients may have responded and achieved remission at some point, but then never again achieve remission; whereas relapsed patients achieve remission but their disease recurs. Collectively, multiply relapsed and refractory patients are known to be highly resistant to therapy and represent an extremely challenging subpopulation of leukemia patients.

Once a pediatric patient relapses, the primary therapeutic alternatives include chemotherapy with or without HSCT. For pediatric patients, the timing of relapse is an important prognostic indicator of the type of treatment that should be considered. Relapses are generally classified as early or late. Early relapses occur while on therapy or within 6 months of completing therapy, and late relapses occur more than 6 months off therapy. Relapses can occur in the bone marrow as well as in extramedullary sites, including the central nervous system (CNS) or testes.

In recent years, treatment strategies for pediatric leukemias have increased in intensity and complexity. A consequence of current chemotherapy practices is that the present relapsed

pediatric population has been exposed to more rigorous and intense chemotherapy treatments than patients were 10 to 20 years ago.[25,26,27] Current treatments of cyclic, rotating therapies with combinations of agents with many different mechanisms of action have resulted in relapsed patients who have broad resistance to most of the currently used oncolytics, and who cannot tolerate further chemotherapies due to accumulated organ toxicities; especially cardiovascular, renal, hepatic, and myelosuppressive toxicities. With more intense therapies, accumulated toxicities have become a more difficult clinical issue. Today's relapsing patients are more resistant to subsequent chemotherapy and are thus more challenging and more compromised, often having intercurrent conditions and residual organ toxicity from prior therapies.

Relapse may occur after initial chemotherapy or after a second or third remission. Patients can also relapse after HSCT. Treatment outcomes appear to be better for patients in first relapse versus patients in second or later relapse[22,28] In general, pediatric patients in second remission have a higher probability of event-free survival and long-term survival than those treated after subsequent relapses.[22,23,24] In this regard, the patients studied in this submission represent a population with highly resistant disease, who have become refractory to standard agents, and who have a dismal prognosis.

2.2 Management of Pediatric Patients with Relapsed/Refractory Leukemia

The treatment outcomes of pediatric patients who relapse in second or third remission are characterized by a substantially decreased long-term probability for a complete cure. In a study by Buchanan, et al. of children with ALL, 258/297 patients achieved a second complete hematologic remission; however, only 23 (7.7%) remained continuously leukemia free for 7 or more years after chemotherapy or BMT.[22,29] Most second relapses in the Buchanan study occurred within the first year after achieving second remission, with a median duration of remission of 7 months and median survival of 12 months. It is probable that hematologic relapse during initial chemotherapy or shortly after its completion signifies drug-resistant leukemia in most cases.

Earlier treatments were predominantly cyclic combinations of chemotherapy and irradiation, but did not involve transplant. Today's treatment regimens for relapsed pediatric ALL[30,31,32,33,34,35,36] and relapsed pediatric AML[28,37,38] incorporate the early use of myeloablative transplant as a major treatment component. For example studies have been conducted using a variety of different combinations of chemotherapy agents, including idarubicin plus fludarabine and cytarabine as treatment for refractory or recurrent AML.[39] Treatments for recurrent ALL in children have included combination regimens such as vincristine in combination with cytarabine, methotrexate, and L-asparaginase; vincristine in combination with cytarabine, methotrexate, teniposide, L-asparaginase, and 6-mercaptopurine, and ifosfamide in combination with methotrexate, 6-thioguanine, vindesine, and daunorubicin. These treatment regimens have evolved from single-arm clinical studies in the absence of randomized, controlled clinical trials in these populations.

Patients who proceed to HSCT have a better probability of obtaining a durable long-term, event-free survival compared with those multiply relapsed patients who are treated with chemotherapy alone. Patients who proceed to HSCT early in the course of their leukemia and with a low tumor burden were found to have improved survival.[40] Therefore, a major goal for patients with multiply relapsed leukemia is to reduce the tumor burden and to proceed to HSCT as quickly as possible.

Hematopoietic stem cell transplant is an established therapeutic intervention for pediatric patients with relapsed or primary refractory ALL or AML; especially for patients in second or later remission. Since positive HSCT outcomes are clearly related to disease burden at the time of transplant, reduction of tumor burden prior to HSCT is a primary goal.

While great strides have been made in the treatment of children newly diagnosed with leukemia, successful treatment of relapsed and refractory pediatric leukemias remains an unmet medical need. The number of children with relapsed or refractory leukemia is higher than the incidence of most pediatric malignancies. Approximately 20% to 30% of patients with ALL and an even higher percentage (50%) of patients with AML relapse to currently available treatments. These patients are more resistant to remission reinduction

attempts and have accumulated organ toxicities, especially cardiovascular, renal, and hepatic. They also have diminished marrow reserves and are prone to prolonged myelosuppression. Clearly this population is in need of new therapeutic options for another remission induction attempt with a drug to which the patient is not cross resistant and does not have toxicities similar to those already experienced. Clofarabine satisfied this unmet medical need.

3. REGULATORY HISTORY AND DEVELOPMENT

In March 2002, ILEX assumed responsibility for the M.D. Anderson Cancer Center (MDACC) Investigational New Drug (IND) No. 43,275. Clofarabine was granted Orphan Drug Designation for adult and pediatric ALL on 07 February 2002 and Orphan Drug Designation for adult and pediatric AML on 14 March 2002. The ILEX pre-IND meeting was held on 30 August 2001 and the ILEX IND No. 63,641 was opened on 07 December 2001. The MDACC studies were transferred to the ILEX IND on 11 April 2002.

An End-of-Phase II meeting was held with the FDA on 29 April 2002. ILEX requested Fast Track Designation on 08 May 2003, which was approved by the FDA on 08 July 2003. A pre-NDA package was submitted to the FDA on 15 July 2003. On 13 August 2003, ILEX and the FDA had a pre-NDA teleconference where the following key points were addressed:

- The study designs for CLO-212 and CLO-222 were determined to be acceptable as pivotal studies.
- The 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 FDA.
- No pre-specified minimum OR rate was agreed upon with the FDA for establishing efficacy. FDA stated that identification of a clinically meaningful response rate would be a review issue.
- 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 pharmacokinetic/pharmacodynamic section of the analysis plan was determined to be acceptable.
- ILEX's study design and the endpoints for the ALL study were accepted by the FDA, who determined this approach would be acceptable as the model for the AML study.
- FDA agreed to ILEX's proposal to increase enrollment on CLO-212 from 40 to 60 patients.

The step-wise submission of the NDA was completed on 29 March 2004 and on 14 July 2004, the FDA granted ILEX 6 months additional pediatric exclusivity for clofarabine.

Following the 01 December 1 2004 ODAC meeting which recommended accelerated approval in pediatric relapsed, refractory ALL, ILEX proposed a 2-step post-marketing plan in the 10 December, 2004 submission which included:

- Step 1: A Phase I/II dose escalation study (CLO-216) of Clolar Plus Cytarabine and L-asparaginase in pediatric patients with Refractory or Relapsed ALL (Clolar in combination with the Capizzi II regimen)

- Step 2: A randomized Phase III Trial of Clolar Plus Cytarabine and L-asparaginase vs. Cytarabine and L-asparaginase, comparing one of these two combination regimens incorporated into one of three induction blocks to the other of these two combination regimens incorporated into one of three induction blocks, in Pediatric ALL patients in 1st relapse. This study was based upon the Children's Oncology Group (COG Protocol AALL01P2), and was intended to confirm clinical benefit.

On 28 December 2004 the FDA granted Clolar marketing approval under 21 CFR 314.500 Subpart H for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory ALL after at least two prior regimens.

Following the 10 December 2004 submission, Genzyme received feedback from the FDA as well as several investigators on the initially proposed post-approval commitments.

Concern was raised by the FDA that the proposed randomized trial, which contemplates rotating multi-drug regimens for re-induction therapy in first relapse ALL, may not demonstrate the clinical benefit of Clolar. Further, in discussions with investigators, Genzyme received feedback that the proposed Phase I/II trial, designed to incorporate Clolar into the Capizzi II regimen[41] (a well recognized re-induction regimen in pediatric ALL), comprised of high dose cytarabine (Ara-C) and L-asparaginase, may not be feasible due to potential toxicity concerns. Genzyme subsequently proposed an alternative post marketing plan which was submitted on 14 March 2005 and discussed at the 19 April 2005 meeting with the FDA.

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