# 1 SCIENTIFIC DISCUSSION

## 1.1 Problem statement

Acute leukemia is the most common form of cancer in children, comprising approximately 30 percent of all childhood malignancies. The two most common types of acute leukemia in children are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). ALL is characterised by malignant transformation of lymphoid progenitor cells and is the most common of the paediatric leukaemias. It occurs about 5 times more commonly than does AML. In the UK, it has been estimated that around 450 new cases of leukemia are diagnosed each year.

Over the years, a large number of antineoplastic agents have been evaluated in standardized research protocols. Survival rates for ALL and AML have improved dramatically during the past 20 years, due to the development of new combination regimens. However, approximately 20-25% of ALL in remission still relapse. Children with ALL at high risk of relapse are those with T-cell phenotype, older than 10 years or younger than 1 year of age, with white blood cell count (WBC) larger than 50,000/µl, and with unfavourable cytogenetics (like the Philadelphia chromosome). In spite of efforts to develop new therapeutic agents and novel treatments for relapsed leukemia, there are still limited therapeutic options for these patients and their prognosis is very poor. In some cases, remission induction is attempted with an intensive chemotherapy and/or a stem cell transplantation. In general, given the intensity and number of previous chemotherapeutic regimens, patients with ALL in relapse have a broad resistance to many currently used agents and have concurrent conditions and accumulated organ toxicity, making it difficult to induce a second or third complete remission.

## 1.2 About the product

Background

Clofarabine is a novel, next-generation, halogenated-adenosine analogue. Based upon its mechanism of action as an inhibitor of both ribonucleotide reductase and DNA polymerase α, clofarabine is a member of the class of nucleoside analogue anti-metabolite anticancer agents that includes gemcitabine, fludarabine, and cladribine.

Clofarabine has several distinguishing features compared to other drugs in its class including greater resistance to cellular degradation by adenosine deaminase, increased stability in gastric acid, decreased susceptibility to phosphorolytic cleavage, more efficiency as a substrate for deoxycytidine kinase (exceeding cladribine and the natural substrate deoxycytidine), and, unlike fludarabine, clofarabine is active in non-dividing cells and in cells with a low proliferation rate by inducing apoptosis through its direct and indirect action on mitochondrial function.

Orphan designation in the EU

The European Commission, following the favourable opinion of the EMEA adopted by the Committee for Orphan Medicinal Products (COMP), granted two separate orphan designations for a medicinal product containing 2-chloro-9-[2-deoxy-2-fluoro-ß-D-arabinofuranosyl]adenine (clofarabine) for the treatment of ALL (5 February 2002) and for the treatment of AML (8 May 2003) according to Regulation (EC) No 141/2000. 2-chloro-9-[2-deoxy-2-fluoro-ß-D-arabinofuranosyl] adenine has been entered in the Community Register of Orphan Medicinal Products under the numbers EU/3/01/082 and EU/3/03/141.

Marketing authorisation application in the EU

The current application seeks approval for the use of clofarabine for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤ 21 years old at initial diagnosis. The recommended dose for paediatric patients is 52 mg/m$^2$ of body surface area administered by intravenous infusion over 2 hours daily for 5 consecutive days. Treatment cycles should be repeated every 2 to 6 weeks following recovery of normal haematopoiesis and return to baseline organ function.

The original submission also sought approval for the treatment of paediatric patients (≤ 21 years old) with acute myeloid leukaemia (AML) who are in first or subsequent relapse or are refractory. During the scientific assessment procedure, the applicant withdrew the claim for this indication as the CHMP considered that the clinical documentation provided was not sufficient to establish the clinical efficacy of clofarabine in this patient population. In particular, although one patient achieved a complete response in the absence of total platelet recovery (CRp), no complete response (CR) was observed with clofarabine in the interim results submitted for the non-randomised study CLO-222. The applicant decided to withdraw the paediatric AML indication from this application after further review of the efficacy data collected from study CLO-222, but informed the CHMP that they are planning a future submission for the treatment of AML pending the results of an ongoing study in adult patients.

## 1.3 Quality aspects

**Introduction**

Evoltra is a sterile concentrate for solution for infusion, which is presented in 20 ml vials containing 1 mg/ml of clofarabine as active substance in unbuffered normal saline (comprising water for injections and sodium chloride). The solution is filled in type I glass vials with rubber stoppers, sealed with aluminium bands and polypropylene flip off caps.

**Active Substance**

Clofarabine has the chemical name 2-chloro-9-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-9H-purine-6-amine. It is an off-white to white solid, and its solubility in saline solution at room temperature is sufficient for the manufacturing process and concentration of the drug product.

The chemical structure of clofarabine is well characterised. There are two possible polymorphic forms of clofarabine (form A and form B). Control of the crystallization and drying steps ensures the manufacturing process yields only form A. There is potential isomerism at the anomeric carbon of the arabinofuranose ring and the desired form for clofarabine is the ß anomer.

- Manufacture

The synthesis of clofarabine is carried out in three steps. Adequate In-Process Controls are applied during the synthesis. Satisfactory control methods for starting materials, reagents and intermediate products have been presented.

Batch analysis data presented confirm consistency and uniformity of the manufacturing process.

- Specification

The active substance specification for clofarabine includes tests for: appearance, identity (IR, HPLC), assay (HPLC, 97.0% - 103.0%), related substances (HPLC), pH, water content, residue on ignition, residual solvents, bacterial endotoxins and microbial limits.

Batch data for eight batches showing compliance with the specifications have been presented. The batches include three full scale production batches manufactured at the proposed manufacturing site.

- Stability

The following parameters have been tested: appearance, identity, assay, impurities, water determination, and microbial quality.

Stability studies were performed on a number of batches of the active substance. Samples were stored at 25°C/60%RH and 40°C/75%RH. The results justify the retest period requested.

**Medicinal Product**

- Pharmaceutical Development

The finished product is formulated as a concentrate for solution for infusion. Since the active substance is soluble in the vehicle used, aspects like particle size and polymorphic form are not relevant. The formulation is simple, excipients are commonly used for this kind of formulation, and compatibility is demonstrated in the stability studies.

The chosen commercial formulation is a solution in unbuffered 0.9 % NaCl, which is terminally sterilised in its final container. The impact of this final step has been adequately tested by controlling the product after double terminal sterilisation. The same formulation has been used in all non-clinical and clinical studies.

The suitability of the container/closure system (type I glass vials) was evaluated with respect to protection, safety, compatibility, physico-chemical testing, performance and stability.

- Manufacture of the Product

Manufacturing consists of preparation of the bulk solution, followed by double sterile filtration and filling into vials. The vials are sealed with stoppers, capped and then terminally sterilised by autoclaving.

The manufacturing process has been adequately validated by a number of studies for the main steps of the manufacturing process.

The batch analysis data showed that the finished product can be repeatedly manufactured according to the agreed finished product specification, which is suitable for control of this preparation.

- Product Specification

The finished product specifications include appropriate tests for: physical examination, identity (HPLC, UV), assay (HPLC, 95.0-105.0%), purity (HPLC), pH, particulate matter, extractable volume, sterility endotoxin and osmolarity.

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control. Impurity limits in the specification are justified by toxicology studies.

- Stability of the Product

Stability data of the finished product packed in the intended commercial vial are available for six batches (3 primary and 3 supportive batches) stored under long-term (25°C/60%RH) and under accelerated (40°C/75%RH) ICH conditions. The samples were stored in the inverted position. Stability data provided include results at 24, 18 and 6 months obtained under long term conditions for the 3 primary batches and results at 24 and 18 months obtained under long term conditions for 2 of the 3 supportive batches. Accelerated study results over 6 months were also provided.

The specifications applied at the end of shelf-life are those described at release and the same analytical methods were used.

Photostability testing was conducted on 1 batch by exposure of 3 samples in a horizontal position at room temperature to: 1.2, 2.4, 3.6 and 4.8 million lux hours. The drug product has been assessed for appearance, assay and impurities. There were no significant changes observed.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

**Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product. The applicant committed to resolve these as follow-up measures after the opinion, within an agreed timeframe.

## 1.4 Non-clinical aspects

**Introduction**

The safety pharmacology studies, two pharmacokinetics studies and the pivotal toxicological studies were stated to be GLP-compliant.

**Pharmacology**

- Primary pharmacodynamics

Clofarabine is a purine nucleoside anti-metabolite. Its antitumour activity is believed to be due to 3 mechanisms: DNA polymerase α inhibition resulting in termination of DNA chain elongation and/or DNA synthesis / repair, ribonucleotide reductase inhibition with reduction of cellular deoxynucleotide triphosphate (dNTP) pools, and disruption of mitochondrial membrane integrity with the release of cytochrome C and other proapoptotic factors leading to programmed cell death even in non-dividing lymphocytes. Clofarabine must first diffuse or be transported into target cells where it is sequentially phosphorylated to the mono- and bi-phosphate by intracellular kinases, and then finally to the active conjugate, clofarabine 5'-triphosphate. Clofarabine has high affinity for one of the activating phosphorylating enzymes, deoxycytidine kinase, which exceeds that of the natural substrate, deoxycytidine. In addition, clofarabine possesses greater resistance to cellular degradation by adenosine deaminase and decreased susceptibility to phosphorolytic cleavage than other active substances in its class whilst the affinity of clofarabine triphosphate for DNA polymerase α and ribonucleotide reductase is similar to or greater than that of deoxyadenosine triphosphate.

*In vitro* studies have demonstrated that clofarabine inhibits cell growth in and is cytotoxic to a variety of rapidly proliferating haematological and solid tumour cell lines. It was also active against quiescent lymphocytes and macrophages.

Clofarabine was evaluated *in vivo* in mice implanted IP with $10^6$ parental or drug-resistant P388 murine leukemia cells. Treatment of ADR-, Taxol- and MTX-resistant murine leukemias with clofarabine resulted in net cell kills comparable to those obtained in the sensitive parental leukaemia cells. Marginal cross-resistance was observed with the VP-16-resistant murine leukemia, whereas the ara-C-resistant murine leukemia showed marked resistance to clofarabine. The *in vivo* efficacy of clofarabine was assessed in the SC implanted CCRF-CEM leukemia model in male SCID mice following once daily IP administration of clofarabine or ara-C for either 5 or 14 days, the response with ara-C was more effective than clofarabine administration. A further study was conducted in male SCID mice to evaluate the combined use of clofarabine and ara-C on *in vivo* anti-leukemic activity. Clofarabine and ara-C exhibited antitumor activity against the CCRF-CEM leukemia model, with the combination treatments of 20 mg/kg clofarabine / 6.25 mg/kg ara-C exhibiting greater activity to that observed for either agent alone at these dose levels.

- Secondary pharmacodynamics

No secondary pharmacodynamics studies have been submitted.

- Safety pharmacology programme

A core battery of safety pharmacology studies were conducted in the rat to assess the effects of clofarabine on the CNS, cardiovascular (including an *in vitro* hERG channel assay in transfected HEK cells), respiratory and renal/urinary systems. Dose levels for the CNS, respiratory and renal/urinary systems studies were 6.25, 25 and 50 mg/kg as a single IV injection and plasma levels at these dose levels were established. The cardiovascular study utilised dose levels of 10 and 25 mg/kg/day administered IV for 5 days. The maximum concentration in the hERG assay was 300 μM. Clofarabine showed little or no effect in these studies, except at the highest dose level or concentration.

- Pharmacodynamic drug interactions

The antitumor efficacy of clofarabine in combination with other cytotoxic drugs (ara-C, oxaliplatin, 5-fluorouracil, taxotere, irinotecan and camptosar) has been investigated in human tumor models in mice. Although some of these drugs were toxic when administered alone, this toxicity was not enhanced by combination therapy with clofarabine. In general, antitumor efficacy with combined drug treatment was similar to or only moderately better than that seen with clofarabine alone.

**Pharmacokinetics**

The pharmacokinetics of clofarabine has been studied *in vivo* in mice, rats, and dogs. No nonclinical pharmacokinetic data in animals have been submitted on the phosphorylated metabolites of clofarabine. However, one published report in the literature on the metabolism of clofarabine by cultured human CCRF-CEM T-lymphoblastic cells has been provided.

Absorption

The plasma pharmacokinetics of clofarabine have been determined in mice, rats and in dogs following IV administration. Clofarabine was shown to have a relatively short plasma half-life in all species studied (generally <3 hours). In the mass balance study, there was evidence for a third-γ phase in the plasma concentration-time profile with a half-life of approximately 18 hours. Linear plasma pharmacokinetics were observed for mice at doses up to 13.3 mg/kg (39.9 mg/m$^2$), rats at doses up to 12.5 mg/kg (75 mg/m$^2$), and dogs at doses up to 3 mg/kg (60 mg/m$^2$). Nonlinear plasma pharmacokinetics (as evidenced by a decrease in clearance and an increase in $C_{max}$) were observed between 12.5 and 25 mg/kg/day (75 and 150 mg/m$^2$/day) in female rats in the 6-month study, in male rats dosed between 10 and 25 mg/kg (60 and 150 mg/m$^2$) in a pharmacokinetic study, and in male rats dosed between 25 and 50 mg/kg (150 and 300 mg/m$^2$) in a mass balance study.

Distribution

Clofarabine has moderate protein binding in humans (~47%), but much lower protein binding in rats (~13%). The volume of distribution was about 1.4 to 2.6 L/kg in mice, 3.2 to 3.6 L/kg in rats, and 0.9 to 1.2 L/kg in dogs.

In tissue distribution studies in mice and rats, clofarabine was rapidly distributed to most tissues, except those with special barriers (e.g., eye, brain, and testes). Tissues with the highest concentrations were generally the highly perfused organs, such as spleen, liver, kidney, thymus, bone marrow, and skin in mice and the excretory/metabolic organs (e.g., kidney and liver) and gastrointestinal tract (e.g., small intestine and colon) in rats. The concentration of clofarabine in these tissues was generally greater than 2-fold higher than plasma. Tissue to plasma ratios in myocardium were greater than unity but less than those seen in the gastrointestinal tract and kidney. In contrast, tissues with special barriers had clofarabine concentrations that were lower than in plasma.

Metabolism

In order to exert its activity, clofarabine must be metabolized within tumor cells - firstly to the 5'-monophosphate metabolite by deoxycytidine kinase followed by sequential formation of the 5'-diphosphate and ultimately the 5'-triphosphate metabolite. Studies in cultured T-lymphoblasts indicated that the predominant metabolite was the monophosphate metabolite and that formation of the diphosphate metabolite from the monophosphate metabolite was the rate-limiting step in the formation of clofarabine triphosphate. The monophosphate metabolite within cells may act as a pool for the formation of the triphosphate metabolite.

Clofarabine was very stable when incubated for 6 hours with dog, rat, or human hepatocytes with 95, 96, and 99.8% of parent clofarabine, respectively, unmetabolized. The largest metabolite which was found in the dog, was either carboxy- or methoxy-clofarabine. Each of the other metabolites was less than 1.25% of the total radioactivity in the sample. Only 1 metabolite (clofarabine sulfate) was observed in human hepatocytes. Clofarabine glucuronide (2 positional isomers) and 2-chloroadenine were seen in rat and dog hepatocytes.

In a mass balance study in rats, 6-ketoclofarabine was the metabolite having the greatest concentration in plasma, urine, feces, heart, and liver. The enzyme responsible for the metabolism of clofarabine to 6-ketoclofarabine is unknown, but is probably not cytochrome P450. Given the close structural similarity of clofarabine to adenosine, a likely possible enzyme is adenosine deaminase, an enzyme of purine metabolism that catalyzes the irreversible deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively.

Excretion

Clofarabine was primarily excreted unchanged through renal elimination in an *in vivo* mass balance study in rats. Using radiolabeled clofarabine, 77%, 11%, 6% of the administered dose was found in the urine, feces, and cage wash, respectively. Of the radioactivity in urine, 87% was parent drug and in the feces 7% was parent drug. Based on mass balance, 76% of the dose was excreted through renal clearance, 22% by metabolic clearance, and <1% by biliary clearance. For clofarabine metabolites, clearance was split equally among renal (50%) and biliary (50%) mechanisms. Comparison of the unbound renal clearance to the glomerular filtration rate in rats suggests that clofarabine was actively secreted into urine.

## Pharmacokinetic drug interactions

No pharmacokinetics drug interaction studies have been conducted with clofarabine.

*In vitro* studies investigating clofarabine metabolism in rat and human hepatocytes (described above) and microsomes were conducted and the data demonstrated little or no involvement of the cytochrome P450 system in the metabolism of clofarabine. Two *in vitro* studies to assess the potential inhibitory effect of clofarabine on cytochrome P450 isozyme activity were performed. Clofarabine did not inhibit CYP1A2, CYP2C9, CYP2D6 and CYP3A4. However, a weak inhibition was observed for CYP2C19 in one study at an IC50 value 18-25 fold higher than the $C_{max}$ value seen clinically making it unlikely that any clinically relevant pharmacokinetic interactions would result.

The potential inducing effect of clofarabine on the activity of two major human cytochrome P450 isozymes was investigated *in vitro*. Clofarabine had no statistically significant effect on the activities of CYP1A2 and CYP3A4 at concentrations of 500, 4000 and 12000 ng/mL. The clofarabine concentrations used were approximately 20-30 times higher than the $C_{max}$ reached in the clinic after a dose of 52 mg/m$^2$, making it therefore, highly unlikely that any clinically relevant induction of cytochromes would result.

### Toxicology

A comprehensive toxicology program has been conducted for clofarabine. Pivotal studies are defined as GLP compliant studies utilizing the intended intravenous clinical route. Non-GLP compliant studies and studies utilizing other routes of administration (intraperitoneal and oral) are deemed non-pivotal.

- Single dose toxicity

A single dose study was conducted in Balb/c mice at 75 mg/kg IP and there were no unscheduled deaths. Histopathological findings included changes to male and female reproductive organs, lymphoid tissues and liver. Additional information on single dose toxicity were derived from repeat dose toxicity studies, in male Fischer 344 rats and the mammalian erythrocyte micronucleus test in Sprague Dawley rats of both sexes. In all these studies, a single dose of 100 mg/kg was lethal to all rats dosed.

- Repeat dose toxicity (with toxicokinetics)

**Studies in mice**

Three repeat-dose studies were conducted with clofarabine in Balb/C mice.

The toxicity of clofarabine appeared to be greater when given twice daily as compared to once daily. The target organs of toxicity were found to be the proliferating tissues/organs such as the bone marrow, lymphoid tissue, gastrointestinal tract, and reproductive organs. Gastrointestinal toxicity was determined to be the dose limiting toxicity (DLT).

**Studies in rats**

Five repeat-dose studies were conducted with clofarabine in Fischer 344 rats.

The target organs of toxicity were the bone marrow, GI tract, heart, kidney, liver, lymphoid tissue and testes. The heart was the primary target of toxicity and the cardiotoxic effects of clofarabine were responsible for the deaths occurring in the studies.

The incidence of cardiotoxicity was dependent on both the dose of clofarabine administered and the duration of treatment. They were reported at exposure levels ($C_{max}$) approximately 7 to 13 fold (after 3 or more dosing cycles) or 16 to 35 fold (after one or more dosing cycles) higher than clinical exposures. The minimal effects seen at lower doses suggest that there is a threshold for toxicities on the heart and nonlinear plasma pharmacokinetics in the rat may play a role in the observed effects. The potential risk for humans is unknown.

**Studies in dogs**

Five repeat-dose studies were conducted with clofarabine in Beagle dogs.

Gastrointestinal toxicity was the DLT.

Histopathological changes were essentially limited to rapidly proliferating tissues (i.e., gastrointestinal tract, lymphoid tissue, bone marrow, and testes). In general, there was evidence of recovery from the dose-dependent toxicity associated with the rapidly proliferating tissues and an absence of deterioration with repeated exposure in the surviving animals indicating no cumulative effects. The induction of toxicity and single cell necrosis in rapidly proliferating tissues is an expected reaction to the administration of cytotoxic compounds.

- Genotoxicity

Clofarabine did not show evidence of mutagenic activity in the bacterial gene mutation assay (Ames test), but did show clastogenic activity in the *in vitro* mammalian cell chromosome aberration assay (CHO cells) in a nonactivated test system and in the *in vivo* rat micronucleus assay. The reason for the negative finding in the bacterial gene mutation assay is not known, but is probably related to a lack of the activating enzyme dCK in *Salmonella typhimurum* and *Escherichia coli*. The absence of dCK in *Escherichia coli* and *Salmonella typhimurium* has been documented in the literature. In view of the clastogenic activity, the inhibitory activity in DNA synthesis, and the known genotoxic effects of other anticancer nucleoside anti-metabolites, clofarabine is assumed to have genotoxic potential.

- Carcinogenicity

No carcinogenicity studies have been submitted. The applicant has justified this based on the CPMP Note for Guidance on the Preclinical Evaluation of Anticancer Medicinal Products [CPMP/SWP/997/96].

- Reproductive toxicity

Repeat dose toxicity studies with clofarabine clearly showed toxic effects on reproductive organs in both male and female animals, as might be expected of a cytotoxic agent. Effects on fertility would thus be expected, although specific studies to investigate this have not been performed. Adverse effects on neonates of mothers treated with clofarabine could also be expected but as treatment of this population could be clearly identified and thus contra-indicated, pre-post natal toxicity studies have not been performed. This approach is in agreement with CPMP guidance [CPMP/SWP/997/96]. Studies to investigate potential embryotoxicity, in the rat and rabbit, have been performed.

Clofarabine was teratogenic in rats and rabbits. Increases in postimplantation loss, reduced foetal body weights and decreased litter sizes together with increases in the number of malformations (gross external, soft tissue) and skeletal alterations (including retarded ossification) were reported in rats receiving doses which produced approximately 2 to 3 fold the clinical exposure (54 mg/m$^2$/day) and in rabbits receiving 1 mg/kg/day (12 mg/m$^2$/day) clofarabine. There are no exposure data in rabbits. The threshold for developmental toxicity was considered to be 1 mg/kg/day (6 mg/m$^2$/day) in rats and 0.1 mg/kg/day (1.2 mg/m$^2$/day) in rabbits. The no-observable effect level for maternal toxicity in rats was 3 mg/kg/day (18 mg/m$^2$/day) and in rabbits was more than 1 mg/kg/day (12 mg/m$^2$/day). No studies in juvenile animals have been conducted.

- Toxicokinetic data

Chronic studies, with toxicokinetics, were conducted with clofarabine in Fisher 344 rats and in Beagle dogs with once daily IV dosing for 5 days followed by 23 days observation; each cycle repeated over a 6 month period.

In the chronic rat study, with up to 6 treatment/recovery cycles, the MTD was 12.5 mg/kg/day (75 mg/m$^2$/day) corresponding to an $AUC_{(0-10)}$ of 10585 to 11240 on Day 145 (end of the sixth period of dosing). In the chronic dog study, with up to 6 treatment/recovery cycles, the MTD was 0.75 mg/kg/day (15 mg/m$^2$/day) corresponding to an $AUC_{(0-12)}$ of 1484 to 1370 on Day 145 (end of the sixth period of dosing).

**Interspecies comparison**

Species differences were noted in the toxicity induced in mice, rats, and dogs following administration of clofarabine. Based upon a comparison of their respective MTD values, the rank order of species sensitivity to clofarabine-induced toxicity is as follows: Dog>Rat>Mouse. Based upon their respective MTD values, clofarabine produces dose-limiting toxicity in the dog at doses approximately 5- to 17-fold lower (mg/m$^2$/day and mg/kg/day basis, respectively) than the rat. Similarly, the rat is approximately 3- to 8-fold more sensitive to the toxic effects of clofarabine than the mouse. Gastrointestinal toxicity was dose limiting and the cause of death for mice and dogs, whilst cardiotoxicity was considered to be responsible for the deaths of most rats. Clofarabine-induced cardiotoxicity was not seen in the dog. One possible explanation for the absence of cardiotoxicity in the dog may be related to the lower systemic exposure of clofarabine in dogs when compared to rats (i.e., the gastrointestinal toxicity in dogs prevented administration of higher doses and systemic exposure). When compared across all studies, the rapidly proliferating organs (bone marrow, lymphoid organs, gastrointestinal tract, and testes) were target organs of toxicity for clofarabine in mice, rats, and dogs. The heart, liver, and kidney were additional target organs of toxicity in the rat, but not in mice or dogs.

- Local tolerance

No local tolerance studies have been conducted with clofarabine. As expected, some injection site reactions were observed following intravenous administration.

**Ecotoxicity/environmental risk assessment**

The potential environmental impact of clofarabine has been assessed in line with the draft Note for Guidance on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00 draft). Regarding the environmental risk assessment, no adverse environmental effects are expected with clofarabine.

**Discussion on the non-clinical aspects**

A core battery of safety pharmacology studies have been conducted in the rat comprising assessment of the effects of clofarabine on the CNS, cardiovascular, respiratory and renal/urinary systems. Clofarabine showed little or no effect in these studies, except at the highest dose level or concentration.

Preclinical pharmacokinetic studies were conducted in mice, rats, and dogs after intravenous administration. In addition, the metabolism of clofarabine was investigated in isolated hepatocytes from rats, dogs, and humans as well as in human T-lymphoblast leukemia CCRF-CEM cells.

Clofarabine was shown to have a relatively short plasma half-life in all species studied (generally <3 hours). In the mass balance study, there was evidence for a third-γ phase in the plasma concentration-time profile with a half-life of approximately 18 hours.

Clofarabine has low protein binding in rats (~13%). The volume of distribution was about 1.4 to 2.6 L/kg in mice, 3.2 to 3.6 L/kg in rats, and 0.9 to 1.2 L/kg in dogs. Tissues with the highest concentrations of clofarabine were generally the highly perfused organs, such as spleen, liver, kidney, thymus, bone marrow, and skin in mice and the excretory/metabolic organs (kidney and liver) and gastrointestinal tract (small intestine and colon) in rats. Tissue to plasma ratios in myocardium were greater than unity but less than those seen in the gastrointestinal tract and kidney.

In order to exert its activity, clofarabine must be metabolized within tumor cells - firstly to the 5'-monophosphate metabolite by deoxycytidine kinase followed by sequential formation of the 5'-diphosphate and ultimately the 5'-triphosphate metabolite. The largest metabolite which was found in the dog, was either carboxy- or methoxy-clofarabine. Clofarabine glucuronide (2 positional isomers) and 2-chloroadenine were seen in rat and dog hepatocytes. In a mass balance study in rats, 6-

ketoclofarabine was the metabolite having the greatest concentration in plasma, urine, feces, heart, and liver.

Clofarabine was primarily excreted unchanged through renal elimination in an *in vivo* mass balance study in rats. Using radiolabeled clofarabine, 77%, 11% and 6% of the administered dose was found in the urine, feces and cage wash, respectively.

No pharmacokinetics drug interaction studies have been conducted with clofarabine. Clofarabine is not detectably metabolised by the cytochrome P450 (CYP) enzyme system. Therefore, it is unlikely to interact with active substances which inhibit or induce cytochrome P450 enzymes. In addition, clofarabine is unlikely to inhibit any of the major 5 human CYP isoforms (1A2, 2C9, 2C19, 2D6 and 3A4) or to induce 2 of these isoforms (1A2 and 3A4) at the plasma concentrations achieved following intravenous infusion of 52 mg/m$^2$/day. As a result, it is not expected to affect the metabolism of active substances which are known substrates for these enzymes.

Toxicology studies of clofarabine in mice, rats and dogs showed that rapidly proliferating tissues were the primary target organs of toxicity.

The heart was the primary target of toxicity and the cardiotoxic effects of clofarabine were responsible for the deaths of most rats**.** The cardiac effects observed in rats were consistent with cardiomyopathy and contributed to signs of cardiac failure after repeated cycles of treatment. The incidence of these toxicities was dependent on both the dose of clofarabine administered and the duration of treatment. They were reported at exposure levels ($C_{max}$) approximately 7 to 13 fold (after 3 or more dosing cycles) or 16 to 35 fold (after one or more dosing cycles) higher than clinical exposures. The minimal effects seen at lower doses suggest that there is a threshold for toxicities on the heart and nonlinear plasma pharmacokinetics in the rat may play a role in the observed effects. The potential risk for humans is unknown. A 5 day repeat dose toxicity study was conducted in rats to evaluate the use of troponin I and creatine kinase MB isoenzyme (CK-MB) as cardiac biomarkers. CK-MB appears to be a biomarker for the observed cardiotoxicity (data not shown).

Glomerulonephropathy was reported in rats at exposure levels 3 to 5 fold higher than the clinical AUC after 6 dosing cycles of clofarabine. It was characterised by minor thickening of the glomerular basement membrane with only slight tubular damage and was not associated with changes in serum chemistry.

Hepatic toxicity was observed in rats following chronic administration of clofarabine. These likely represent the superimposition of degenerative and regenerative changes as a result of treatment cycles, and were not associated with changes in serum chemistry. Histological evidence of hepatic effects was seen in dogs following acute administration of high doses, but was also not accompanied by changes in serum chemistry.

Dose related toxicities on male reproductive organs were observed in mice, rats and dogs. These effects included bilateral degeneration of the seminiferous epithelium with retained spermatids and atrophy of interstitial cells in rats at exaggerated exposure levels (150 mg/m$^2$/day), and cell degeneration of the epididymis and degeneration of the seminiferous epithelium in dogs at clinically relevant exposure levels ($\geq$ 7.5 mg/m$^2$/day clofarabine). Delayed ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice at the only dose used of 225 mg/m$^2$/day clofarabine.

Clofarabine did not show evidence of mutagenic activity in the bacterial gene mutation assay (Ames test), but did show clastogenic activity in the *in vitro* mammalian cell chromosome aberration assay (CHO cells) in a nonactivated test system and in the *in vivo* rat micronucleus assay.

No carcinogenicity studies have been conducted with clofarabine. This is in agreement with the CPMP Note for Guidance on the Preclinical Evaluation of Anticancer Medicinal Products [CPMP/SWP/997/96]. Taking into account the short life-expectancy of patients with relapsed or refractory ALL, the lack of such studies can be considered justified.

No studies to investigate the effects on fertility and pre-post natal developmental toxicity have been performed. Embryo-foetal developmental toxicity studies were conducted in rats and rabbits. Clofarabine was teratogenic in rats and rabbits. The threshold for developmental toxicity was considered to be 1 mg/kg/day (6 mg/m$^2$/day) in rats and 0.1 mg/kg/day (1.2 mg/m$^2$/day) in rabbits. The

no-observable effect level for maternal toxicity in rats was 3 mg/kg/day (18 mg/m$^2$/day) and in rabbits was more than 1 mg/kg/day (12 mg/m$^2$/day). No studies in juvenile animals have been conducted.

There are no data on the use of clofarabine in pregnant women. Studies in animals have shown reproductive toxicity including teratogenicity. Clofarabine may cause serious birth defects when administered during pregnancy. Therefore, Evoltra should not be used during pregnancy, especially not during the first trimester, unless clearly necessary (i.e. only if the potential benefit to the mother outweighs the risk to the foetus). If a patient becomes pregnant during treatment with clofarabine, they should be informed of the possible hazard to the foetus.

It is unknown whether clofarabine or its metabolites are excreted in human breast milk. The excretion of clofarabine in milk has not been studied in animals. Because of the potential for serious adverse reactions in nursing infants, breastfeeding should be discontinued prior to, during and following treatment with Evoltra.

Females of childbearing potential and sexually active males must use effective methods of contraception during treatment. Dose related toxicities on male reproductive organs have been observed in mice, rats and dogs, and toxicities on female reproductive organs have been observed in mice. As the effect of clofarabine treatment on human fertility is unknown, reproductive planning should be discussed with patients as appropriate.

No local tolerance studies have been conducted with clofarabine.

## 1.5 Clinical aspects

### Introduction

Evoltra is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients $\leq 21$ years old at initial diagnosis (see SPC section 5.1). Therapy must be initiated and supervised by a physician experienced in the management of patients with acute leukaemias.

For paediatric patients, the recommended dose is 52 mg/m$^2$ of body surface area administered by intravenous infusion over 2 hours daily for 5 consecutive days. Body surface area must be calculated using the actual height and weight of the patient before the start of each cycle. Treatment cycles should be repeated every 2 to 6 weeks (from the starting day of the previous cycle) following recovery of normal haematopoiesis (i.e. ANC $\geq 0.75 \times 10^9$/l) and return to baseline organ function. A 25% dose reduction may be warranted in patients experiencing significant toxicities.

Evoltra 1 mg/ml concentrate for solution for infusion must be diluted prior to administration (see SPC section 6.6). The recommended dosage should be administered by intravenous infusion although it has been administered via a central venous catheter in ongoing clinical trials. Evoltra must not be mixed with or concomitantly administered using the same intravenous line as other medicinal products (see SPC section 6.2).

The applicant originally filed in July 2004 using interim data from study CLO-212 to support the claim for efficacy in ALL. The data cut-off date for this interim report was 21 November 2003 and at that time 40 patients had been enrolled in the study. A second interim report was generated using a data cut-off date of 30 September 2004. At this time, recruitment was complete and 61 patients had received clofarabine in study CLO-212. The applicant submitted further updated efficacy data using a data cut-off date of 30 September 2005, which included longer follow-up of the 61 patients in study CLO-212.

Likewise, the original submission included an interim report for study CLO-222 (AML) with a database cut-off date of 21 November 2003; 30 patients had received clofarabine at this time. Two further updates for study CLO-222 were generated to expand the safety data. The first update was based on data collected up to 30 September 2004, at this time recruitment was complete with 42 patients treated; the second update (data cut-off date 30 September 2005) provided additional safety data on the ongoing patients.

**Pharmacokinetics**

Pharmacokinetics of clofarabine have been studied in five of the clinical trials (see table PK1). Clofarabine was initially studied in a phase I dose escalating study in adults with haematologic and solid tumors (DM93-06). Significant efficacy in heavily pre-treated patients with relapsed or refractory leukemia in this study led to a dose escalating study in paediatric patients with either relapsed or refractory ALL or relapsed or refractory AML (study ID99-383), which is in accordance with NfG CPMP/EWP/569/02. Pharmacokinetic data from these two dose escalating studies was sparse.

Pharmacokinetic parameters were calculated from some patients in the pivotal study CLO-212 and study CLO-222 in paediatric patients. Study CLO-221 in adult patients provided supportive pharmacokinetic information.

In addition to non-parametric evaluation of the pharmacokinetics of clofarabine in CLO-212 and CLO-222, data obtained in studies ID99-383, CLO-212 and CLO-222 have been combined and pharmacokinetic parameters were estimated by population pharmacokinetic analysis of the data. Nonlinear mixed effects modeling using NONMEM (Version 5) was used to characterize the pharmacokinetics of clofarabine in plasma and intracellular clofarabine triphosphate in the paediatric patient population.

**Table PK1. Clinical studies in which pharmacokinetic data were obtained.**

| Protocol number Patients | Objective(s) of the study | Cancer type | n[1] | Doses | Regimen |
|---|---|---|---|---|---|
| DM93-036 Adults | Maximum tolerated dose | Solid and hematologic malignancies | 51/40 | 1.5 to 55 mg/m$^2$ | IV for 1 hour every day for 5 days every 3 to 4 weeks |
| ID99-383 Paediatrics | Maximum tolerated dose | Hematologic malignancies | 25/12 | 11 to 70 mg/m$^2$ | IV for 1 to 3 hours every day for 5 days every 2 to 6 weeks |
| CLO-212 Paediatrics (Nov 2003 cut-off) | Efficacy / safety | ALL | 40/14 | 52 mg/m$^2$ | IV for 2 hours every day for 5 days every 2 to 6 weeks |
| CLO-222 Paediatrics (Nov 2003 cut-off) | Efficacy / safety | AML | 30/14 | 52 mg/m$^2$ | IV for 2 hours every day for 5 days every 2 to 6 weeks |
| CLO-221 Adults | Efficacy / safety | AML | 40/13 | 40 mg/m$^2$ | IV for 1 hour every day for 5 days every 28 days |

[1] Denotes the number of patients enrolled who received study drug and the number of patients for whom pharmacokinetic data were obtained.

Study DM93-036 was a phase I, open-label, dose escalating study of clofarabine administered to adult patients with solid tumors or hematologic malignancies who failed standard therapy. The primary objective of this study was to determine the MTD and toxicity profile of clofarabine administered IV over 1 hour each day for 5 consecutive days in adult patients. Dose range of clofarabine administered was 1.5 to 55 mg/m$^2$. Of the 51 patients enrolled in the study, pharmacokinetic data were available from 40 patients. Blood samples were not drawn at specific times. Blood samples were analysed for clofarabine, intracellular clofarabine triphosphate and 2-chloroadenine (at the two highest doses). The data were insufficient to characterize the pharmacokinetics using non-compartmental methods and too sparse for the use of population-based pharmacokinetic methods.

The safety and efficacy of clofarabine were evaluated in a phase I, open-label, non-comparative, dose-escalation study in 25 paediatric patients with relapsed or refractory leukaemia (17 ALL;

8 AML) who had failed standard therapy or for whom no other therapy existed (Study ID99-383). Dosing commenced at 11.25 with escalation to 15, 30, 40, 52 and 70 mg/m$^2$/day by intravenous infusion for 5 days every 2 to 6 weeks depending on toxicity and response. Thirteen of these patients (9 ALL, 4 AML) were treated with the 52 mg/m$^2$/day clofarabine regimen. Of the 17 ALL patients, 4 achieved a complete remission (24%; CR) and 1 a partial remission (6%; PR) at varying doses. Dose-limiting toxicities in this study were hyperbilirubinaemia, elevated transaminase levels and maculo-papular rash experienced at 70 mg/m$^2$/day (2 ALL patients; see SPC section 4.9).

The design of study CLO-212 (ALL) is described in the section on Clinical Efficacy. Study CLO-222 was a phase II, non-randomised, open-label, single arm study of clofarabine at 52 mg/m$^2$/day iv administered over 2 hours daily for 5 consecutive days and repeated every 2 to 6 weeks in patients with refractory or relapsed AML. Of the 40 patients initially enrolled in study CLO-212, pharmacokinetics were available from 14 patients (mean age of 11.4 years; range from 2 to 17 years). Of the 30 patients initially enrolled in study CLO-222, pharmacokinetics were available from 14 patients (mean age of 12.3 years; range from 2 to 19 years). In both CLO-212 and CLO-222 studies, blood samples for pharmacokinetic analysis were taken predose and at 2 (end of infusion), 3, 4, 5, 10 (or just prior to leaving clinic), and 24 hours. The same sampling schedule was used on day 5 with the exception that a 24 hour sample was not collected. Urine samples were collected prior to infusion on day 1 and at 0 to 8 hours and 8 to 24 hours on days 1 and 5.

Study CLO-221 was a phase II, open label, single-arm study with clofarabine 40 mg/m$^2$ administered by 1 hour intravenous infusion once daily for 5 days every 28 days in adult patients with refractory or relapsed AML. Of the 40 patients enrolled, pharmacokinetics were available from 13 patients. Blood samples for pharmacokinetic analysis were drawn predose, at 0.5, 1 (end of infusion), 2, 3, and 7 (or just prior to leaving clinic), and 24 hours (pre-dose on day 2) on day 1 and predose (0 hours), at the end of infusion (1 hour) and 7 hours (or just prior to leaving clinic) on day 5. Urine samples were collected prior to infusion on day 1 and at 0 to 6 hours and 6 to 24 hours on days 1 and 5.

- Absorption

To date, clofarabine has only been administered by intravenous infusion. Bioavailability of clofarabine is 100% and no studies regarding bioequivalence or influence of food have been conducted.

Plasma clofarabine concentrations were generally maximal at the end of infusion. Plasma concentrations declined rapidly thereafter and exhibited biphasic kinetics. Table PK2 summarises the pharmacokinetic parameters determined in two paediatric studies (CLO-212 and CLO-222) and in a study in adult patients with AML (CLO-221). Clofarabine showed similar pharmacokinetic behavior both in children with ALL (CLO-212) and in those with AML (CLO-222). Clofarabine showed comparable pharmacokinetic behaviour in adult patients after administration of clofarabine at 40 mg/m$^2$ as in paediatric patients after administration of 52 mg/m$^2$ clofarabine. Clofarabine plasma terminal half-life was approximately 5 to 6 hours in paediatric and adult patients.

- Distribution

Clofarabine had a relatively large volume of distribution of about 260 L in paediatric patients suggesting extensive tissue distribution. Using equilibrium dialysis, clofarabine was 27% ± 2% (mean ± SD) bound to human serum albumin and 47.1% ± 7.6% bound to human plasma proteins at a concentration of 304 ng/ml (1μM) [Reichelova et al. 1995].

**Table PK2: Summary statistics for pharmacokinetic parameters for paediatric patients in studies CLO-212 and CLO-222 receiving a single dose of 52 mg/m$^2$ clofarabine over 2 hours by intravenous infusion or for adult patients in study CLO-221 receiving a single dose of 40 mg/m$^2$ clofarabine over 1 hour by intravenous infusion.**

| | CLO-212 Paediatric: 52 mg/m$^2$ | | CLO-222 Paediatric: 52 mg/m$^2$ | | CLO-221 Adult: 40 mg/m$^2$ | |
|---|---|---|---|---|---|---|
| | **n** | **Mean ± SD** | **n** | **Mean ± SD** | **n** | **Mean ± SD** |
| AUC(0-∞) (ng*h/mL) | 11 | 1726 ± 586 | 10 | 2044 ± 480 | 7 | 2618 ± 826 |
| AUC(0-8h) | | | | | | |
| day 1 | 11 | 1224 ± 351 | 13 | 1358 ± 417 | | |
| day 5 | 10 | 1757 ± 1043 | 9 | 1606 ± 407 | | |
| Cmax (ng/mL) | | | | | | |
| day 1 | 11 | 403 ± 171 | 13 | 418 ± 229 | 13 | 621 ± 468 |
| day 5 | 12 | 559 ± 302 | 11 | 471 ± 128 | | |
| CL (L/h) | 11 | 43 ± 19 | 10 | 39 ± 16 | 7 | 31 ± 16 |
| Half-life (h) | 11 | 4.7 ± 1.8 | 10 | 5.7 ± 2.0 | 7 | 6.2 ± 1.6 |
| Vdss (L) | 11 | 251 ± 142 | 10 | 274 ± 156 | 7 | 173 ± 77 |
| Renal CL (L/h) | | | | | | |
| Day 1 | 7 | 29 ± 28 | 10 | 27 ± 21 | 11 | 18 ± 12 |
| Day 5 | 7 | 21 ± 17 | 6 | 35 ± 25 | 11 | 25 ± 19 |
| % dose | | | | | | |
| excreted in | 7 | 49 ± 21 | 11 | 61 ± 37 | 11 | 58 ± 33 |
| urine | 7 | 47 ± 32 | 7 | 69 ± 30 | 11 | 53 ± 13 |

- Elimination

Based on preclinical studies and previous experience with nucleoside analogs there are four possible major metabolic routes that could be responsible for the biotransformation of clofarabine in man: intracellular metabolism to the phosphate derivatives, metabolism by cytochrome P450 enzymes, metabolism to 2-chloroadenine, and metabolism to 6-ketoclofarabine.

Clofarabine is absorbed via diffusion into peripheral mononuclear cells whereupon it is sequentially metabolized to its mono-, di-, and ultimately active triphosphorylated form. Non-renal clearance may represent metabolism to the mono-, di-, and triphosphate metabolites, although it seems unlikely that this route of metabolism is responsible for the major biotransformation of clofarabine.

In isolated human hepatocytes, clofarabine showed metabolic stability with < 0.2% of the drug metabolized after 6 hours suggesting that clofarabine is not metabolized by cytochrome P450 enzymes and as such would not be expected to be affected by other drugs that are metabolized by this enzyme system or by drugs that induce or inhibit the metabolism by this class of enzymes.

Clofarabine did not appear to be metabolized to 2-chloroadenine in humans as all clinical samples analyzed (Study DM93-036) were below the detection limit of 10 ng/mL. 6-ketoclofarabine concentrations were not monitored in clinical studies as preclinical data suggested that this was a minor metabolite.

In study ID99-383, from 10 paediatric patients, 29 quantifiable samples of clofarabine triphosphate were measured. Intracellular triphosphate concentrations ranged from 2990 to 10329 ng/mL 1 hour after the end of infusion of 52 mg/m$^2$ clofarabine. No clear correlation between the administered dose of clofarabine and cellular clofarabine triphosphate concentration nor between cellular triphosphate concentration and time was observed. At 24 hours post-dose, all five paired samples at the end of infusion and 24 hours later had retained more than half their initial triphosphate concentration.

Estimation of clofarabine triphosphate concentrations in the mononuclear cell fraction isolated from blood samples taken from 26 adult patients with hematologic malignancies in study DM93-036 revealed wide between-subject variability with variability increasing with increasing dose. At 40 mg/m$^2$, the maximum tolerated dose, intracellular clofarabine triphosphate concentrations ranged from 706 to 30986 ng/mL at the end of infusion on day 1. At 24 hours post-dose, 15 of 24 patients who had paired samples at the end of infusion and 24 hours later had retained more than half their initial triphosphate concentration.

About 57% of the clofarabine dose was excreted unchanged in urine in a 24 hour period (CLO-212 and CLO-222) resulting in a renal clearance of 28 L/h (Table PK2). Renal clearance was not affected after repeated dosing (comparison day 5 vs day 1).

Given an unbound fraction of 0.53 in human plasma [Reichelova et al. 1995], the unbound renal clearance of clofarabine was estimated at about 20.4 L/h/$m^2$, which was much greater than the glomerular filtration rate in humans (4.1 L/h/$m^2$) suggesting filtration and tubular secretion as kidney elimination mechanisms. It is difficult to speculate the nature of the active transport site or what other substrates may inhibit the secretion of clofarabine but the human organic acid transporter 1 (hOAT1) may be a likely candidate as it is responsible for the transport of other types of nucleoside analogs, like acyclovir and ganciclovir [Takeda et al. 2002].

**Table PK3: Pharmacokinetics in patients aged between 2 to 19 years old with relapsed or refractory ALL or AML following administration of multiple doses of clofarabine by intravenous infusion**

| Parameter | Estimates based on non-compartmental analysis (n = 14 / n = 14) | Estimates based on other analysis |
|---|---|---|
| ***Distribution:*** | | |
| Volume of distribution (steady state) | 172 l/$m^2$ | |
| Plasma protein binding | | 47.1% |
| Serum albumin | | 27.0% |
| ***Elimination:*** | | |
| β half-life of clofarabine | 5.2 hours | |
| Half-life of clofarabine triphosphate | | > 24 hours |
| Systemic clearance | 28.8 l/h/$m^2$ | |
| Renal clearance | 10.8 l/h/$m^2$ | |
| Dose excreted in urine | 57% | |

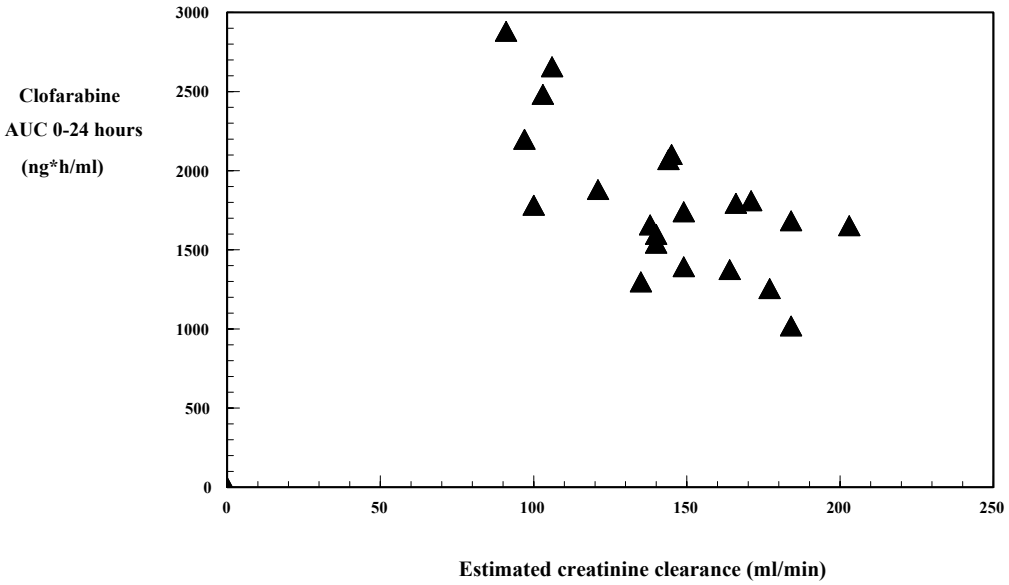
- Special populations

There are currently insufficient data to establish the safety and efficacy of clofarabine in adult patients (> 21 years old including the elderly).

Multivariate analysis showed that the pharmacokinetics of clofarabine are weight dependent and although white blood cell (WBC) count was identified as having an impact on clofarabine pharmacokinetics, this did not appear sufficient to individualise a patient's dosage regimen based on their WBC count. Intravenous infusion of 52 mg/$m^2$ clofarabine produced equivalent exposure across a wide range of weights. However, $C_{max}$ is inversely proportional to patient weight and, therefore, small children may have a higher $C_{max}$ at the end of infusion than a typical 40 kg child given the same dose of clofarabine per $m^2$. Accordingly, longer infusion times should be considered in children weighing < 20 kg.

The pharmacokinetics of clofarabine have not been studied in patients with renal or hepatic dysfunction. However, based on limited data, clofarabine may accumulate in patients with decreased creatinine clearance (see figure 1).

**Figure 1. Clofarabine $AUC_{0-24}$ hours by baseline estimated creatinine clearance in patients aged between 2 to 19 years old with relapsed or refractory ALL or AML (n = 11 / n = 12) following administration of multiple doses of clofarabine by intravenous infusion (Creatinine clearance estimated using Schwartz formula)**




- Pharmacokinetic interaction studies

No clinical drug-drug interaction studies have been conducted.

**Pharmacodynamics**

No clinical pharmacodynamic studies were submitted.

**Discussion on Clinical pharmacology**

Population kinetic modelling indicated that children weighing <20 kg may have higher maximum concentrations of clofarabine at the end of infusion. Therefore, the applicant has recommended a dose adjustment in children weighing <20 kg in section 4.2 of the SPC to avoid unduly high maximum concentrations of clofarabine, which is acceptable.

There is currently limited experience of patients receiving more than 3 treatment cycles (see SPC section 4.4). The majority of patients who respond to clofarabine achieve a response after 1 or 2 treatment cycles (see SPC section 5.1). Therefore, the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after 2 treatment cycles should be assessed by the treating physician (see SPC section 4.4).

There are no data on the pharmacokinetics, safety or efficacy of clofarabine in infants (children < 1 year old). Therefore, a safe and effective dosage recommendation for patients (< 1 year old) has yet to be established.

There is no experience in patients with renal insufficiency (serum creatinine ≥ 2 x ULN for age) and clofarabine is predominately excreted via the kidneys. Therefore, clofarabine is contraindicated in patients with severe renal insufficiency (see SPC section 4.3) and should be used with caution in patients with mild to moderate renal insufficiency (see SPC section 4.4). To date, there are insufficient data on the pharmacokinetics of clofarabine in patients with decreased creatinine clearance to advise a dose reduction in such patients. However, these limited data indicate that clofarabine may accumulate in patients with decreased creatinine clearance (see SPC sections 4.4 and 5.2).

There is no experience in patients with hepatic impairment (serum bilirubin > 1.5 x ULN plus AST and ALT > 5 x ULN) and the liver is a potential target organ for toxicity. Therefore, clofarabine is contraindicated in patients with severe hepatic impairment (see SPC section 4.3) and should be used with caution in patients with mild to moderate hepatic impairment (see SPC section 4.4).

No clinical drug-drug interaction studies have been conducted. On the basis of the limited metabolism seen in isolated human hepatocytes, cytochrome P450 inhibitors or inducers are not likely to affect clofarabine's metabolism. In addition, clofarabine is unlikely to inhibit any of the major 5 human CYP isoforms (1A2, 2C9, 2C19, 2D6 and 3A4) or to induce 2 of these isoforms (1A2 and 3A4) at the plasma concentrations achieved following intravenous infusion of 52 mg/m$^2$/day. As a result, it is not expected to affect the metabolism of active substances which are known substrates for these enzymes.

Clofarabine is predominately excreted via the kidneys and the liver is a potential target organ for toxicity. Hence, the concomitant use of medicinal products that have been associated with renal toxicity and those eliminated by tubular secretion should be avoided particularly during the 5 day clofarabine administration period (see SPC sections 4.4, 4.8 and 5.2). In addition, the concomitant use of medicinal products that have been associated with hepatic toxicity should be avoided wherever possible (see SPC sections 4.4 and 4.8). Patients taking medicinal products known to affect blood pressure or cardiac function should be closely monitored during treatment with clofarabine (see SPC sections 4.4 and 4.8).

**Clinical efficacy**

One non-comparative phase II study in paediatric patients has been submitted in children with refractory or relapsed ALL (CLO-212). Currently clofarabine is being studied in adults with solid tumors and AML, and in combination with Ara-C in adults with acute leukaemias. The applicant is currently conducting an uncontrolled Phase II study in paediatric patients with refractory or relapsed ALL and a study in elderly adults with AML who are not suitable for intensive chemotherapy.

- Dose response studies

Clofarabine was initially studied in an exploratory, dose-finding study in adults with hematologic and solid tumours (DM93-036). Activity was observed in patients with acute leukaemia at 40 mg/m$^2$. The dose limiting toxicity in patients with acute leukaemia was hepatotoxicity and the MTD was determined to be 40 mg/m$^2$. This study led to a dose-ranging study (ID99-383) in children with a diagnosis of either relapsed or refractory ALL or relapsed or refractory AML.

Study ID99-383 has been described under clinical pharmacokinetics. A total of 25 patients (17 with ALL and 8 with AML) were included. The DLT was grade 4 hyperbilirubinaemia and grade 3 maculopapular rash, and the MTD for this patient population was 52 mg/m$^2$. All patients received at least one cycle of clofarabine and more than half of the patients received 52 mg/m$^2$. Overall, 8/25 (32%) of the patients achieved either a CR (5/25, 20%) or PR (3/25, 12%). Of the 5 complete responders, 1 ALL patient had received 30 mg/m$^2$, two ALL patients had received 40 mg/m$^2$, one AML patient had received 52 mg/m$^2$, and one ALL patient had received 70 mg/m$^2$ clofarabine. No clear correlation between the administered dose of clofarabine and cellular clofarabine triphosphate concentration nor between cellular triphosphate concentration and time was observed.

- Main study

Study CLO-212

METHODS

Study CLO-212 was a phase II, non-randomized, open-label, single-arm study of clofarabine in paediatric patients with ALL who were not eligible for therapy of higher curative potential, and who were in second or subsequent relapse and/or refractory.

*Study Participants*

Inclusion criteria for study CLO-212 required paediatric patients with a diagnosis ALL who were ineligible for therapy of higher curative potential, and who were in second or subsequent relapse and/or refractory. The definition of paediatric included all patients who were ≤ 21 years of age at the time of initial diagnosis. The diagnosis of ALL was according to the French American British (FAB) classification with ≥ 25% blasts in the bone marrow and was confirmed by an independent pathologist. Patients with a Karnofsky Performance Status ≥ 50 with adequate renal (serum creatinine < 2 x upper limit of normal for age [ULN]) and liver function (serum bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 5 x ULN) measured within 2 weeks before registration were eligible to enrol.

*Treatments*

Patients received clofarabine 52 mg/m$^2$ day for 5 consecutive days as an iv infusion over 2 hours. Treatment cycles could be repeated every 2 to 6 weeks following recovery of normal haematopoiesis (i.e. ANC $\geq 0.75 \times 10^9$/l) and return to baseline organ function. Treatment was continued until disease relapse for a potential maximum of 12 cycles. Patients who achieved a CR were eligible to receive a haematologic stem cell transplant (HSCT). Doses were reduced by 25% in case of non-haematologic or haematologic toxicities.

*Objectives*

The primary objective of this study was to determine overall remission (OR) rate. The OR rate was defined as the sum of the number of patients with either complete remission (CR) or complete remission in the absence of total platelet recovery (CRp) divided by the total number of eligible patients.

Secondary objectives included documentation of CR, CRp, and of partial response (PR) rates, as well as duration of remission and overall survival (OS), and the safety profile and tolerability of clofarabine for this dosing regimen in this population.

*Outcomes/endpoints*

The efficacy endpoint was the number of patients achieving disease remission. Remission has been categorized as complete remission (CR), complete remission without platelet recovery (CRp) and partial remission (PR). To enable systematic evaluation of the responses seen in patients, an unblinded Independent Response Review Panel (IRRP) was convened in March 2003.

The IRRP produced the following definitions of response rates in leukaemic patients based on definitions produced by the Children's Oncology Group (Table 4).

**Table 4. Response criteria for trial**

| | |
|---|---|
| Complete remission (CR): | Patients who met each of the following criteria:<br>• No evidence of circulating blasts or extramedullary disease<br>• An M1 bone marrow (≤ 5% blasts)<br>• Recovery of peripheral counts (platelets ≥ 100 x $10^9$/L and ANC ≥ 1.0 x $10^9$/L) |
| Complete remission in the absence of total platelet recovery (CRp): | • Patients who have met all of the criteria for a CR except for recovery of platelet counts to > 100 x $10^9$/L |
| Partial remission (PR): | Patients who met each of the following criteria:<br>• Complete disappearance of circulating blasts<br>• An M2 bone marrow (≥ 5% and ≤ 25% blasts) and appearance of normal progenitor cells<br>• An M1 marrow that does not qualify for CR or CRp |

In addition to evaluating the overall remission rate (CR+CRp), the partial remission rate (PR) has also been assessed. Partial remission is considered to afford significant clinical benefit in acute paediatric leukaemias in as much as a PR can provide an opportunity to proceed to bone marrow transplant. PR may also provide prolongation and improved quality of life by controlling the leukaemia and its associated symptoms.

*Sample size*

Sixty eligible patients were enrolled in a Fleming 2-stage sequential study design 1. The sample size of this study was based on overall remission (CR or CRp). The targeted OR rate was 40%. Under the

original study design, by enrolling 40 eligible patients, an observed remission rate of 40% would have a 95% confidence interval of 25% to 55%.

Under the original study design, 20 eligible patients were to be enrolled into the first stage of the study. If <4 patients achieved a CR or CRp following clofarabine therapy, the accrual was to be stopped. If ≥4 patients achieved a CR or CRp, another 20 eligible patients were to be enrolled into the second stage of the study. If <14 patients exhibited a CR or CRp by the end of the second accrual stage, by which time 40 eligible patients would have been enrolled in the study, the conclusion would be drawn that a 40% OR rate was not likely in this indication. If ≥14 of 40 patients achieved a CR or CRp after the second accrual stage, the conclusion would be drawn that the treatment was promising.

Under Amendment 5, the stopping rule was not to be applied. Interim analysis of the first 20 patients demonstrated 1 CRp and 3 PR. Accrual of up to 40 patients was to continue in the second stage of the study in an effort to better estimate the response rate and gather additional safety information in this patient population.

After discussions with the FDA, Amendment 6 increased the total number of patients enrolled to 60 to obtain additional efficacy and safety information.

*Randomisation*

All studies in the clinical development program were of an open-label, non-randomized design. Due to the nature of the patients included in the clinical development program, active comparator studies were not considered to be appropriate as standard chemotherapy had already failed in these patients and there were no other recognised therapeutic options available for them. Furthermore, given the efficacy of clofarabine observed early on in the clinical program, studies using a placebo comparator were considered to be clinically unethical.

*Blinding (masking)*

Not applicable.

*Statistical methods*

Given the non-comparator design of the study, efficacy outcomes cannot be compared with response in a placebo or active arm. Furthermore, comparison of efficacy results with published data is considered to be inappropriate as there does not appear to be any published data from comparable studies. A review of the literature indicates that published studies are usually very small, do not involve an independent review of response nor a consistent definition of CR. Also, the patients enrolled in published studies appear to be much less heavily pretreated, with many patients in first relapse and very few studies appear to have enrolled any patients who had undergone prior transplant.

Consequently, efficacy has been assessed on the basis of response rates in comparison to what would be expected by expert clinical evaluation and by comparison with previous experience in this type of patient. This approach is considered to be scientifically acceptable for the evaluation of clinical efficacy in the patient population under investigation and is considered to provide the most ethically acceptable method of investigation for the patients under study.

*Data cut-off dates*

First interim study report (21 November 2003): 41 patients.

Second interim study report (30 September 2004): 61 patients (recruitment complete).

Third interim analysis (30 September 2005): longer follow-up of the 61 patients.

RESULTS

*Participant flow*

At the first data cut-off date (November 2003), forty patients had entered the study. A total of 17/40 (43%) patients discontinued because of failure to respond after 2 cycles of treatment and 7/40 (18%) discontinued due to disease progression; 3 (8%) were discontinued by investigator, 2 of which so they could receive transplant; 3 (8%) refused further treatment; 3 (8%) were discontinued due to death; 2 (5%) were listed as discontinued to receive transplant; 1 (3%) discontinued due to an AE; and 4 (10%)

were still on study at the time of the data cut-off. Therefore, a total of 4 (10%) patients were discontinued to receive transplant.

The most recent update (September 2005) indicates that 27/61 (44%) patients discontinued because of failure to respond after 2 cycles of treatment and 10/61 (16%) discontinued due to disease progression; 3 (5%) were discontinued by investigator, 2 of which so they could receive transplant; 3 (5%) refused further treatment; 9 (16%) were discontinued due to death; 6 (10%) were listed as discontinued to receive transplant; and 1 (2%) discontinued due to an AE. Therefore, a total of 7 (11%) patients were discontinued to receive transplant.

*Recruitment*

Eighteen sites in the US participated in the study. However, at the first data cut-off date, only 14 sites had enrolled 41 patients in the study. One of the patients did not receive study drug due to insufficient hepatic function and was not included in the efficacy analyses. When recruitment was complete, 16 sites in the US had treated 61 patients.

*Conduct of the study*

Protocol violations were present in 40% of the patients in the first interim study report. The diagnosis of ALL was confirmed by an independent pathologist for 36/40 patients in this study. Four patients did not meet all eligibility criteria and were enrolled with waivers. Subsequent analyses showed that multiple patients (30/40) received steroids as per investigator decision, while steroid use was an exclusion criterion. Patients who achieved a CR were eligible to receive a HSCT. However, in practice, because the patient population under investigation was at high risk of relapse, and because of HSCT scheduling logistics, many investigators had patients proceed to transplant as soon as there was complete or even substantial clearance of bone marrow blasts without allowing for peripheral blood count recovery. The implication of this practice pattern is that some of these patients could have become a CRp or CR given sufficient time for recovery of blood counts or additional cycles of clofarabine. The most recent update indicates 40% of patients had protocol violations.

*Baseline data*

The demographic and baseline characteristics for patients enrolled in CLO-212 are summarized in Table 5.

**Table 5: Summary of Baseline Characteristics for Study CLO-212**

| | First data cut-off date (Nov 03) | Most recent update (Sept 05) |
|---|---|---|
| Males | 25 (63%) | 37 (61%) |
| Females | 15 (38%) | 24 (39%) |
| Median age (range) (years) | 12.5 (1-20) | 12.0 (1-20) |
| Subtype of haematological malignancy | | |
| L1 | N=16/40 (40%) | N=27/61 (44%) |
| L2 | N=10/40 (25%) | N=13/61 (21%) |
| Unknown | N=14/40 (35%) | N=21/61 (34%) |
| Number of prior regimens | | |
| 2 | N=12/40 (30%) | N=21/61 (34%) |
| 3 | N=12/40 (30%) | N=23/61 (38%) |
| 4 | N=12/40 (30%) | N=14/61 (23%) |
| 5 | N=1/40 (2.5%) | N=1/61 (1.6%) |
| 6 | N=3/40 (7.5%) | N=2/61 (3.3%) |
| Number of prior transplants | | |
| 1 | N=11/40 (28%) | N=15/61 (25%) |
| 2 | N=2/40 (5%) | N=3/61 (4.9%) |
| Exposure | | |
| median cumulative dose | 520mg | 530 mg |
| range of doses | 29 to 1355 mg | 29 to 2815 mg |
| median cycles | 2 | 2 |
| range of cycles | 1 to 5 | 1 to 12 |
| Number of cycles | | |
| 1 | 17/40 (43%) | 25/61 (41%) |

| | | |
|---|---|---|
| 2 | 16/40 (40%) | 27/61 (44%) |
| 3 or more | 7/40 (18%) | 9/61 (15%) |

At the first data cut-off date (November 2003), the median age of the treated patients was 12.5 years. Three patients were ≤ 2 years, 17/40 were between 2 and 12 years and the remainder was above 12 years of age. There were more males (63%) enrolled than females (38%). In addition, most of the patients were either Caucasian (n=17, 43%) or Hispanic (n=15, 38%) with only 15% Black (n=6), and 5% other race (n=2). Most patients (83%) received 1 or 2 cycles of clofarabine with a median cumulative dose of 520 mg. Patients had subtypes of L1 (40%) and L2 (25%) ALL, and 35% had an unknown subtype. Analysis of immuno-phenotype showed that 27/40 (68%) patients had a pre-B cell phenotype, 6/40 (15%) had B cell phenotype, 4/40 (10%) had T cell/pre-T cell phenotype, 1 (3%) had a mixed phenotype, and 2 (5%) had an unknown phenotype. All patients had received prior induction regimens; most patients (36/40, 90%) had received 2 to 4 prior regimens. Before enrolling in the trial, 33% of patients had undergone at least 1 prior transplant.

In the most recent update (September 2005), the median age of the treated patients was 12.0 years. Three patients were ≤ 2 years, 30/61 were between 2 and 12 years and the remainder was above 12 years of age. There were more males (61%) enrolled than females (39%). In addition, most of the patients were either Caucasian (n=26, 44%) or Hispanic (n=23, 38%) with only 12% Black (n=7), and 7% other race (n=4). Most patients (85%) received 1 or 2 cycles of clofarabine with a median cumulative dose of 530 mg. Patients had subtypes of L1 (44%) and L2 (21%) ALL, and 34% had an unknown subtype. Analysis of immuno-phenotype showed that 41/61 (62%) patients had a pre-B cell phenotype, 9/61 (15%) had B cell phenotype, 6/61 (9.8%) had T cell/pre-T cell phenotype, 2 (3.3%) had a mixed phenotype, and 3 (5%) had an unknown phenotype. All patients had received prior induction regimens; most patients (58/61, 95%) had received 2 to 4 prior regimens. Before enrolling in the trial, 30% of patients had undergone at least 1 prior transplant.

*Numbers analysed*

*First interim study report (November 2003)*

Eligible patient population: All 40 patients that received at least one dose of study drug (partial or complete dose) and that had a centrally confirmed diagnosis of ALL were included in the eligible patient analyses.

Intention-to-treat (ITT) population: All 40 patients that received at least one dose of study drug (partial or complete dose) were included in the ITT analyses.

*Third interim analysis (September 2005)*

Eligible patient population: All 61 patients that received at least one dose of study drug (partial or complete dose) and that had a centrally confirmed diagnosis of ALL were included in the eligible patient analyses.

Intention-to-treat (ITT) population: All 61 patients that received at least one dose of study drug (partial or complete dose) were included in the ITT analyses.

*Outcomes and estimation*

*First interim study report (November 2003)*

Seven patients (18%) achieved overall remission (4 CR and 3 CRp), and 4 additional patients (10%) achieved a PR. The median duration of remission was 9.7 weeks for CR (duration of remission was 1.1+, 6.1, 9.3+ and 9.7 weeks) and 33.5 weeks for CRp (duration of remission was 1.6+, 28.6, and 38.3 weeks). The duration of PR tended to be shorter at 2.5, 5.0, 7.6 and 14.3 weeks. Ten patients (25%) were still alive at the time of data cut-off. These included the patients who achieved a CR, with survival times of 4.9+, 17.6+, 18.0+, and 46.0+ weeks. Two of the 3 patients who achieved a CRp were still alive, with survival times of 6.1+ and 37.0+ weeks. One CRp patient died at 42 weeks. No patient who achieved a PR was still alive at the time of data cut-off. The median survival of patients who achieved PR was 23.9 weeks. The median survival of patients classified as treatment failures or not evaluable was 7.1 weeks. There were 5 patients who went on to receive an HSCT: 1 after achieving CR, 2 after CRp, 1 after PR as well as 1 patient who was not evaluable due to the poor quality of his bone marrow sample but who the investigator considered a PR. Three of these patients

were still alive at data cut-off, with survival times of 18.0+ weeks (CR), 37.0+ weeks (CRp) and 16.1+ weeks (non-evaluable patient). Karnofsky Performance Scores worsened in 53%, stayed the same in 29% and improved in 18%. A summary of the main efficacy variables of study CLO-212 is given in Table 6.

**Table 6: Summary of Efficacy Variables for Patients included in study CLO-212**

| | | |
|---|---|---|
| Overall Remission n (%) | 7/40 (18%) | 95% CI: 7% to 33% |
| CR | 4/40 (10%) | |
| CRp | 3/40 (8%) | |
| Number (%) of Patients with PR | 4/40 (10%) | |
| Number (%) of Patients with at least PR | 11/40 (28%) | 95% CI: 15% to 44% |
| Number (%) of Patients Not Evaluable | 5/40 (13%) | |
| Treatment Failure | 24/40 (60%) | |
| Median duration of remission | | |
| Patients with at least PR (n=11) | 9.7 weeks | 95% CI: 6.1 to 28.6 weeks |
| Patients with CR (n=4) | 9.7 weeks | 95% CI: 6.1 to 9.7 weeks |
| Patients with CRp (n=3) | 33.5 weeks | 95% CI: 28.6 to 38.3 weeks |
| Patients with OR [CR+CRp] (n=7) | 28.6 weeks | 95% CI: 6.1 to 38.3 weeks |
| Patients with PR (n=4) | 6.3 weeks | 95% CI: 2.3 to 14.3 weeks |
| Median time to progression | | |
| All patients (n=40) | 5.1 weeks | 95% CI: 3.9 to 6.1 weeks |
| Patients with at least PR (n=11) | 18.1 weeks | 95% CI: 10.6 to 37.0 weeks |
| Patients with CR (n=4) | 20.4 weeks | 95% CI: 13.7 to 20.4 weeks |
| Patients with CRp (n=3) | 39.5 weeks | 95% CI: 37.0 to 42.0 weeks |
| Patients with OR (n=7) | 37.0 weeks | 95% CI: 13.7 to 42.0 weeks |
| Patients with PR (n=4) | 8.8 weeks | 95% CI: 6.3 to 18.1 weeks |
| Treatment Failure/Not Eval (n=29) | 4.0 weeks | 95% CI: 3.4 to 5.1 weeks |
| Median time for survival | | |
| All patients (n=40) | 8.0 weeks | 95% CI: 7.0 to 18.4 weeks |
| Patients with at least PR (n=11) | 36.3 weeks | 95% CI: 18.1 to . weeks (range=4.9+ to 46.0+) |
| Patients with CR (n=4) | 4 still alive as of cut-off date: 4.9+, 17.6+, 18.0+, 46.0+ | |
| Patients with CRp (n=3) | 2 of 3 still alive; 6.1+, 37.0+, one died at 42.0 weeks | |
| Patients with OR (n=7) | 6 of 7 still alive (range 4.9+ to 46.0+ weeks) | |
| Patients with PR (n=4) | 23.9 weeks | 95% CI: 7.0 to 36.3 weeks |
| Treatment Failure/Not Eval (n=29) | 7.1 weeks | 95% CI: 6.3 to 9.6 weeks |
| Clinical Benefit | | |
| Transplant (HSCT) | 5/40 (13%) | |
| Best On-Study Karnofsky scores | | |
| Improved | 6/34 (18%) | |
| Stayed the Same | 10/34 (29%) | |
| Worsened | 18/34 (53%) | |
| Not assessed | 6 | |

CR=complete remission, CRp=complete remission without platelet recovery, OR=overall remission, PR=partial remission, PBSCT=peripheral blood stem cell transplant

*Second interim study report (September 2004)*

This first update included efficacy data for 21 additional patients. Before enrolling in the trial, 58 of the 61 patients (95%) had received 2 to 4 different induction regimens and 18/61 (30%) of these patients had undergone at least 1 prior HSCT. The median age of treated patients (37 males, 24 females) was 12 years old. Administration of clofarabine resulted in a dramatic and rapid reduction in peripheral leukaemia cells in 31 of the 33 patients (94%) who had a measurable absolute blast count at baseline. The overall remission rate was 20% (12/61) for the enlarged 61 patient data set with the following median durations of remission: patients with CR 28.8 weeks (95% CI: 6.1 - 47.9 weeks), patients with CRp 28.6 weeks (95% CI: 4.6 - 28.6 weeks), patients with PR 5.2 weeks (95% CI: 2.3 - 7.6 weeks). Responses were seen in different immunophenotypes of ALL, including pre-B cell and

T-cell. Nine patients (9/61) were transplanted after clofarabine treatment. Median survival time of patients with overall remission (CR + CRp) was 58.6 weeks (53.7 weeks for patients with CRp and not reached for patients with CR as most (6/7) were still alive at the time of data cut-off).

*Third interim analysis (September 2005)*

A second update with a data cut-off date of 30 September 2005 was submitted (Table 7).

**Table 7. Efficacy results from the pivotal study in patients (≤ 21 years old at initial diagnosis) with relapsed or refractory ALL after at least two prior regimens**

| Response category | ITT* patients (n = 61) | Median duration of remission (weeks) | Median time to progression (weeks)** | Median overall survival (weeks) |
|---|---|---|---|---|
| Overall remission (CR + CRp) | 12 (20%) | 28.6 (95% CI: 9.7 to 58.6) | 37.0 (95% CI: 15.4 to 61.9) | 66.6 (95% CI: 53.7 to 89.4) |
| CR | 7 (12%) | 47.9 (95% CI: 6.1 to -) | 56.1 (95% CI: 13.7 to -) | 66.6 (95% CI: 66.6 to 89.4) |
| CRp | 5 (8%) | 28.6 (95% CI: 4.6 to 35.4) | 37.0 (95% CI: 9.1 to 39.4) | 53.7 (95% CI: 9.1 to -) |
| PR | 6 (10%) | 5.2 (95% CI: 2.3 to -) | 8.6 (95% CI: 6.3 to -) | 33.0 (95% CI: 18.1 to -) |
| CR + CRp + PR | 18 (30%) | 11.7 (95% CI: 6.1 to 47.9) | 20.4 (95% CI: 10.6 to 56.1) | 66.6 (95% CI: 42.0 to 89.4) |
| Treatment failure | 33 (54%) | N/A | 4.0 (95% CI: 3.4 to 5.1) | 7.6 (95% CI: 6.7 to 12.6) |
| Not evaluable | 10 (16%) | N/A | | |
| All patients | 61 (100%) | N/A | 5.4 (95% CI: 4.0 to 6.1) | 12.9 (95% CI: 7.9 to 18.1) |

*ITT = intention to treat.
**Patients alive and in remission at the time of last follow up were censored at that time point for the analysis.

Although transplantation rate was not a study endpoint, a total of 10 children treated with clofarabine subsequently underwent a HSCT, including 8/18 patients who achieved a response (3 after achieving a CR, 2 after a CRp, 3 after a PR, 1 patient that was considered a treatment failure by the IRRP and 1 that was considered not evaluable by the IRRP). Response durations are confounded in patients who received a HSCT. None of the patients who proceeded to transplant post-clofarabine treatment in study CLO-212 for whom data is available (9/10 patients) have developed veno-occlusive disease (VOD). Regarding responding patients who did not receive a HSCT (10 out of 18), 2 patients are known to be alive. According to the applicant, multifactorial reasons probably explain why these 10 patients did not undergo transplant including lack of donor availability, patient/parental withdrawal of consent, and institutional/physician standard practice. None of the 10 patients had any clofarabine-related or clinically significant toxicity that would have prevented HSCT. In particular, no hepatotoxicity that would have precluded HSCT was reported in any of these patients.

*Ancillary analyses*

Examination of response by subgroups in the first data cut (November 2003) showed that 6 out of the 33 pre-B cell/B-cell immunophenotypes achieved CR or CRp and 1 out of the 4 pre-T-cell/T-cell immunophenotypes achieved CR or CRp. One of the 2 Philadelphia (t[9;22]) positive patients achieved a PR. Only one of the 12 patients with 2 prior treatment regimens showed a response, while 2 out of 12 patients for each group having received 3 or 4 prior regimens achieved a CR or CRp. Two out of 3 patients who received 6 prior regimens achieved a CR or CRp.

Analysis of the most recent update showed that 8 out of the 41 pre-B cell/B-cell immunophenotypes achieved CR or CRp and 2 out of the 6 pre-T-cell/T-cell immunophenotypes achieved CR or CRp. Two of the 3 Philadelphia (t[9;22]) positive patients achieved a PR. Three of the 23 patients with 2 prior treatment regimens showed a response, while 4 out of 22 patients having received 3 prior

regimens and 4 out of 13 patients having received 4 prior regimens achieved a CR or CRp. One out of 3 patients who received 5 or 6 prior regimens achieved a CR or CRp.

- Supportive studies

Phase II study in adults with CLL (DM99-225). This was a phase II, open-label, single-site study of clofarabine administered to patients with CLL who had failed fludarabine and alkylator therapy. Patients were treated with clofarabine 4 mg/m$^2$ ivi over 1 hour for 5 days every 4 weeks. Eleven adults were treated. This study was closed to further enrolment by the investigator due to apparent lack of clinical efficacy.

Phase II study in adults with haematological tumors (ID00-038). This was a single-center, non-randomised, open-label, phase II study of clofarabine in patients 12 years or older with ALL, AML, MDS, or CML in transformation that was refractory to therapy, or in relapse for patients who were not candidates for treatment of higher efficacy or priority. Patients received clofarabine 40 mg/m$^2$ ivi over 1 hour for 5 days every 2 to 6 weeks. A total of 64 patients were enrolled in this study, 62 of whom were treated. This was a non-registration investigator initiated trial and after the study was transferred to ILEX, case record forms were designed to retrieve and verify the data collected by MDACC. Efficacy and safety data were collected for 8 responders. SAE data were collected by ILEX for 31 patients, none of whom were paediatric patients. ILEX discontinued data retrieval due to the initiation of an ILEX sponsored phase II adult AML study with clofarabine (CLO-221). The results of this study have been published by the study investigators [Kantarjian, Gandhi et al. 2003]. They reported that 20/62 (32%) patients achieved complete response (CR), 1 had a partial response (PR), and 9 (15%) achieved CR but without platelet recovery (CRp), for an overall response rate of 48%. In AML, responses were noted in 2 (18%) of 11 patients in first salvage with short first CR (< 12 months), in 7 (87%) of 8 patients with longer first CR, and in 8 (67%) of 12 patients in second or subsequent salvage. Responses were observed in 4 of 8 patients with high-risk MDS (50%), in 7 (64%) of 11 with CML-BP, and in 2 (17%) of 12 with ALL. Severe reversible liver dysfunction was noted in 15% to 25% of patients.

Phase II study in adults with AML (CLO-221). This was a phase II, open-label, single-arm study of clofarabine administered to adult patients with refractory or relapsed AML who were not eligible for therapy of higher curative potential. In the Induction phase, patients were treated with clofarabine 40 mg/m$^2$/day by ivi over one hour for 5 consecutive days every 28 days for up to 2 cycles. Patients who achieved a CR or CRp during Induction therapy were treated with clofarabine 30 mg/m$^2$/day for up to 3 cycles (for a maximum of up to 4 total treatment cycles). Forty adults and 1 paediatric patient were treated. The majority of patients in this population of heavily pre-treated refractory adults with AML did not respond to treatment with clofarabine. One patient achieved a CR (duration 20.4 weeks) and one failed to respond but benefited from treatment and was able to receive an allogeneic transplant 137 days after starting treatment with clofarabine.

Phase I study in adults with AML or ALL receiving clofarabine in combination with Ara-C (CLO-141). This was an open-label, single-arm study of clofarabine administered with Ara-C in adult patients in first relapse or first salvage of primary refractory AML or ALL; with high-risk MDS; or with CML blast phase as front line therapy or in first salvage. No efficacy analysis is currently available for this study as it is ongoing.

Current and planned studies

Two open-label Phase II studies are ongoing (studies BIOV 111 and BIOV 121). Study BIOV-111 is a study of clofarabine in pediatric patients with refractory / relapsed ALL and study BIOV-121 is in older patients (≥65 years) with untreated AML who are unsuitable for intensive chemotherapy. Based on an interim status report of study BIOV-111, in total, 12/23 patients treated with two courses of clofarabine were evaluable for response (no IRRP assessment was available). Of the 12 patients, 2 patients reached complete remission (CR) and 3 patients reached complete remission in the absence of total platelet recovery (CRp).

A programme of further clinical studies investigating the use of clofarabine in the treatment of ALL is planned. Two phase I/II studies investigating the activity of clofarabine as a combination therapy in patients with pediatric leukemias are being initiated in the US.

- Discussion on clinical efficacy

The demonstration of efficacy in ALL is based on the non-comparative, phase II study CLO-212. No randomized controlled trials with clofarabine in ALL have been submitted. Lack of a comprehensive clinical development program has been justified in view of the small size of the population of patients in second relapse.

Patients recruited into study CLO-212 were heavily pre-treated (2-6 prior intensive treatments) with two thirds of patients having received three or more prior treatments and were required by the protocol to not be eligible for 'therapy of a high curative potential' than anticipated with clofarabine. Just over half of patients had characteristics at diagnosis that would predict that they were at a high or very high risk of relapse after their first treatment (i.e. were considered to be difficult to treat). Most of the remaining patients were considered to have a standard risk whilst only 7% had a low risk based on their characteristics at diagnosis. Around a half of patients were refractory to their last prior treatment, the remainder had relapsed.

The results obtained from interim analysis of CLO-212 demonstrate that treatment with clofarabine at the dose of 52 mg/m$^2$/day for 5 days can induce remissions in relapsed or refractory paediatric patients with ALL. Updated results of study CLO-212 showed that treatment with clofarabine was associated with an overall remission rate of 20% and facilitated HSCT in 8 of the 18 responding patients in an otherwise extremely poor prognostic relapsed or refractory ALL population.

Clofarabine can induce remission both in patients who had relapsed after intensive treatment and also, importantly, in patients who had been refractory to their prior treatments. Indeed, a response was seen in one patient who had been refractory to all four of their prior treatments. Responses were seen in patients regardless of whether they were classified as standard, high or very high risk at diagnosis.

Attempts have been made to compare survival following clofarabine treatment with that seen after other treatment of multiply relapsed pediatric ALL by analysing the data held in the German and Dutch cancer registries. The data indicate that patients with multiply relapsed ALL have an estimated median survival of 9-10 weeks without further intervention. Although historical comparisons are notoriously difficult and prone to bias, median survival following clofarabine treatment (all patients) was 17.7 weeks, and was greater than one year in patients who respond to clofarabine treatment.

The majority of patients who respond to clofarabine achieve a response after 1 or 2 treatment cycles. Therefore, the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after 2 treatment cycles should be assessed by the treating physician.

There are currently insufficient data to establish the safety and efficacy of clofarabine in adult patients (> 21 years old including the elderly).

**Clinical safety**

- Patient exposure

As of 30 September 2005, a total of 132 patients (> 1 and < 21 years old) with either ALL or AML received at least one dose of clofarabine (79 ALL and 53 AML); they were defined as paediatrics on the basis of their age being ≤ 21 years at the time of initial diagnosis.

Studies ID99-383, CLO-212 and CLO-222 were specifically designed to evaluate clofarabine in a paediatric population and provided 128 patients. Two patients aged 19 and 18 years at diagnosis took part in adult trials (CLO-221; Patient 221-004-0010 and CLO-141; Patient 141-001-0013). (Study CLO-221 was similar to the paediatric AML protocol although the highest dose of clofarabine permitted was 40 mg/m$^2$/day. Study CLO-141 examined clofarabine up to 40 mg/m$^2$/day in combination with cytarabine in first relapse or first salvage of primary refractory AML or ALL patients.) Finally, two children were included in the safety database from study DM93-036, the Phase I dose escalation study.

The safety data collected from these 132 patients has been combined and the overall incidence of adverse events in ALL and AML paediatric patients has been assessed. One hundred and fifteen (87%) patients received the recommended clofarabine dose of 52 mg/m$^2$/day unless the dose was adjusted in response to safety considerations with 14 patients receiving less than 52 mg/m$^2$/day and 3 patients

receiving more than 52 mg/m$^2$/day. Most of the 132 paediatric leukaemia patients in the integrated safety database received clofarabine for two treatment cycles although 25 patients received treatment for three or more cycles.

The safety data from paediatric patients recruited into the emergency expanded access/compassionate use program or recruited into studies where the protocol differed significantly from that of the paediatric ALL and AML studies and those generated in adult patients with a variety of malignancies, both haematological and solid, have not been integrated but have been considered on a study-by-study basis.

- Adverse events

One hundred and thirty one patients in the integrated database experienced at least one adverse event and, almost all, a drug-related adverse event. The most common toxicities observed during exposure to clofarabine were gastrointestinal system AEs (vomiting, nausea, and diarrhoea), adverse haematologic effects (febrile neutropenia and neutropenia), pruritus, headache and pyrexia (Table 8). A similar spectrum of common adverse events was observed in studies in adult patients.

Most patients who entered the studies already had a wide spectrum of concomitant medical conditions, many as a consequence of prior regimen toxicity. Furthermore, many patients were receiving therapies to ameliorate the effects of these prior toxic effects. This complicated background of pre-existing medical conditions makes the interpretation of adverse event data difficult and potentially predisposes patients to a higher likelihood of experiencing toxicity whilst on any drug. In particular, it is difficult to distinguish disease progression from drug toxicity and to assess whether toxicity is related to the study medication or to toxicity from prior therapies or from concomitantly administered medications.

**Table 8: ALL and AML Pediatric Patients Combined: Number (≥ 5%) with Incidence of Adverse Events Regardless of Relationship to Study Drug by Preferred Term and Maximum Grade (NCI CTC Toxicity Grade)**

| MedDRA Version 3.3 Preferred Term[1] | ALL/AML (n=132) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | | Grade 5 | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Total Patients with Adverse Events | 131 | 99.2 | 1 | 0.8 | 6 | 4.5 | 70 | 53.0 | 30 | 22.7 | 24 | 18.2 |
| Vomiting NOS | 104 | 78.8 | 29 | 22.0 | 63 | 47.7 | 11 | 8.3 | 1 | 0.8 | . | . |
| Nausea | 94 | 71.2 | 16 | 12.1 | 58 | 43.9 | 19 | 14.4 | 1 | 0.8 | . | . |
| Febrile Neutropenia | 75 | 56.8 | . | . | 1 | 0.8 | 69 | 52.3 | 5 | 3.8 | . | . |
| Diarrhoea NOS | 68 | 51.5 | 34 | 25.8 | 19 | 14.4 | 15 | 11.4 | . | . | . | . |
| Pruritus NOS | 61 | 46.2 | 25 | 18.9 | 35 | 26.5 | 1 | 0.8 | . | . | . | . |
| Headache NOS | 59 | 44.7 | 26 | 19.7 | 25 | 18.9 | 8 | 6.1 | . | . | . | . |
| Dermatitis NOS | 50 | 37.9 | 17 | 12.9 | 25 | 18.9 | 8 | 6.1 | . | . | . | . |
| Pyrexia | 50 | 37.9 | 12 | 9.1 | 20 | 15.2 | 18 | 13.6 | . | . | . | . |
| Abdominal Pain NOS | 47 | 35.6 | 22 | 16.7 | 16 | 12.1 | 9 | 6.8 | . | . | . | . |
| Fatigue | 46 | 34.8 | 25 | 18.9 | 17 | 12.9 | 3 | 2.3 | 1 | 0.8 | . | . |
| Rigors | 45 | 34.1 | 27 | 20.5 | 15 | 11.4 | 3 | 2.3 | . | . | . | . |
| Tachycardia NOS | 43 | 32.6 | 25 | 18.9 | 12 | 9.1 | 6 | 4.5 | . | . | . | . |
| Anorexia | 38 | 28.8 | 12 | 9.1 | 12 | 9.1 | 6 | 4.5 | 8 | 6.1 | . | . |
| Pain in Limb | 38 | 28.8 | 12 | 9.1 | 19 | 14.4 | 7 | 5.3 | . | . | . | . |
| Petechiae | 38 | 28.8 | 19 | 14.4 | 10 | 7.6 | 9 | 6.8 | . | . | . | . |
| Hypotension NOS | 36 | 27.3 | 2 | 1.5 | 11 | 8.3 | 13 | 9.8 | 10 | 7.6 | . | . |

| MedDRA Version 3.3 Preferred Term[1] | ALL/AML (n=132) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | | Grade 5 | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Epistaxis | 34 | 25.8 | 16 | 12.1 | 1 | 0.8 | 17 | 12.9 | . | . | . | . |
| Anxiety NEC | 29 | 22.0 | 11 | 8.3 | 16 | 12.1 | 2 | 1.5 | . | . | . | . |
| Cough | 29 | 22.0 | 22 | 16.7 | 7 | 5.3 | . | . | . | . | . | . |
| Mucosal Inflammation NOS | 26 | 19.7 | 13 | 9.8 | 10 | 7.6 | 3 | 2.3 | . | . | . | . |
| Constipation | 25 | 18.9 | 11 | 8.3 | 14 | 10.6 | . | . | . | . | . | . |
| Erythema NEC | 25 | 18.9 | 18 | 13.6 | 7 | 5.3 | . | . | . | . | . | . |
| Flushing | 24 | 18.2 | 24 | 18.2 | . | . | . | . | . | . | . | . |
| Oedema NOS | 23 | 17.4 | 4 | 3.0 | 15 | 11.4 | 2 | 1.5 | 2 | 1.5 | . | . |
| Pain NOS | 22 | 16.7 | 2 | 1.5 | 11 | 8.3 | 8 | 6.1 | 1 | 0.8 | . | . |
| Arthralgia | 21 | 15.9 | 6 | 4.5 | 11 | 8.3 | 4 | 3.0 | . | . | . | . |
| Sore Throat NOS | 20 | 15.2 | 16 | 12.1 | 4 | 3.0 | . | . | . | . | . | . |
| Depression NEC | 19 | 14.4 | 7 | 5.3 | 11 | 8.3 | 1 | 0.8 | . | . | . | . |
| Gingival Bleeding | 19 | 14.4 | 9 | 6.8 | 2 | 1.5 | 7 | 5.3 | 1 | 0.8 | . | . |
| Hypertension NOS | 19 | 14.4 | 6 | 4.5 | 5 | 3.8 | 8 | 6.1 | . | . | . | . |
| Sepsis NOS | 19 | 14.4 | . | . | . | . | 10 | 7.6 | 4 | 3.0 | 5 | 3.8 |
| Appetite Decreased NOS | 18 | 13.6 | 12 | 9.1 | 6 | 4.5 | . | . | . | . | . | . |
| Dyspnoea NOS | 17 | 12.9 | 3 | 2.3 | 4 | 3.0 | 6 | 4.5 | 4 | 3.0 | . | . |
| Haematuria | 17 | 12.9 | 11 | 8.3 | 4 | 3.0 | 2 | 1.5 | . | . | . | . |
| Myalgia | 17 | 12.9 | 8 | 6.1 | 8 | 6.1 | 1 | 0.8 | . | . | . | . |
| Dizziness (Exc Vertigo) | 16 | 12.1 | 12 | 9.1 | 4 | 3.0 | . | . | . | . | . | . |
| Pleural Effusion | 16 | 12.1 | 7 | 5.3 | 3 | 2.3 | 4 | 3.0 | 2 | 1.5 | . | . |
| Back Pain | 15 | 11.4 | 4 | 3.0 | 8 | 6.1 | 3 | 2.3 | . | . | . | . |
| Bacteraemia | 15 | 11.4 | . | . | . | . | 15 | 11.4 | . | . | . | . |
| Contusion | 15 | 11.4 | 11 | 8.3 | 3 | 2.3 | 1 | 0.8 | . | . | . | . |
| Herpes Simplex | 15 | 11.4 | 3 | 2.3 | 6 | 4.5 | 6 | 4.5 | . | . | . | . |
| Injection Site Pain | 15 | 11.4 | 7 | 5.3 | 7 | 5.3 | 1 | 0.8 | . | . | . | . |
| Insomnia NEC | 15 | 11.4 | 10 | 7.6 | 5 | 3.8 | . | . | . | . | . | . |
| Jaundice NOS | 15 | 11.4 | 8 | 6.1 | 5 | 3.8 | 2 | 1.5 | . | . | . | . |
| Transfusion Reaction | 15 | 11.4 | 4 | 3.0 | 6 | 4.5 | 5 | 3.8 | . | . | . | . |
| Weight Decreased | 15 | 11.4 | 7 | 5.3 | 7 | 5.3 | 1 | 0.8 | . | . | . | . |
| Hepatomegaly | 14 | 10.6 | 6 | 4.5 | . | . | 8 | 6.1 | . | . | . | . |
| Irritability | 14 | 10.6 | 10 | 7.6 | 3 | 2.3 | 1 | 0.8 | . | . | . | . |
| Oral Candidiasis | 14 | 10.6 | 5 | 3.8 | 7 | 5.3 | 2 | 1.5 | . | . | . | . |
| Abdominal Distension | 13 | 9.8 | 6 | 4.5 | 4 | 3.0 | 3 | 2.3 | . | . | . | . |
| Bone Pain | 13 | 9.8 | 2 | 1.5 | 7 | 5.3 | 4 | 3.0 | . | . | . | . |

| MedDRA Version 3.3 Preferred Term[1] | ALL/AML (n=132) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | | Grade 5 | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Cellulitis | 13 | 9.8 | 1 | 0.8 | 2 | 1.5 | 10 | 7.6 | . | . | . | . |
| Face Oedema | 13 | 9.8 | 7 | 5.3 | 6 | 4.5 | . | . | . | . | . | . |
| Palmar-Plantar Erythrodysaesthesia Syndrome | 13 | 9.8 | 3 | 2.3 | 6 | 4.5 | 4 | 3.0 | . | . | . | . |
| Rash Pruritic | 13 | 9.8 | 4 | 3.0 | 7 | 5.3 | 2 | 1.5 | . | . | . | . |
| Cardiac Murmur NOS | 12 | 9.1 | 12 | 9.1 | . | . | . | . | . | . | . | . |
| Lethargy | 12 | 9.1 | 8 | 6.1 | 3 | 2.3 | 1 | 0.8 | . | . | . | . |
| Neutropenia | 12 | 9.1 | . | . | . | . | 3 | 2.3 | 9 | 6.8 | . | . |
| Pneumonia NOS | 12 | 9.1 | 3 | 2.3 | . | . | 6 | 4.5 | 2 | 1.5 | 1 | 0.8 |
| Respiratory Distress | 12 | 9.1 | . | . | 2 | 1.5 | 5 | 3.8 | 4 | 3.0 | 1 | 0.8 |
| Somnolence | 12 | 9.1 | 8 | 6.1 | 3 | 2.3 | 1 | 0.8 | . | . | . | . |
| Weakness | 12 | 9.1 | 4 | 3.0 | 5 | 3.8 | 2 | 1.5 | 1 | 0.8 | . | . |
| Dry Skin | 11 | 8.3 | 8 | 6.1 | 3 | 2.3 | . | . | . | . | . | . |
| Haematoma NOS | 11 | 8.3 | 8 | 6.1 | 2 | 1.5 | 1 | 0.8 | . | . | . | . |
| Hallucination NOS | 11 | 8.3 | 3 | 2.3 | . | . | 8 | 6.1 | . | . | . | . |
| Nasal Congestion | 11 | 8.3 | 10 | 7.6 | 1 | 0.8 | . | . | . | . | . | . |
| Tremor NEC | 11 | 8.3 | 10 | 7.6 | 1 | 0.8 | . | . | . | . | . | . |
| Agitation | 10 | 7.6 | 2 | 1.5 | 6 | 4.5 | 2 | 1.5 | . | . | . | . |
| Dehydration | 10 | 7.6 | 2 | 1.5 | 7 | 5.3 | 1 | 0.8 | . | . | . | . |
| Ecchymosis | 10 | 7.6 | 6 | 4.5 | 1 | 0.8 | 2 | 1.5 | 1 | 0.8 | . | . |
| Tachypnoea | 10 | 7.6 | 3 | 2.3 | 2 | 1.5 | 4 | 3.0 | 1 | 0.8 | . | . |
| Chest Pain NEC | 9 | 6.8 | 4 | 3.0 | 4 | 3.0 | 1 | 0.8 | . | . | . | . |
| Lip Dry | 9 | 6.8 | 9 | 6.8 | . | . | . | . | . | . | . | . |
| Pericardial Effusion | 9 | 6.8 | 6 | 4.5 | 2 | 1.5 | . | . | 1 | 0.8 | . | . |
| Proctalgia | 9 | 6.8 | 2 | 1.5 | 5 | 3.8 | 2 | 1.5 | . | . | . | . |
| Renal Failure Acute | 9 | 6.8 | 1 | 0.8 | 3 | 2.3 | 3 | 2.3 | 2 | 1.5 | . | . |
| Septic Shock | 9 | 6.8 | . | . | . | . | 1 | 0.8 | 4 | 3.0 | 4 | 3.0 |
| Abdominal Pain Upper | 8 | 6.1 | 5 | 3.8 | 3 | 2.3 | . | . | . | . | . | . |
| Candidal Infection NOS | 8 | 6.1 | 3 | 2.3 | 4 | 3.0 | 1 | 0.8 | . | . | . | . |
| Conjunctival Haemorrhage | 8 | 6.1 | 5 | 3.8 | 2 | 1.5 | 1 | 0.8 | . | . | . | . |
| Dyspepsia | 8 | 6.1 | 7 | 5.3 | 1 | 0.8 | . | . | . | . | . | . |
| Fungal Infection NOS | 8 | 6.1 | 1 | 0.8 | . | . | 5 | 3.8 | 2 | 1.5 | . | . |
| Herpes Zoster | 8 | 6.1 | . | . | 2 | 1.5 | 6 | 4.5 | . | . | . | . |
| Hypersensitivity NOS | 8 | 6.1 | 1 | 0.8 | 3 | 2.3 | 4 | 3.0 | . | . | . | . |
| Implant Infection | 8 | 6.1 | 1 | 0.8 | 2 | 1.5 | 4 | 3.0 | 1 | 0.8 | . | . |

| MedDRA Version 3.3 Preferred Term[1] | ALL/AML (n=132) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | | Grade 5 | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Loose Stools | 8 | 6.1 | 6 | 4.5 | 2 | 1.5 | . | . | . | . | . | . |
| Mouth Ulceration | 8 | 6.1 | 4 | 3.0 | 3 | 2.3 | 1 | 0.8 | . | . | . | . |
| Neck Pain | 8 | 6.1 | 4 | 3.0 | 3 | 2.3 | 1 | 0.8 | . | . | . | . |
| Proteinuria Present | 8 | 6.1 | 4 | 3.0 | 2 | 1.5 | 2 | 1.5 | . | . | . | . |
| Rash Maculo-Papular | 8 | 6.1 | 2 | 1.5 | 3 | 2.3 | 2 | 1.5 | 1 | 0.8 | . | . |
| Skin Hyperpigmentation | 8 | 6.1 | 8 | 6.1 | . | . | . | . | . | . | . | . |
| Splenomegaly | 8 | 6.1 | 3 | 2.3 | 1 | 0.8 | 4 | 3.0 | . | . | . | . |
| Staphylococcal Infection NOS | 8 | 6.1 | . | . | 1 | 0.8 | 7 | 5.3 | . | . | . | . |
| Tumour Lysis Syndrome | 8 | 6.1 | . | . | . | . | 8 | 6.1 | . | . | . | . |
| Abdominal Tenderness | 7 | 5.3 | 4 | 3.0 | 2 | 1.5 | . | . | 1 | 0.8 | . | . |
| Colitis Pseudomembranous | 7 | 5.3 | . | . | 3 | 2.3 | 4 | 3.0 | . | . | . | . |
| Haematemesis | 7 | 5.3 | 2 | 1.5 | 1 | 0.8 | 4 | 3.0 | . | . | . | . |
| Multi-Organ Failure | 7 | 5.3 | . | . | . | . | . | . | . | . | 7 | 5.3 |
| Oedema Peripheral | 7 | 5.3 | 3 | 2.3 | 4 | 3.0 | . | . | . | . | . | . |
| Rhinorrhoea | 7 | 5.3 | 7 | 5.3 | . | . | . | . | . | . | . | . |
| Skin Disorder NOS | 7 | 5.3 | 2 | 1.5 | 2 | 1.5 | 3 | 2.3 | . | . | . | . |
| Skin Lesion NOS | 7 | 5.3 | 5 | 3.8 | 2 | 1.5 | . | . | . | . | . | . |
| Staphylococcal Bacteraemia | 7 | 5.3 | . | . | . | . | 6 | 4.5 | 1 | 0.8 | . | . |
| Urticaria NOS | 7 | 5.3 | 2 | 1.5 | 5 | 3.8 | . | . | . | . | . | . |

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

The information provided in the SPC is based on the integrated database of 132 patients, but only relates to those adverse events reported as drug-related.

One hundred and twenty nine patients (98% of the total population) experienced at least one adverse event considered by the study investigator to be related to clofarabine. Those most frequently reported were nausea (61% of patients), vomiting (61%), febrile neutropenia (32%), headache (24%), pyrexia (21%), pruritus (21%) and dermatitis (20%). Although 76 patients (58%) experienced at least one serious clofarabine-related adverse event, only 2 patients discontinued treatment because of an adverse reaction; both with hyperbilirubinaemia, one after receiving 52 mg/m$^2$/day and one after 70 mg/m$^2$/day clofarabine. However, the deaths of 4 patients were considered by the study investigator to be related to treatment with clofarabine: one patient experienced clofarabine-related acute vascular leak syndrome that contributed to cardiac arrest; one patient died from respiratory distress and hepatocellular damage; one patient from septic shock and multi-organ failure; and one patient from multi-organ failure (see below).

Adverse events considered by the study investigator to be related to clofarabine that are specifically discussed in section 4.8 of the SPC are: infections and infestations adverse events, SIRS or capillary leak syndrome, cardiac disorders adverse events, vascular disorders adverse events, renal and urinary disorders adverse events and hepato-biliary disorders adverse events. Further details of the incidences of drug-related adverse events are given in the adopted SPC text.

- Serious adverse events/deaths/other significant events

Serious adverse events were common with 107 (81%) patients experiencing a serious adverse event. The spectrum of events reported was febrile neutropenia, pyrexia, infections, hypotension and sepsis. More than half of the serious adverse events reported were considered by the investigator to be related to treatment with the study drug (76 patients, 58%).

A total of 22% of paediatric patients exposed to clofarabine died on-study or within 30 days of the last dose of clofarabine.

Four of the deaths were considered by the investigator to be related to treatment with clofarabine: acute vascular leak syndrome that contributed to cardiac arrest, respiratory failure and liver damage, septic shock and multi-organ failure, and multi-organ failure (see above). These events may be related to cytokine release. Typically SIRS is manifested by the rapid development of tachypnoea, tachycardia and hypotension that contributed to cardiac arrest, respiratory failure, liver damage, septic shock and multi-organ failure. According to the applicant, it is possible that release of cytokines contributes to the development of SIRS/capillary leak syndrome.

As of February 2004, there were six deaths in the adult studies that were considered to be related to treatment with the study drug: infection (2 patients), renal failure (1 patient), cardiac failure (1 patient) and hepato-renal failure (1 patient) in study DM93-036, and sepsis NOS (1 patient) in study CLO-221.

- Laboratory findings

Virtually all patients had pre-existing haematologic abnormalities at the start of treatment. Haematologic toxicity was frequently observed during exposure to clofarabine and was not unexpected.

Febrile neutropenia was the most common grade 3 AE that the investigators considered to be related to study drug. The incidence of febrile neutropenia remained constant with each successive cycle of clofarabine. The infusion and/or the dose of clofarabine was temporarily interrupted and/or reduced when grade 3 or 4 neutropenia occurred.

- Safety in special populations

Headache, fatigue and constipation showed a trend for increasing incidence with increasing age, while the incidence of dermatitis and cough trended to decrease with increasing age.

The incidence of hypotension was greatest in the oldest group of patients (42%), and 16% to 42% greater than the incidence in the 3 younger groups of patients.

- Safety related to drug-drug interactions and other interactions

No drug-drug interactions studies or other interactions studies have been submitted. Based on a review of available clinical cases, no obvious drug-drug interactions have been identified. Non-clofarabine chemotherapy was specifically prohibited in the pediatric clinical trials although there were no specific restrictions on other types of concomitant medications that could be administered. The pediatric patients in this safety population were exposed to many concomitant medications during treatment with clofarabine. All or nearly all pediatric patients received at least one anti-infective (100% overall), gastrointestinal tract agent (100% overall), analgesic/NSAID (99% overall) or antihistamine (98% overall). Other frequent concomitant medications were anti-fungals, narcotic analgesics, benzodiazepines, vitamins/minerals/electrolytes, antiseptics and topical agents, corticosteroids, anesthetics, hypouricemics, diuretics and antivirals.

- Discontinuation due to adverse events

Of the 132 patients who had either ALL or AML and were defined as pediatrics on the basis of age $\leq 21$ years at the time of initial diagnosis, 4 patients withdrew from protocol treatment due to an adverse event. Two patients due to hyperbilirubinaemia (considered by the investigator to be treatment related, see above), one patient due to a ventricular arrhythmia (not considered by the investigator to be treatment related) and one patient due to disease progression (not considered by the investigator to be treatment related).

- Post marketing experience

Some limited post-marketing data have been submitted for clofarabine following the product's launch in the US in January 2005.

- Discussion on clinical safety

The interpretation of safety data from uncontrolled studies is notoriously difficult in heavily pre-treated patients. Most patients who entered the studies already had a wide spectrum of concomitant medical conditions, many as a consequence of prior regimen toxicity. Furthermore, many patients were receiving therapies to decrease ongoing toxicity. The cumulative toxicity with clofarabine has not been studied in CLO-212 and CLO-222 since there is limited experience of patients exceeding a total of 3 cycles with most patients receiving one or two cycles of treatment.

It must be pointed out that clofarabine shares chemical and pharmacodynamic properties with fludarabine, a drug that is known to induce infections as a severe side-effect. Some adverse events reported in this dossier might have been explained by septic events (e.g., hypotension, liver dysfunction) in addition to documented sepsis.

Clofarabine contraindicated in patients with hypersensitivity to clofarabine or to any of the excipients (see SPC section 6.1), patients with severe renal insufficiency or severe hepatic impairment, and breastfeeding should be discontinued prior to, during and following treatment with Evoltra (see SPC section 4.6).

Evoltra is a potent antineoplastic agent with potentially significant haematological and non-haematological adverse reactions (see SPC section 4.8). The following parameters should, therefore, be closely monitored in patients undergoing treatment with clofarabine:

- Complete blood and platelet counts should be obtained at regular intervals, more frequently in patients who develop cytopenias.
- Renal and hepatic function prior to, during active treatment and following therapy. Clofarabine should be discontinued immediately if substantial increases in creatinine or bilirubin are observed.
- Respiratory status, blood pressure, fluid balance and weight throughout and immediately after the 5 day clofarabine administration period.

There is a serious concern about SIRS / capillary leak syndrome. Six cases of SIRS / capillary leak syndrome were reported in total: 3 cases of treatment-related capillary leak syndrome were reported in study CLO-212; two of which were fatal. One patient had treatment-related SIRS in study CLO-212 as did another in study CLO-222. One further case of capillary leak syndrome was reported for a patient in study CLO-212 that was not considered related to clofarabine. The applicant reported that 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 general, the tumour lysis mechanism induced by chemotherapy is not accompanied by capillary leak syndrome. In a review of all cases, more subtle signs and/or symptoms of SIRS / capillary leak syndrome may have occurred, such as respiratory difficulty or effusion (pleural and pericardial) in other patients who developed septic shock.

The applicant has committed to monitor SIRS. Patients undergoing treatment with clofarabine should be evaluated and monitored for signs and symptoms of tumour lysis syndrome and cytokine release (e.g. tachypnoea, tachycardia, hypotension, pulmonary oedema) that could develop into SIRS / capillary leak syndrome or organ dysfunction (see SPC section 4.8). Clofarabine should be discontinued immediately if patients show early signs or symptoms of SIRS / capillary leak syndrome or substantial organ dysfunction and appropriate supportive measures should then be instituted. Further treatment with clofarabine, generally at a lower dose, can be considered when patients are stabilised and organ function has returned to baseline.

The majority of patients who respond to clofarabine achieve a response after 1 or 2 treatment cycles. Therefore, the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after 2 treatment cycles should be assessed by the treating physician.

In rats receiving clofarabine, myocardial degeneration shown by measuring the creatine kinase MB isozyme has been noted. The applicant has committed to monitor cardiac toxicity in humans, since

cardiac AEs have been reported. Patients with cardiac disease and those taking medicinal products known to affect blood pressure or cardiac function should be closely monitored during treatment with clofarabine (see SPC sections 4.5 and 4.8).

There is no experience in patients with renal insufficiency (serum creatinine ≥ 2 x ULN for age) and clofarabine is predominately excreted via the kidneys. Therefore, clofarabine is contraindicated in patients with severe renal insufficiency and should be used with caution in patients with mild to moderate renal insufficiency (see SPC sections 4.2 and 4.3). To date, there are insufficient data on the pharmacokinetics of clofarabine in patients with decreased creatinine clearance to advise a dose reduction in such patients. However, these limited data indicate that clofarabine may accumulate in patients with decreased creatinine clearance (see SPC sections 4.2 and 5.2). The concomitant use of medicinal products that have been associated with renal toxicity and those eliminated by tubular secretion should be avoided particularly during the 5 day clofarabine administration period (see SPC sections 4.5 and 4.8).

There is no experience in patients with hepatic impairment (serum bilirubin > 1.5 x ULN plus AST and ALT > 5 x ULN) and the liver is a potential target organ for toxicity. Therefore, clofarabine is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild to moderate hepatic impairment (see SPC sections 4.2 and 4.3). The concomitant use of medicinal products that have been associated with hepatic toxicity should be avoided wherever possible (see SPC sections 4.5 and 4.8).

Hepatic toxicities reported were cytolysis and hyperbilirubinaemia. As reported by the applicant, one death due to severe hepatic toxicity was observed. One case of grade 4 hyperbilirubinaemia was reported in study CLO-212. As most responding patients undergo BMT when a donor is identified, the use of clofarabine should be monitored carefully since BMT conditioning can cause VOD. The applicant has committed to ensure that monitoring hepatic function be part of the daily survey in transplanted patients.

There are currently limited data on the safety and efficacy of clofarabine when administered for more than 3 treatment cycles.

Each vial of Evoltra contains 180 mg of sodium chloride. This is equivalent to 3.08 mmol (or 70.77 mg) of sodium and should be taken into consideration for patients on a controlled sodium diet.

No studies on the effects of clofarabine on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, light-headedness or fainting spells during treatment and told not to drive or operate machines in such circumstances.

No case of overdose has been reported. However, possible symptoms of overdose are expected to include nausea, vomiting, diarrhoea and severe bone marrow depression. To date, the highest daily dose administered to human beings is 70 mg/m$^2$ for 5 consecutive days (2 paediatric ALL patients). The toxicities observed in these patients included vomiting, hyperbilirubinaemia, elevated transaminase levels and maculo-papular rash. No specific antidotal therapy exists. Immediate discontinuation of therapy, careful observation and initiation of appropriate supportive measures are recommended.

Concerning dose reduction for patients experiencing haematological toxicities, if the ANC does not recover by 6 weeks from the start of a treatment cycle, a bone marrow aspirate / biopsy should be performed to determine possible refractory disease. If persistent leukaemia is not evident, it is recommended that the dose for the next cycle be reduced by 25% of the previous dose following recovery of ANC to $\geq 0.75 \times 10^9$/l. Should patients experience an ANC $< 0.5 \times 10^9$/l for more than 4 weeks from the start of the last cycle, it is recommended that the dose for the next cycle be reduced by 25%.

The following recommendations have been provided in the SPC for patients experiencing non-haematological toxicities:

*Infectious events:* If a patient develops a clinically significant infection, clofarabine treatment may be withheld until the infection is clinically controlled. At this time, treatment may be reinitiated at the

full dose. In the event of a second clinically significant infection, clofarabine treatment should be withheld until the infection is clinically controlled and may be reinitiated at a 25% dose reduction.

*Non-infectious events:* If a patient experiences one or more severe toxicities (US National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Grade 3 toxicities excluding nausea and vomiting), treatment should be delayed until the toxicities resolve to baseline parameters or to the point where they are no longer severe and the potential benefit of continued treatment with clofarabine outweighs the risk of such continuation. It is then recommended that clofarabine be administered at a 25% dose reduction.

Should a patient experience the same severe toxicity on a second occasion, treatment should be delayed until the toxicity resolves to baseline parameters or to the point where it is no longer severe and the potential benefit of continued treatment with clofarabine outweighs the risk of such continuation. It is then recommended that clofarabine be administered at a further 25% dose reduction.

Any patient who experiences a severe toxicity on a third occasion, a severe toxicity that does not recover within 14 days (see above for exclusions), or a life-threatening or disabling toxicity (US NCI CTC Grade 4 toxicity) should be withdrawn from treatment with clofarabine (see SPC section 4.4).

## 1.6 Pharmacovigilance

**Detailed description of the Pharmacovigilance system**

The CHMP considered that the pharmacovigilance system as described by the applicant fulfils the legislative requirements.

**Risk Management Plan**

A Risk Management Plan for clofarabine has been provided in accordance with the requirements of ICH E2E Pharmacovigilance Planning, the ICH Step 4 Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03), and the draft 'CHMP Guideline on Risk Management Systems for Medicinal Products for Human Use'.

**Table 9. Summary of the risk management plan**

| Safety issue | Proposed pharmacovigilance activities | Proposed risk minimisation activities |
|---|---|---|
| Hepatic toxicity | Enhanced post-marketing surveillance using suspected adverse event reporting forms and guidelines for completion. | Set up a voluntary adverse event reporting system to collect information for all registered patients on any serious (especially unexpected) treatment-emergent possibly drug-related events, any emergent CTC grade 3 or higher renal, hepatic, or cardiac events, all possibly drug-related deaths, all cases of suspected tumour lysis syndrome, SIRS and capillary-leak syndrome, all cases with a suspected drug interaction, all grade 3 or higher possibly drug-related events occurring after 3 or more cycles of use, and any suspected cases of VOD. |
| Cardiac toxicity | | |
| Tumour lysis syndrome, SIRS and capillary-leak syndrome | | |
| Renal toxicity | | |
| Safety ≥ 3 cycles | | |
| Drug interactions | | |

The applicant has planned to produce educational material for physicians and patients, and an enhanced adverse event reporting system which is aimed at risk minimisation and monitoring the safety of clofarabine in the setting of normal use. The educational material for physicians and patients is planned to include:

- Information on what is clofarabine, pharmacy / administration guidelines (storage and preparation instructions, body surface area calculation etc), therapeutic indication, toxicity management (information on how to proceed should patients develop certain toxicities), and dosage recommendations.
- Patient medication guide.

- A description of the enhanced adverse event reporting scheme and a request to register.
- Specified suspected adverse event reporting forms and guidelines for completion to encourage reporting of any serious drug-related, hepatic, cardiac, SIRS-like, renal and suspected drug interaction adverse events, and those adverse events occurring after 3 or more cycles of treatment.

The applicant committed to update the RMP as recommended in the CHMP Guideline on Risk Management Systems for Medicinal Products for Human use, namely: to submit the RMP at the same time as PSURs, when new information is received, within 60 days of an important milestone being reached or the results of a study become available (see specific obligations timelines), and upon the request of a Competent Authority.

## 1.7 Overall conclusions, risk/benefit assessment and recommendation

**Quality**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product. The applicant gave Letters of Undertaking and committed to resolve these as follow-up measures after the opinion, within an agreed timeframe.

**Non-clinical pharmacology and toxicology**

Clofarabine is a purine nucleoside anti-metabolite. *In vitro* studies have demonstrated that clofarabine inhibits cell growth in and is cytotoxic to a variety of rapidly proliferating haematological and solid tumour cell lines. It was also active against quiescent lymphocytes and macrophages. In addition, clofarabine delayed tumour growth and, in some cases, caused tumour regression in an assortment of human and murine tumour xenografts implanted in mice.

Toxicology studies of clofarabine in mice, rats and dogs showed that rapidly proliferating tissues were the primary target organs of toxicity. Cardiac effects were observed in rats consistent with cardiomyopathy and contributed to signs of cardiac failure after repeated cycles of treatment. The incidence of these toxicities was dependent on both the dose of clofarabine administered and the duration of treatment. The potential risk for humans is unknown.

Glomerulonephropathy was reported in rats at exposure levels 3 to 5 fold higher than the clinical AUC after 6 dosing cycles of clofarabine.

Hepatic toxicity was observed in rats following chronic administration of clofarabine. Histological evidence of hepatic effects was seen in dogs following acute administration of high doses. These effects were not accompanied by changes in serum chemistry.

Dose related toxicities on male reproductive organs were observed in mice, rats and dogs. Delayed ovarian atrophy or degeneration and uterine mucosal apoptosis were observed in female mice.

Clofarabine was teratogenic in rats and rabbits. No fertility studies have been conducted.

Clofarabine induced clastogenic effects in the non-activated chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells and in the *in vivo* rat micronucleus assay. No carcinogenicity studies have been performed.

**Efficacy**

The demonstration of efficacy in ALL is based on the non-comparative phase II study CLO-212. No randomized controlled trials with clofarabine in ALL have been submitted. Lack of a comprehensive clinical development program has been justified in view of the small size of the population of patients in second relapse. Study CLO-212 was a multi-centre, phase II, open-label, non-comparative study of clofarabine and was conducted to determine the overall remission (CR + CRp) rate in heavily pre-treated patients ($\leq$ 21 years old at initial diagnosis) with relapsed or refractory ALL (N=61). Clofarabine 52 mg/m$^2$/day was administered by intravenous infusion for 5 consecutive days every 2 to 6 weeks. Patients must not have been eligible for therapy of higher curative potential and must have been in second or subsequent relapse and/or refractory i.e. failed to achieve remission after at

least two prior regimens (95% of patients had received 2 to 4 different induction regimens). The overall remission rate was 20%. The 12 patients who achieved an overall remission had a median survival time of 66.6 weeks as of the data collection cut-off date. 10/61 patients (16%) went on to receive a HSCT after treatment with clofarabine.

**Safety**

One hundred and twenty nine patients (98% of the total paediatric safety population, N=132) experienced at least one adverse event considered by the study investigator to be related to clofarabine. Those most frequently reported were nausea (61% of patients), vomiting (61%), febrile neutropenia (32%), headache (24%), pyrexia (21%), pruritus (21%) and dermatitis (20%). Although 76 patients (58%) experienced at least one serious clofarabine-related adverse event, only 2 patients discontinued treatment because of an adverse reaction; both with hyperbilirubinaemia, one after receiving 52 mg/m$^2$/day and one after 70 mg/m$^2$/day clofarabine. However, the deaths of 4 patients were considered by the study investigator to be related to treatment with clofarabine: one patient experienced clofarabine-related acute vascular leak syndrome that contributed to cardiac arrest; one patient died from respiratory distress and hepatocellular damage; one patient from septic shock and multi-organ failure; and one patient from multi-organ failure. Important identified risks with clofarabine are hepatic and cardiac toxicity, tumour lysis syndrome / SIRS / capillary-leak syndrome, and, potentially, renal toxicity. Important missing information is safety of use for more than 3 cycles, and drug interactions with commonly used co-medication. Adequate information has been provided in the SPC to help treating physicians minimize potential clofarabine toxicity, and to minimise the incidence and severity of hepatic, cardiac and renal toxicities. The risk management plan submitted was considered adequate.

The applicant committed to conduct user testing and to submit the results as a follow-up measure.

**Risk-benefit assessment**

According to CHMP guidelines, this full application should have been based on data generated by randomised, controlled clinical trials rather than by open-label, non-comparator studies. However, the lack of a randomized trial in this very heavily treated population is justified in view of the small size of the population of patients in second relapse. Furthermore, even in the absence of adequately controlled trials, clofarabine treatment achieved a meaningful remission rate and facilitated HSCT in a significant proportion of patients that before treatment were considered not eligible for therapy of higher curative potential. In the context of an invariably poor prognosis with a median survival in the order of 9-10 weeks, facilitating HSCT constitutes a meaningful clinical effect that may have an impact on duration of survival.

Important identified risks with clofarabine are hepatic and cardiac toxicity, tumour lysis syndrome / SIRS / capillary-leak syndrome, and, potentially, renal toxicity. Important missing information is safety of use for more than 3 cycles, and drug interactions with commonly used co-medication. Adequate information has been provided in the SPC to help treating physicians minimize potential clofarabine toxicity, and to minimise the incidence and severity of hepatic, cardiac and renal toxicities. However, regarding the safety profile of clofarabine there are still many uncertainties due to the limited size of the safety database. This is justified in view of the small size of the population of patients in second relapse, but required the applicant to introduce specific procedures concerning the safety of the product. A risk management plan was submitted. The CHMP agreed that the following additional risk minimisation activities were required:

- The marketing authorisation holder is required to implement specific strategies to minimize cardiac, hepatic, and renal toxicity with clofarabine use, including a recommendation that treating physicians assess the potential benefit and risks associated with continued therapy in patients who do not show haematological and/or clinical improvement after two clofarabine treatment cycles. To this end, the holder will ensure that prescribers receive a clofarabine user's information pack including recommendations for safe use of the drug.
- The marketing authorisation holder is required to encourage prescribers to participate in a voluntary adverse event reporting system. The system will seek to collect relevant information about patient and disease characteristics, and treatment (including concomitant medications) for all registered patients together with information on any serious (especially unexpected) treatment-

emergent possibly drug-related events, any emergent CTC grade 3 or higher renal, hepatic, or cardiac events, all possibly drug-related deaths, all cases of suspected tumour lysis syndrome, SIRS and capillary-leak syndrome, all cases with a suspected drug interaction, all grade 3 or higher possibly drug-related events occurring after 3 or more cycles of use, and any suspected cases of VOD in patients receiving clofarabine treatment.

In conclusion, the effect of clofarabine in terms of remission and facilitating HSCT is considered to be clinically significant effect that may have a significant impact on long-term treatment outcome. There are still many uncertainties due to the limited size of the safety database and the lack of a randomized, controlled, efficacy trial to demonstrate the effect of clofarabine on overall survival. However, it is acknowledged that the indication for which the medicinal product is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive data on the clinical efficacy and safety of the medicinal product. Therefore, the marketing authorisation should be granted under exceptional circumstances.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered, by consensus, that the risk-benefit balance of Evoltra in the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response was favourable and, therefore, recommended the granting of a marketing authorisation under exceptional circumstances. Safety and efficacy have been assessed in studies of patients ≤ 21 years old at initial diagnosis.