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, in concurrence with the Oncologic Drugs Advisory Committeee (ODAC), believes that the pediatric ALL application is approvable under CFR 314.500 Subpart H--Accelerated approval while the pediatric AML indication is not approvable. As indicated in CFR 314.510, post marketing clinical studies should usually be underway at the time of accelerated approval under Subpart H. No such post marketing clinical studies are underway. In addition, a clofarabine regimen suitable for testing in such clinical studies has not been identified. There is uncertainty whether such a regimen can be identified. Further none of the proposed post marketing studies has a realistic chance of demonstrating clofarabine clinical benefit in children with ALL. Clofarabine clinical benefit is difficult to assess in the present 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 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

Approval will be conditional on FDA review of the Phase 1 part of your proposed 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 clinical benefit in children with ALL. Your proposed Phase 1-2 study and time-lines follow.

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 your submission of a clinical study protocol with a realistic chance of demonstrating clofarabine clinical benefit in children with ALL and your commitment to conduct the study and submit the results in an acceptable time frame.

Phase 3 trials, conducted in less refractory pediatric ALL and AML populations, Comparing a clofarabine containing regimen ± transplant to an appropriate control regimen ± 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 (b)(4) (b)(4)) 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.
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 ± 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

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.

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/s/

Martin Cohen

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