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Human Medicines Development and Evaluation

Evoltra

(clofarabine)

Procedure No. EMEA/H/C/613/A46/033

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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INTRODUCTION

On 6 December 2010, the MAH submitted a completed paediatric study for Evoltra (clofarabine), in accordance with Article 46 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Evoltra (clofarabine) and that there is no consequential regulatory action.

SCIENTIFIC DISCUSSION

1. Information on the pharmaceutical formulation used in the clinical study

According to the MAH, clofarabine finished product, 1 mg/ml concentrate for solution for infusion, is formulated in 0.9% sodium chloride (normal saline) and is diluted for injection in 0.9% sodium chloride. The finished product formulation does not contain antioxidants or antimicrobial preservatives and is considered suitable for the paediatric use. The IV formulation of clofarabine used in CLO21800205 is the same formulation that has been extensively studied and approved in the US and EU for single-agent clofarabine therapy in paediatric patients with relapsed or refractory ALL.

2. Non-clinical aspects

NA

3. Clinical aspects

Introduction

Clofarabine (Evoltra) is a second generation purine nucleoside that has a wide range of anti-tumour activity in both *in vitro* and *in vivo* human tumour models

On 29 May 2006, clofarabine was approved under exceptional circumstances in the EU for treatment of 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 between 1 and 21 years old at initial leukaemia diagnosis.

In accordance with Article 46 of Regulation (EC) No 190112006, the MAH submitted a report for Study CL021800205: a Phase 1/2 dose-escalation study of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute leukemias.

Clinical study

Study CL021800205*:*
A Phase 1/2 dose-escalation study of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute leukemias

- **Description**

This was a phase 1/2 open label dose-escalation study of clofarabine in combination with etoposide and cyclophosphamide in paediatric patients with refractory or relapsed acute leukaemias (ALL or AML). This multicenter study included 16 investigators and 15 study centres in the United States.

The study started on 11 March 2006 (first patient treated) and ended on 25 November 2009 (last phase 2 patient completed study drug); Date of data cut off: 11 May 2010.

- **Methods**
  - Objective(s)

Phase 1

Primary Objective:

• To determine maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and the recommended Phase 2 dose (RP2D) of clofarabine when used in combination with etoposide and cyclophosphamide and to assess the feasibility and safety of this combination regimen to treat children with refractory or relapsed acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML).

Secondary Objectives:

• To determine the safety and tolerability of clofarabine when used in combination with etoposide and cyclophosphamide and determine the duration, seriousness, and relationship of adverse events that occur during the treatment and follow-up periods;

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

• To document the rate of partial remission [PR] in the study population; and

• To document time-to-event parameters, including duration of remission, event-free survival [EFS], 4 month EFS, and overall survival (OS).

Phase 2

Primary Objective:

• To estimate the response rate (CR + CRp) at the RP2D in this study population.

Secondary Objectives:

• To determine the duration of remission, EFS, 4-month EFS, and OS in the study population;

• To determine the safety and tolerability of clofarabine when used in combination with etoposide and cyclophosphamide and the duration, seriousness, and relationship of adverse events that occur during the treatment and follow-up periods; and

• To document the rate of PR(s) and "any response" (CR + CRp + PR) in the study population.

Exploratory Studies:

• To characterize the pharmacokinetics of clofarabine, cyclophosphamide, and etoposide when administered in combination.

• To define apoptotic pathways in response to therapy in order to determine unique cell death pathways that are agent specific and also to identify pathways predictive of response.

• To determine gene expression profiles at the time of second or subsequent relapse in order to discover mechanisms of resistance by comparing samples at the time of diagnosis and first relapse, and to isolate profiles that predict complete response.

• To quantitate the level of nucleoside transporters (e.g., hENT1, hENT2, hCNT2, and hCNT3) in the blasts of children with relapsed or refractory ALL and correlate with the intracellular accumulation of clofarabine triphosphate and with clinical outcomes.

• To correlate post remission events (relapse, death) with minimal residual disease at the end of the first induction and reinduction cycles and during consolidation.

- Study design

This was a phase I/II multi-centre, open-label, dose-escalation study designed to characterize the feasibility, safety, and efficacy of clofarabine in combination with etoposide and cyclophosphamide in refractory or relapsed ALL and AML (Phase 1 only) paediatric patients.

- Study population /Sample size

Phase 1 consisted of 5 dose cohorts with a total enrolment of 25 patients (20 ALL and

5 AML patients).

Twenty-five ALL patients were enrolled in the Phase 2 portion.

- Treatments

  Clofarabine in Combination with Etoposide and Cyclophosphamide Treatment Regimen

Dose-Escalation Scheme				
Phase 1				
Cohort	**No. of Pts**	**Clofarabine**	**Etoposide**	**Cyclophosphamide**
1	3 to 6	20 mg/m^2	75 mg/m^2	340 mg/m^2
2	3 to 6	20 mg/m^2	75 mg/m^2	440 mg/m^2
3	3 to 6	20 mg/m^2	100 mg/m^2	440 mg/m^2
4	3 to 6	30 mg/m^2	100 mg/m^2	440 mg/m^2
5[1]	3 to 6	40mg/m^2	100 mg/m^2	440 mg/m^2
Phase 2[2]				
No. of Pts		**Clofarabine**	**Etoposide**	**Cyclophosphamide**
25		40mg/m^2	100 mg/m^2	440 mg/m^2

[1] In the event an MTD is not identified earlier, Cohort 5 was to be RP2D
[2] Patients in the Phase 2 portion of the study were to be treated at the RP2D of clofarabine in combination with etoposide and cyclophosphamide as determined in the Phase 1 portion of the study.

Duration of treatment:

Patients could receive a maximum of 8 cycles (2 induction and 6 consolidation cycles or 1 induction and 7 consolidation cycles) of treatment.

Safety:

All patients who received any amount of any of the study drugs were included in the safety analyses.

Safety analyses included the following:

• The incidence, severity, duration, causality, seriousness, and type of adverse events and changes in clinical laboratory results.

• In addition, deaths and other SAEs were tabulated.

• Withdrawals due to adverse events.

Efficacy:

Efficacy analyses were performed on 3 efficacy populations, with the "Primary Efficacy Analysis Patients" considered as the primary analysis set.

Analyses on the other 2 populations were considered secondary.

The estimation of efficacy parameters was the primary objective of the Phase 2 portion of the study.

Endpoints include OR, CR, CRp, and PR rates, duration of remission, time to remission, overall survival (OS), EFS, and the 4-month EFS rate. Information regarding the number of patients who proceed to transplant was evaluated in a separate analysis. The investigator-determined responses were used for efficacy analyses. Efficacy endpoints were summarized using descriptive statistics.

The proportion of responders (OR, CR, CRp, PR, OR+PR) and the proportion of patients receiving transplant were computed and presented with exact 95% confidence intervals.

The Kaplan-Meier method was used to summarize the distributions of EFS, OS, and duration of remission.

Summary statistics for a subset of efficacy endpoints was presented for AML patients and for ALL patients treated at doses other than the RP2D.

- **Results**
  - Efficacy results

In Phase 1: 16 (16/25; 64.0%) patients (ALL and AML) experienced overall remission (OR), based on the investigators' assessment. The median duration of remission (DOR) censored at the last follow-up visit for these 16 responders was 18.2 weeks (Min/Max: 6.6/105.1+). The median DOR censored at the earlier date of alternative therapy or at the last follow-up visit for these responders was 17.0 weeks (Min/Max: 2.3+/61.4+). The 25 Phase 1 patients experienced a median event-free survival (EFS) of 19.3 weeks and median overall survival (OS) of 27.1 weeks. Thirteen (13/25; 52.0%) Phase 1 patients remained event-free at 4 months post first dose of study drugs. In general, the efficacy endpoints appear to be similar across the Phase 1 cohorts with the exception of OS. Median OS ranged from 52.9 weeks in Cohort 1 to 14.3 weeks in Cohort 5. Ten (10/25; 40.0%) Phase 1 patients were able to proceed to transplant, including 9 (9/25; 36.0%) patients who had achieved CR or CRp.

In Phase 1, 11 (11/20; 55.0%) ALL and 5 (5/5; 100.0%) AML patients experienced OR.

The median DOR censored at last follow-up visit for the ALL and AML responders was 22.6 weeks (Min/Max: 6.6/105.1+) and 15.6 weeks (Min/Max: 7.3/105.0+), respectively.

The median DOR censored at the earlier date of alternative therapy or at the last follow up visit for the ALL and AML responders was 19.3 weeks (Min/Max: 2.3+/61.4) and 12.4 weeks (Min/Max: 4.9+/17.0), respectively. Median EFS for ALL and AML patients was 18.0 and 19.3 weeks, respectively. Median OS was 28.4 weeks for the 20 ALL patients and 23.1 weeks for the 5 AML patients. Ten (10/20; 50.0%) ALL and 3 (3/5; 60.0%) AML patients remained event-free at 4 months post first dose of study drugs.

In the Phase 2 portion of the study (ALL patients only): 11 (11/25; 44.0%) patients experienced OR, based on the investigator's assessment. The median DOR censored at last follow-up visit for these 11 responders was 67.3 weeks (Min/Max: 2.9/109.6+), substantially longer compared to Phase 1 responders. The median DOR censored at the earlier date of alternative therapy or at the last follow-up visit for Phase 2 patients was not estimable because the majority of events occurred after the initiation of alternative therapy. The median EFS and median OS for all 25 Phase 2 patients were the same at 10.7 weeks. Eleven (11/25; 44.0%) Phase 2 patients remained event-free at 4 months post first dose of study drugs. Ten (10/25; 40.0%) Phase 2 patients were able to proceed to transplant, including 7 (7/25; 28.0%) who had achieved CR or CRp.

- Safety results

Exposure

Phase 1 (25 patients): the median cumulative amount of clofarabine received was 252.00 mg (range: 85.0 to 1046.0 mg), **median cumulative number of cycles received was 2** (range: 1 to 8 cycles), and the median duration between cycles was 34.0 days (range: 23 to 75 days). There were no significant differences in study drug exposure between ALL and AML patients.

Phase 2 (25 patients)**:** the median cumulative amount of clofarabine received was 370.00 mg (range: 95.0 to 841.2 mg), **median cumulative number of cycles received was 1** (range: 1 to 3 cycles), and the median duration between cycles was 28.5 days (range: 19 to 59 days).

Dosing Modifications

Phase 1: 4/25 (16.0%) patients experienced 1 or more dose modifications. Two patients experienced dose reductions and 2 patients experienced infusion interruption.

•Pt 004-0015 (Cohort 4) experienced a total dose reduction of approximately 25% during Cycles 2 through 5 due to AEs of **increased lipase or pancreatitis**. This patient also missed a clofarabine dose on Day 5 of Cycle 1 due to an AE (increased lipase).

• Pt 004-0010 (Cohort 4) experienced a dose reduction of approximately 25% during Cycle 2 due to **increased lipase**.

• Pt 005-0019 (Cohort 4) experienced an infusion interruption during Cycle 1 due to allergic reaction (flushing, agitation, throat tightness) to clofarabine. Patient received a subsequent cycle of clofarabine (Re-Induction Cycle 2) without any dosing complications.

• Pt 005-0020 (Cohort 5) experienced an infusion interruption during Cycle 1 due to vomiting.

Phase 2: 3/25 (12.0%) patients experienced 1 or more dose modifications. One patient experienced a dose reduction and 2 patients experienced infusion interruption.

• Pt 003-0027 experienced an infusion interruption during Cycle 1 due to vomiting.

• Pt 012-0048 experienced an infusion interruption during Cycle 1 due to **capillary leak syndrome**.

• Pt 015-0037 experienced a dose reduction of approximately 25% during Cycle 2 due to **pancreatitis**.

Overall Summary of Patients with Adverse Events

	Phase 1 (N=25)	**Phase 2 (N=25)**
Number (%) of Patients:		
With at least one AE regardless of relationship to clofarabine	25 (100.0)	25 (100.0)
With at least one AE related to clofarabine	25 (100.0)	25 (100.0)
With at least one serious AE regardless of relationship to clofarabine	24 (96.0)	21 (84.0)
With at least one serious AE related to clofarabine	22 (88.0)	20 (80.0)
Who discontinued due to AE	0	1 (4.0)
Who died	21 (84.0)	16 (64.0)
With at least one AE with a maximum (worst) NCI Common Terminology Criteria of::		
Grade 1	0	0
Grade 2	0	0
Grade 3	10 (40.0)	1 (4.0)
Grade 4	11 (44.0)	16 (64.0)
Grade 5	4 (16.0)	8 (32.0)

Summary of Adverse Events

Phase 1

All 25 patients reported at least 1 AE, regardless of relationship to clofarabine. The most common AEs (≥Grade 3), regardless of relationship to clofarabine, reported by ≥10% of patients overall were febrile neutropenia (n=16), hypokalaemia (n=12), thrombocytopenia (n=11), anaemia (n=8), neutropenia (n=7), decreased appetite (n=5), pyrexia (n=4), headache (n=4), epistaxis (n=4), hypoxia (n=4), caecitis (n=4), hyponatremia (n=3), device-related infection (n=3), and staphylococcal infection (n=3).

Based on maximum grade experienced by a patient for each event, 10 (10/25; 40.0%) patients experienced a Grade 3 event, 11 (11/25; 44.0%) patients experienced a Grade 4 event, and 4 (4/25; 16.0%) patients experienced a Grade 5 event.

Twenty-four (24/25; 96.0%) patients experienced at least 1 SAE regardless of relationship to clofarabine, and 22 (22/25; 88.0%) patients experienced at least 1 SAE that was considered related to clofarabine per the investigator's assessment.

No patient discontinued due to an AE in Phase 1.

Twenty-one (21/25; 84.0%) patients died during the study treatment period or during the follow-up period:

- Eleven of these deaths were due to malignant disease.
- Two of the deaths were due to drug-related AEs (Pt 004-0013 [cohort 4] died due to cerebral haemorrhage; Pt 010-0021 [cohort 5] died due to meningitis bacterial).
- Eight deaths were due to 'other' causes (transplant complications, intracranial hemorrhage, multiorgan failure [2 patients], progressive respiratory failure after transplant, cardiac arrest, pneumonia, and infection).

Both ALL and AML patient groups experienced similar relative frequencies of AEs, SAEs, and death.

Phase 2

All 25 patients reported at least 1 AE, regardless of relationship to clofarabine. The most common AEs (≥Grade 3), regardless of relationship to clofarabine, reported by ≥10% of patients overall were febrile neutropenia (n=18), anaemia (n=16), thrombocytopenia (n=16), hypokalaemia (n=14), neutropenia (n=13), aspartate aminotransferase increased (n=10), decreased appetite (n=7), hypotension (n=7), alanine aminotransferase increased (n=7), nausea (n=5), hypophosphataemia (n=5), hyponatremia (n=5), lipase increased (n=5), pyrexia (n=4), leukopenia (n=4), renal failure acute (n=4), septic shock (n=4), hyperbilirubinaemia (n=3), gingival bleeding (n=3), caecitis (n=3), coagulopathy (n=3), enterococcal bacteraemia (n=3), lung infection (n=3), pulmonary oedema (n=3), and **veno-occlusive liver disease (n=3)**. Based on maximum grade experienced by a patient for each event, 1 (1/25; 4.0%) patient experienced a Grade 3 event, 16 (16/25; 64.0%) patients experienced a Grade 4 event, and 8 (8/25; 32.0%) patients experienced a Grade 5 event.

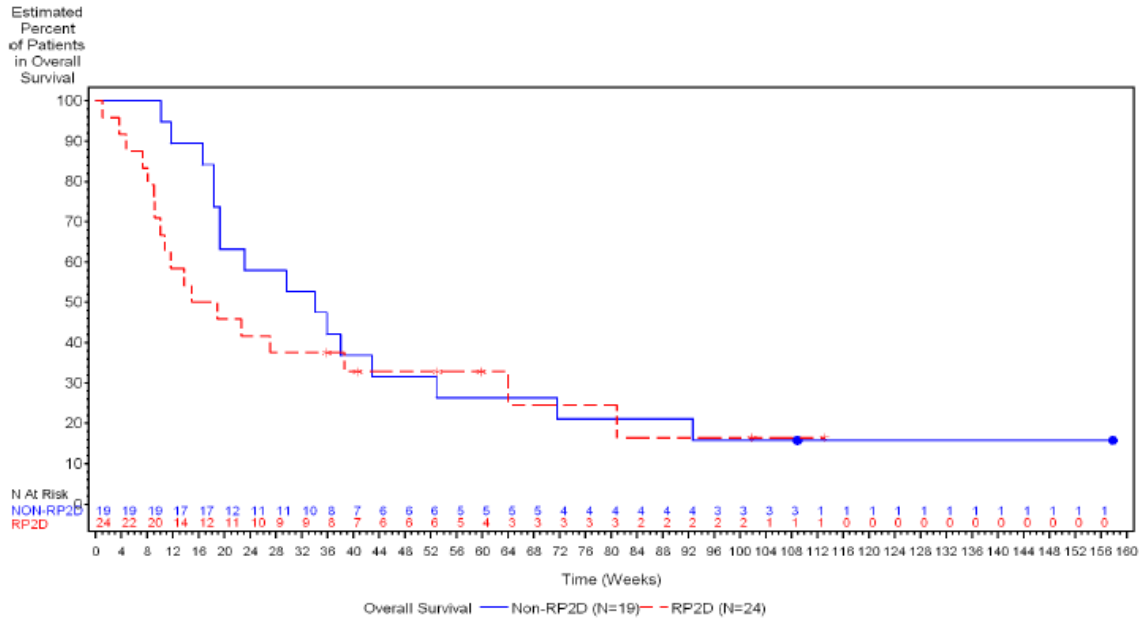
Twenty-one (21/25; 84.0%) patients experienced at least 1 SAE, regardless of relationship to clofarabine and 20 (20/25; 80.0%) patients experienced at least 1 SAE that was considered related to clofarabine per the investigator's assessment.

There was 1 patient who discontinued due to an AE (Pt 004-0036 due to fungal sinusitis).

Overall sixteen (16/25; 64.0%) patients died during the study treatment period or during the follow-up period.

- Six of these deaths were due to malignant disease.
- Seven deaths were due to AEs, of which, 6 were due to drug-related AEs.
- Three deaths were due to 'other' causes: 1-generalized infection lung/brain, 2-multiorgan failure and non-engraftment, veno-occlusive disease 3- haemorrhage due to opportunistic infection

Figure 12-1: Kaplan-Meier Curve for Overall Survival (For CSR Death Section) Censored at Last Known Follow-Up Visit Patients with Baseline Lansky/Karnofsky Performance Status ≥80 (RP2D Patients versus Non-RP2D Patients)



The number represents the number of patients at risk per group at the start of each four week period. The symbols represent a censored patient(s).
Log Rank p-value=0.4632; Wilcoxon p-value=0.1273 Source: Figure 14.2.1

Discussion on safety

VOD/SOS

Globally, seven patients developed AEs in which signs/symptoms of VOD represented a prominent component of each case (4 patients during the treatment period of the study and 3 patients after completion of the study in a post-transplant setting).

For the 4 patients that developed these AEs during the treatment period of the study, these events were considered serious and related to clofarabine.

For the 3 patients that developed these AEs after completion of the study in a post-transplant setting, these events were not considered to be related to clofarabine. An expert panel concluded that VOD was present in 1 patient and that VOD/sinusoidal obstructive syndrome (SOS) could not be ruled in or out in 1 patient. Ongoing infections preceded hepatoxicity in patients who were diagnosed with VOD or VOD-like symptoms. However, 2 of the 4 patients who were diagnosed with VOD while on study treatment had received total body irradiation as conditioning for a HSCT prior to study entry. The combination of the above factors likely contributed to the occurrence of VOD.

After amending the protocol to exclude patients with prior HSCT, no new cases of VOD were reported in patients on study treatment.

Myelosuppression

Due to prolonged myelosuppression from prior therapies, this population was susceptible to a wide range of illnesses, particularly infections. Infections were experienced as AEs, regardless of relationship to clofarabine, by the majority of patients in Phase 1 (20/25 [80.0%] patients) and Phase 2 (19/25 [76.0%] patients).

Of the various types of infections, bacterial infection was the most common (Phase 1: 14/25 [56.0%] patients, Phase 2: 14/25 [56.0%] patients). The majority (68%) of AEs of infection were ≤Grade 3 in Phase 1 patients.

Serious adverse events of infections, or sepsis/septic shock, were also associated with early deaths (defined as those deaths occurring within the first 8 weeks from start of study therapy).

Deaths

This study was not designed or powered to detect differences in survival, and patient assignment to dose or phase was not randomized. However, there is a numerical difference noted in the median OS of Phase 1 patients (27.1 weeks; 95% CI 18.3, 42.9) and Phase 2 patients (10.7 weeks; 95% CI 8.1, 38.6). This difference is largely accounted for by the frequency of early ("early" is defined, for the purposes of this discussion, as those deaths occurring within the first 8 weeks from start of study therapy) deaths observed in Phase 2 (7/25; 28.0%) and in Phase 1 (1/25; 4.0%).

Furthermore, **in comparing median OS across the Phase 1 cohorts, the medians appear to decrease with increasing dose, albeit the numbers in each separate cohort are too few to draw any conclusions about dose effect in the individual early dose cohorts.**

In order to overcome the issue of small patient numbers within individual cohorts treated at lower doses and to allow more formal exploratory analysis of the numerically longer survival in these Phase 1 cohorts, post-hoc, we further analyzed OS for all patients receiving RP2D (i.e., Phase 2 patients plus Phase 1 Cohort 5 patients; n=31), comparing against patients treated in Phase 1 Cohorts 1 to 4. As with the comparison of Phase 1 and Phase 2, the proportion of early deaths observed in patients treated at RP2D was imbalanced compared with Phase 1 Cohorts 1 to 4 (8/31 [25.8%] vs. 0/19 [0.0%]). Exploratory analyses were undertaken to identify confounding factors and their impact on the observed difference on survival (Table 12-15). Without adjusting for other covariates, Phase 1 cohorts 1 to 4 appeared to have a lower risk of death (hazard ratio [HR] of 0.668 [95% CI 0.353, 1.263; p=0.2139]). Various clinical covariates were then evaluated as potential confounders, including leukemic cell lineage (T cell vs. B cell vs. AML), baseline ANC (Grade 3 or 4 at baseline vs. normal, Grade 1 or 2), prior HSCT (yes vs. no), refractoriness to prior chemotherapy regimen (yes vs. no) and baseline Lansky/Karnofsky performance status (≤70 vs. ≥80). In both univariate and multivariate

RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Currently, clofarabine is used as monotherapy in ALL paediatric patients who have relapsed or are refractory after receiving at least two prior regimens. The recommended dose is 52 mg/m^2 of body surface area administered by intravenous infusion over 2 hours daily for 5 consecutive days.

CLO21800205 study is a phase 1/2 open label dose-escalation study of ***clofarabine in combination with etoposide and cyclophosphamide*** *in paediatric patients with refractory or relapsed acute leukaemias (ALL or AML). Only the Phase 1 portion of the study was open to both ALL and AML patients.*

The primary objective was

- *Phase I: to determine maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and the recommended Phase 2 dose (RP2D) of clofarabine when used in combination with etoposide and cyclophosphamide*
- *Phase II: to assess the feasibility and safety of this combination regimen to treat children with refractory or relapsed acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML).*

Phase I: Based on efficacy results of phase I study, the recommended phase 2 dose (RP2D) was determined to be: clofarabine 40 mg/m2, cyclophosphamide 440 mg/m2 and etoposide 100 mg/m2, each given daily for 5 days. There were responses seen across all cohorts in Phase 1 suggesting an efficacious effect at doses less than the RP2D. Additionally, responses were seen in ALL as well as in AML patients.

- *The overall response rate was 64.0% among the 25 patients enrolled in Phase 1.*
- *Durability of remission as measured by the secondary endpoint of DOR was 18.2 weeks.*
- *Median EFS and OS were 19.3 and 27.1 weeks, respectively.*
- *Ten (40.0%) patients were able to proceed to transplant, including 9 (9/25; 36.0%) patients who had achieved CR or CRp.*
- *Twenty-one (84.0%) patients died during the study treatment period or during the follow-up period.*

The phase II of the study was designed to evaluate the efficacy of the combination of Clofarabine with Etoposide and Cyclophosphamide in ALL paediatric patients. Inclusion criteria were the following:

- Age ≤21 years at time of initial leukemia diagnosis.

- Patients with ALL received no more than 3 prior induction regimens.

Due to VOD (seven cases reported), the protocol was later amended to exclude patients who received prior hematopoietic stem cell transplant (HSCT).

- *The median cumulative number of cycles received was 1 (range: 1 to 3 cycles)*
- *Overall Response rate = 44 %, median DOR = 67.3 weeks,*
- *Median EFS and OS= 10.7 weeks each*
- *Ten (10/25; 40.0%) Phase 2 patients were able to proceed to transplant, including 7 (7/25; 28.0%) who had achieved CR or CRp.*
- *20 patients (80.0%) experienced at least 1 SAE that was considered related to clofarabine per the investigator's assessment.*

- *1 patient (1/25; 4.0%) experienced a Grade 3 event,*
- *16 (16/25; 64.0%) patients experienced a Grade 4 event,*
- *8 (8/25; 32.0%) patients experienced a Grade 5 event.*
- *3 patients experienced a veno-occlusive liver disease.*
- *Overall sixteen (16/25; 64.0%) patients died during the study treatment period or during the follow-up period.*

In conclusion any new regimen with different combined chemotherapy to increase treatment options is awaited and should be more explored. These efficacy results suggest a clinical benefit for paediatric patients with refractory or relapsed acute leukaemias when clofarabine is used in combination with other drugs and allow some of them to undergo HSCT.

*However no sufficient data have been submitted in the frame of this procedure to clearly **justify the choice of the R2PD**. In contrast, safety results show that the combined regimen at the R2PD is associated with **a very high toxicity** as evidenced by the 80.0% patients who experienced at least 1 related SAE and the 3 cases of veno-occlusive disease reported in the phase II study.*

*This outstanding toxicity could be acceptable if it can be translated into a clinical benefit for the patients. For the time being, **HSCT is the only chance of cure in relapsed ALL patients**. In the non randomized clinical trial CLO-212 which led to the approval of the current indication, a few number of ALL children relapsing after a previous HSCT could undergo a further HSCT.*

Hence the amendment to CL021800205 study protocol excluding patients who previously underwent HSCT may question the feasibility of HSCT in children who received the combination with R2PD. For the time being no data regarding procedures and outcome of HSCT are available. These data should be provided within the next PSUR.

- **Recommendation**

Based on the data submitted, the MAH should provide, as part of this procedure P46, within the next PSUR, results regarding procedures and outcome of HSCT, from ALL studies investigating new combined regimen.

ADDITIONAL CLARIFICATIONS REQUESTED

The amendment to CL021800205 study protocol excluding patients who previously underwent HSCT may question the feasibility of HSCT in children who received the combination with R2PD. For the time being no data regarding procedures and outcome of HSCT are available. These data should be provided within the next PSUR.