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EVOLTRA

(Clofarabine)

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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

Clofarabine is currently approved, as a single agent, 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. The recommended dose is 52 mg/m^2 of body surface area administered by intravenous infusion over 2 hours daily for 5 consecutive days.

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 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.

The primary objective of the phase 1 was 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.

The phase II of the study was designed to evaluate the efficacy of the combination of Clofarabine with Etoposide and Cyclophosphamide at the recommended Phase 2 dose in ALL paediatric patients.

The combined regimen at the R2PD was 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 (VOD) reported in the phase II study (4 cases were also reported during the phase I period).

Following the 3 cases of VOD reported in the phase II, **CL021800205** study protocol was amended in order to exclude patients who previously underwent HSCT. This amendment raised into question the feasibility of HSCT in children who received the combination with R2PD.

Thus, the MAH was requested to provide results regarding procedures and outcome of HSCT, from ALL studies investigating the new combined regimen.

MAH Response

The studies in ALL with the regimen clofarabine, etoposide and cyclophosphamide are **CLO21800205** and VHR Pilot (**CLO08808**).

CLO21800205

PHASE 1 :

In this phase, 10 patients (40.0%) underwent HSCT, including 7 patients with ALL and 3 patients with AML.

Of these 10 patients, 3 patients received bone marrow stem cells, 2 patients received peripheral blood stem cells, and 5 patients received cord blood stem cells. Of the patients receiving bone marrow stem cells, 2 received allogeneic bone marrow with 6/6 antigen match and 1 received matched unrelated donor bone marrow with 9/10 antigen match. Both patients who received peripheral blood stem cells were a 10/10 antigen match. One of these patients received two allogeneic peripheral blood stem cell transplants within a nine-month interval. Five patients received cord blood stem cells with antigen matches ranging from 4/6-6/6. Out of the 10 patients, 7 received total body preparative radiotherapy and for 8 patients G-CSF or GM-CSF was used.

For the cellularity of the infused graft: CD34+ ranged from 3-71x106/kg recipient weight and nucleated cell count from 2.67-11.17x108/kg recipient weight.

Six patients had CR, 3 patients CRp and 1 patient had progressive disease as best investigator response. The average OS is 55.96 weeks and the average initial poststudy transplant survival, the time from date of initial post-study transplant to date of death, or if the patient is still alive, censoring at date of last known follow-up visit, is 55.07 weeks. Two patients were alive at last follow-up.

Eight patients had post-transplant AEs: 29 infections, 1 hepatic VOD grade 4, 1 multiorgan failure, 2 cardiac arrests, 1 moderate liver lesions, 4 Graft Versus Host Disease (GVHD), 1 hemorrhage pulmonary, 2 acute distress syndromes and 1 platelet transfusion reaction.

In total, 4 patients developed acute GVHD (3 grade 1-2 and 1 grade 3-4). One patient recovered from GVHD and one patient had a mixed response. Two patients developed chronic GVHD. Of the 2 patients with chronic GVHD, 1 patient initially developed grade 2 acute GVHD which subsequently improved to grade 1. The second patient experienced two separate episodes of acute GVHD (grade 1-2). Both patients eventually established a stable disease.

PHASE 2:

In this phase, 10 patients (40.0%) underwent HSCT, of which all had ALL.

Of these 10 patients, 4 patients received bone marrow stem cells, 3 patients received peripheral blood stem cells, and 3 patients received cord blood stem cells. Of the patients receiving bone marrow stem cells, 1 received allogeneic bone marrow with 10/10 antigen match and 3 received matched unrelated donor bone marrow with 6/6, 10/10 and as reported on the CRF a 1.0 antigen match. Two patients who received peripheral blood stem cells were a 10/10 antigen match. The antigen match of the third patient is unknown. Three patients received cord blood stem cells; two with antigen matches of 4/6 and 5/6. Out of the 10 patients, 5 received total body preparative radiotherapy and for 8 patients G-CSF or GM-CSF was used. For the cellularity of the infused graft: CD34+ ranged from 2.6-9.8 x 106/kg recipient weight and nucleated cell count from 0.11-18.42 x 108/kg recipient weight.

Four patients had CR, 3 patients CRp, 2 patients had partial remission and 1 patient was not evaluable as best investigator response. The average OS is 55.17 weeks and the average initial post-study transplant survival is 41.66 weeks. Six patients were alive at last follow-up.

Nine patients had post-transplant AEs: 53 infections or infection related investigations, 4 GVHD, 1 grade 4 renal failure (acute oliguric renal failure), 1 grade 3 pericardial effusion, 2 hepatic VOD (grades 3 and 4), 2 multiorgan failure, 1 pulmonary hemorrhage, 1 pancytopenia, 1 respiratory distress, 1 hepatic insufficiency grade 2, 1 ascites and 1 febrile neutropenia.

In total, 4 patients developed acute GVHD (grades 1-2). One patient recovered from GVHD and one patient established a stable disease. The other two patients developed chronic GVHD: 1 patient had GVHD grade 2 and established a stable disease and the other patient had GVHD grade 2 and second time initially grade 2 turning into grade 1, establishing partial response.

VHR Pilot (CLO08808)

Open-Label, Multi-Center Safety and Tolerability Pilot Combination Study of Clofarabine (40mg/m2 D1-5), Etoposide (100 mg/m2 D1-5), Cyclophosphamide (440 mg/m2 D1-5), PEGasparaginase, and Vincristine in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL) in First Relapse.

Two patients (001-0001 and 002-0002) out of the 8 patients enrolled received post study HSCT. Both patients received bone marrow stem cells.

Patient 001-0001 had an unrelated bone marrow transplant with a 6/6 antigen match. The patient underwent total body preparative radiotherapy. The cellularity of the graft was 2.50 x 106 CD34+ cells/kg recipient weight. No G-CSF or GM-CSF was used.

Patient 002-0002 had a related bone marrow transplant with a 6/6 antigen match. The patient underwent total body preparative radiotherapy. The cellularity of the graft was 57.10 x 108 nucleated cells/kg recipient weight and CD 7.76 x 106 CD34+ cells/kg recipient weight. No G-CSF or GM-CSF was used.

Both achieved successful neutrophil engraftment. Both patients experienced acute GVHD, but recovered.

Neither patient reported other post-transplant AEs. Patient 002-0002 achieved CR and patient 001-0001 achieved PR (75 days after HSCT and 87 days after HSCT, respectively). Both patients were alive at last follow-up.

MAH Discussion

Review of the summary table above reveals the following findings. There were a total of 22 patients who received post study HSCT. Ten of these patients were alive at last follow up. Six patients died within 100 days of transplant, and 6 others died more than 100 days after transplant.

The causes of death for the patients dying within 100 days of transplant included 3 cases of multi-organ failure, one case each of ARDS and pulmonary hemorrhage and one case unspecified. Significant peri-transplant adverse events for these 6 patients included 2 cases of grade 4 VOD and various infections (viral, bacterial and fungal).

Of the 10 patients alive at last follow up, seven experienced events of infection. There were 32 total infectious events in seven patients; 3 patients experienced 2-3 events each and 4 patients experienced 5-8 events each. Infections occur commonly in patients undergoing HSCT. The nature and severity of infections experienced by these patients was consistent with what is expected for allogeneic HSCT.

The incidence of VOD in the pediatric transplant population has been reported to be in the range of 11–31%, with an associated death rate of up to 50% (SH Lee, et al. 2010). In our series of pediatric patients undergoing HSCT following treatment with clofarabine, etoposide and cyclophosphamide, the incidence of VOD is 13.6% (3/22), with a fatality rate of 66% (2/3). Thus, there is no evidence to suggest that induction with clofarabine-containing regimens would preclude successful HSCT. On the contrary, 45% (10/22) of these patients were alive and in CR at last follow up, representing a successful outcome in these relapsed/ refractory patients without many therapeutic options.

GVHD is an expected outcome in allogeneic HSCT, and for some malignancies has been linked to therapeutic success through Graft-vs-Leukemia responses. The severity of GVHD is related to type of transplant (related vs. unrelated), cell source (peripheral blood vs. bone marrow vs. cord), degree of match between recipient and donor, and GVHD chemoprophylaxis. As these variables were not captured for each patient in this series, it is difficult to determine expected GVHD rates for the population. However, of the patients in this series, the reported GVHD experience was generally mild. Two patients experienced GVHD that was ≥ grade 3 in severity, and there were no fatal events of GVHD.

In summary, patients undergoing HSCT following ALL induction regimens containing the combination of clofarabine, etoposide, and cyclophosphamide experience a similar spectrum of adverse events to those experience by patients undergoing HSCT following other ALL induction regimens. Patient outcomes are promising as well, with several patients alive >2 years post-HSCT.

Rapporteur's Overall Conclusion and Recommendation

58 patients with acute leukaemia were enrolled in studies where they received the combination regimen of clofarabine, etoposide and cyclophosphamide.

22 of these 58 patients (**38%**) were able to proceed to post study HSCT:

- 10 out of the 25 patients enrolled in the phase 1 of the study **CLO21800205**;
- 10 out of the 25 patients enrolled in the phase 2 of the study **CLO21800205**;
- 2 out of the 8 patients enrolled in the study **CLO08808**.

13 out of the 20 patients of phase ½ study **CLO21800205** who underwent HSCT received the recommended phase 2 dose (dose of the cohort 5 of the phase 1 of the study: Clofarabine (40mg/m2 D1-5), Etoposide (100 mg/m2 D1-5), Cyclophosphamide (440 mg/m2 D1-5)). The 7 remaining patients received lower doses of chemotherapy: 2 were from cohort 1, 1 from cohort 2, 1 from cohort 3 and 3 from cohort 4.

For the 10 patients of phase 1 of study **CLO21800205** who underwent post study HSCT, the average OS is **55.96** weeks and the average initial poststudy transplant survival, is **41.93** weeks. Two patients were alive at last follow-up with a post study transplant survival of 99.1 weeks and 100.3 weeks respectively, one was enrolled in cohort 2 and one was enrolled in cohort 4, one was suffering from ALL and one was suffering from AML.

For the 10 patients of phase 2 of study **CLO21800205** who underwent post study HSCT, the average OS is **55.17** weeks and the average initial post-study transplant survival is **41.66** weeks. Six patients were alive at last follow-up with a post study transplant survival of 100.6 weeks, 26.6 weeks, 94.6 weeks, 49.3 weeks, 41.4 weeks and 38 weeks respectively.

The 2 patients enrolled in the study **CLO08808** who underwent HSCT after study were alive at the last follow up (respectively 26 weeks and 20 weeks after post study transplant).

Thus, 10 out of the 22 patients who underwent HSCT were alive at the last follow up (**45%**).

Regarding the 12 remaining patients, 6 died within 100 days of transplant included 3 cases of multi-organ failure, one case of acute respiratory distress syndrome, one case of pulmonary hemorrhage and one case unspecified.

The following post-transplant AEs of interest were reported

- **VOD:**

3 cases of VOD were reported in this series of paediatric patients undergoing HSCT following treatment with clofarabine, etoposide and cyclophosphamide: 2 cases of grade 4 VOD (patient 004-0007 and patient 010-0041) and one case of grade 3 VOD (patient 010-0026). Thus, **incidence of VOD was 13.6%** (3/22). A **fatality rate of 66%** (2/3) was noted. Two patients received RP2 Dose and for 2 patients the graft was from unrelated donors (the type of transplant was not documented for the remaining patient). As states by the MAH, these

results are in line with the reported incidence and fatalities of VOD in the pediatric transplant population.

- **GVHD:**

Acute GVHD: 10 patients experienced event of acute GVHD (10/22: **45%**). For 2 patients GVHD was severe (grade 3) and for the remaining patients the reported event of acute GVHD was mild/moderate. For 9 of these patients the graft was from unrelated donors.

Chronic GVHD: 4 patients experienced events of chronic GVHD, severity grade I/II.= (for 3 patients, a previous event of acute GVHD was reported).

In Conclusion,

- among the 58 patients with acute leukaemia enrolled in studies where they received the combination regimen of clofarabine, etoposide and cyclophosphamide, 22 (**38%**) were able to proceed to post study HSCT;
- 10 out of the 22 patients who underwent HSCT were alive at the last follow up (**45%**), with for some patients a prolonged post study transplant survival (more than one year for 4 patients);
- Nature and incidence of post transplant AE reported, especially VOD and GVHD, were consistent with was is expected for allogenic HSCT;
- For the time being and taking into account the limited data available, there is no evidence to suggest that induction with clofarabine-containing regimens affect the feasibility of HSCT in children who received the combination with R2PD.