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Human Medicines Development and Evaluation

Evoltra

(clofarabine)

Procedure No. EMEA/H/C/613/A46/036

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 24 October 2011, 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

Information on the pharmaceutical formulation used in the clinical study(ies)

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 CLO08808 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.

Non-clinical aspects

Not applicable

Clinical aspects

1. Introduction

The MAH submitted a report for:

- Study CLO08808, A Phase I Open-Label, Multi-Center Safety and Tolerability Pilot Combination Study of Clofarabine, Etoposide, Cyclophosphamide, PEG-asparaginase, and Vincristine in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL) in First Relapse

2. Clinical study

Study CLO08808: A Phase I Open-Label, Multi-Center Safety and Tolerability Pilot Combination Study of Clofarabine, Etoposide, Cyclophosphamide, PEG-asparaginase, and Vincristine in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL) in First Relapse

Description

This was a phase I trial of clofarabine in combination with etoposide, cyclophosphamide, PEG-asparaginase, and vincristine in paediatric patients in first relapse of acute lymphoblastic leukaemia (ALL).

This multicenter study was conducted at 6 centers in the United States.

The study started on 8 January 2010 (first patient consented) and ended on 26 April 2011 (last Patient Out).

- **Methods**

  - Objectives :

The primary objective was to evaluate the safety of 1 cycle of the 5-drug regimen (clofarabine, etoposide, cyclophosphamide, PEG-asparaginase, and vincristine) in paediatric patients with ALL who were in first bone marrow relapse.

The secondary objectives were to evaluate the tolerability of the 5-drug regimen and to examine the efficacy of the 5-drug regimen in paediatric patients with ALL who were in first bone marrow relapse.

The exploratory objectives were to determine the proportion of paediatric patients with ALL who were able to proceed to hematopoietic stem cell transplant after receiving the 5-drug regimen and to quantify the amount of minimal residual disease after 1 cycle of the 5-drug regimen.

  - Study design

Phase 1, multi-center, open-label, non-randomized, safety and tolerability pilot combination study.

  - Study population /Sample size

Main criteria for inclusion/exclusion:

Patients ≥1 and ≤30 years old with a diagnosis of pre-B or T-cell ALL in first relapse with a duration of remission of ≥6 months (and have received no more than 2 prior induction regimens prior to the date of first relapse) with >25% blasts in the bone marrow; no active central nervous system leukemia or Burkitt's lymphoma; Karnofsky Performance Status of ≥50 for patients >10 years of age or a Lansky Performance Status of ≥50 for patients ≤ 10 years of age; adequate liver, renal, pancreatic, and cardiac function as defined by the protocol; and no previous stem cell transplantation, treatment with clofarabine, or high-dose chemotherapy with stem cell rescue regimen.

Sample size:

Six patients were to be initially enrolled to receive a cycle of study drugs. If no excessive toxicity was seen (as defined by dose-limiting toxicities [DLTs]), up to 6 additional patients were to be enrolled for a total of 12 patients who were evaluable for toxicity.

  - Treatments

Treatment: Patients received a maximum of 2 cycles of the intravenous (IV) 5-drug regimen (clofarabine, etoposide, cyclophosphamide, PEG-asparaginase, and vincristine) plus intrathecal methotrexate, and then entered follow-up. Patients who achieved complete remission (CR) or complete remission with incomplete platelet recovery (CRp) after 1 cycle of study drugs were eligible to receive a second cycle of study drugs upon recovery of peripheral blood counts, and patients who did not have leukemic progression were eligible to receive a second treatment cycle at the investigator's discretion. After treatment with 2 cycles of the study regimen, any further treatment was to be at the discretion of the investigator. After the study treatment period, all patients were to be followed for a minimum of 4 months beyond the final study visit.

5-drug regimen schedule:

Clofarabine IV 40 mg/m2 (lot # 09-001132 and 10-001565) on Days 1-5.

Commercially available: etoposide 100 mg/m2 IV on Days 1-5, cyclophosphamide 440 mg/m2 IV on Days 1-5, PEG-asparaginase 2500 IU/m2 IV on Day 15, vincristine 1.5 mg/m2 (maximum dose: 2 mg) IV on Days 15 and 22.

Intrathecal methotrexate (dosing based on age) on Day 1 and Day 15 (Cycle 1) and Day 1 (Cycle 2).

- Outcomes/endpoints

Primary endpoint:

- Safety of 1 cycle of the 5-drug regimen, as assessed by the incidence of dose-limiting toxicities (DLTs) reported in this patient population.

Secondary endpoints:

- Tolerability of the 5-drug regimen, as assessed by the overall toxicity profile (i.e., incidence of adverse events [AEs], serious adverse events [SAEs], and/or DLTs), in patients who were able to receive at least 80% of the total planned doses of clofarabine, etoposide, and cyclophosphamide in addition to the Day 15 PEG-asparaginase and vincristine doses

- Efficacy of the 5-drug regimen, as assessed by:

  Complete remission (CR)

  Time to remission

  Duration of remission

  Event-free survival (EFS), 4-month EFS, disease-free survival, and overall survival

Exploratory endpoints:

- Proportion of patients who were able to proceed to HSCT

- Quantification of MRD after 1 cycle of the 5-drug regimen

- Statistical Methods

Descriptive statistics were provided for the patient disposition, demographics, clofarabine exposure, and safety data. Continuous variables were summarized using N, mean, standard deviation (SD), median, range; and categorical variables were summarized using the frequency count and the percentage of patients in each category. Efficacy data were listed by patient. All 8 enrolled and treated patients were included in the analyses.

➢ **Results**

- Recruitment/ Number analysed

8 patients were enrolled, treated, and analyzed.

All 8 patients initiated the 5-drug regimen (all 8 patients received clofarabine, etoposide, and clyclophosphamide; 6 of the patients also received vincristine; 5 of the patients also received PEG-asparaginase), and 7 of the patients also received IT methotrexate.

- Baseline data

The patients ranged from 4 to 23 years old (mean age 11.0 years, standard deviation 7.09 years). Two patients were male and 6 patients were female. Five patients were White, 2 patients were Black or African American, and 1 patient was El Salvadorian/Mexican. Each of the 8 patients initiated 1 cycle of study drugs.

- Efficacy results

Of the 8 treated patients, 3 achieved CR, 1 achieved CRp, and 2 achieved partial remission (PR). Of the patients with CR, time to remission ranged from 5.7 to 6.7 weeks, duration of remission ranged from 0.1 to 2.7 weeks, and DFS ranged from 12.3 to 35.0 weeks. Among all 8 patients, EFS and overall survival each ranged from 7.7 to 45.4 weeks, and 6 of the 8 patients achieved 4-month EFS. Two of the 3 patients who achieved CR (002-0002 and 003-0006) were alive at last follow-up. One of the patients with CR and 1 of the patients with PR (002-0002 and 001-0001, respectively) received post-study hematopoietic stem cell transplant (allogeneic bone marrow transplant), and both achieved successful neutrophil engraftment (in 21 days and 30 days, respectively). Both patients were alive at last follow-up.

A total of 4 patients died, all during the study follow-up period. One patient died because of an AE, fungal (mucormycosis) pneumonia; the other 3 patients died due to progression of ALL.

No summary analyses of efficacy data were performed since no efficacy conclusions could be drawn from the study due to the small number of patients enrolled.

- Safety results

Four of the 8 patients experienced a DLT, which met the protocol-specified criterion for stopping the study (DLTs in >3 of 9 patients).

For 3 of the 4 patients with DLTs, the DLT occurred after the patient received clofarabine, etoposide, and cyclophosphamide but before receipt of any vincristine or PEG-asparaginase. Each of the DLTs was considered by the investigator to be related to clofarabine, etoposide, and cyclophosphamide. All of the DLTs were SAEs: 1 patient had Grade 3 bone marrow aplasia, 1 patient had Grade 4 bone marrow aplasia, 1 patient had Grade 4 increased total bilirubin, and 1 patient had Grade 4 increased lipase.

Each of the 8 enrolled patients experienced at least 1 AE during the study. Blood and Lymphatic System Disorders, Gastrointestinal Disorders, Metabolism and Nutrition Disorders, and Skin and Subcutaneous Tissue Disorders were the most commonly affected system organ classes. The AEs occurring in the majority of patients (at least 5 of 8 patients) were nausea (8 [100.0%] patients each); anemia, decreased appetite, and vomiting (7 [87.5%] patients each); abdominal pain, febrile neutropenia, and thrombocytopenia (6 [75.0%] patients each); and diarrhea (5 [62.5%] patients). The most frequent Grade 3 AEs were febrile neutropenia (6 [75.0%] patients) and anemia and decreased appetite (3 [37.5%] patients each); and the most common Grade 4 events were thrombocytopenia (6 [75.0%] patients), anemia (4 [50.0%] patients), leukopenia and neutropenia (3 [37.5%] patients

each), and lipase increased and lymphopenia (2 [25.0%] patients each. One patient had a Grade 5 AE (fungal pneumonia), which was considered related to clofarabine, etoposide, and cyclophosphamide.

Among the most common AEs, most were considered by the investigator to be related to the study regimen (i.e., related to at least 1 of the drugs in the 5-drug regimen and/or methotrexate). Most of the AEs were considered related to clofarabine as well as at least 1 of the other study drugs. The AEs that were considered related to clofarabine only were headache (Patient 001-0001); mucosal inflammation (Patient 003-0006); dry skin, palmar erythema, skin exfoliation, and blister (Patient 003-0008); and pyrexia, chills, and rash (Patient 006-0007). All of the AEs related to clofarabine only were nonserious and Grade 1 or 2 with the exception of pyrexia, which was nonserious and Grade 3.

Four patients had SAEs. The most common SAE was bone marrow aplasia, which occurred in 2 patients. Most of the SAEs were considered related to clofarabine, etoposide, and cyclophosphamide. Two patients discontinued study treatment because of AEs (increased bilirubin; bone marrow aplasia); both of these events were SAEs and DLTs.

With respect to AEs of particular interest, 4 patients had hepatic AEs (increased transaminases or bilirubin), which were considered related to clofarabine, etoposide, and cyclophosphamide; however, there were no incidences of veno-occlusive disease. Three patients had AEs of increased lipase. For 1 of these patients, the increase in lipase was an SAE and a DLT. This patient had a concomitant increase in amylase, and an abdominal ultrasound revealed a mildly swollen pancreas. The increased lipase for the other 2 patients was considered nonserious; 1 of these patients had a concomitant increase in amylase.

Three patients had at least 1 infection during the study, and most of the infections were considered related to clofarabine and at least 1 of the other study drugs.

A total of 4 patients died, all during the study follow-up period. One patient died because of an AE, fungal (mucormycosis) pneumonia, 54 days after the first dose of study drug and 50 days after the last dose. The other 3 patients died due to progression of ALL, ≥118 days after the first dose and ≥97 days after the last dose.

Hematology and chemistry laboratory parameters were assessed at baseline and post baseline. For hematology, most patients had treatment-emergent worsening to Grade 3 or Grade 4 lymphopenia, leukopenia, thrombocytopenia, and anemia. For neutropenia, 4 patients had treatment-emergent worsening to Grade 4, and the other 4 patients had Grade 4 neutropenia at both baseline and post-baseline. For chemistry, the worst post-baseline grade for most patients was ≤ Grade 2, with the exception of lipase. Five patients had a treatment- emergent worsening to Grade 3 or Grade 4 lipase.

3. Discussion on clinical aspects

Along with the results of the Phase I/II CLO21800205 study, this study was designed to inform the detailed design of an upcoming Phase III randomized controlled trial (AALL1131), which is being planned by the Children's Cancer Group (COG) to confirm clinical benefit in a population of pediatric patients with newly diagnosed very high risk ALL. In CLO21800205, the recommended Phase II doses (RP2Ds) of the 3-drug regimen of clofarabine, etoposide, and cyclophosphamide were determined and showed promising efficacy results and an acceptable toxicity profile in pediatric patients with relapsed or refractory ALL or acute myeloid leukemia. However, there was a high incidence of severe infections in Phase II of the study, and outcomes were particularly poor in patients with poor performance status at baseline.

The current study was designed to assess the feasibility of adding vincristine and PEG-asparaginase to the RP2Ds of clofarabine, etoposide, and cyclophosphamide as determined in CLO21800205. If

acceptable safety and tolerability were demonstrated in this study, the 5-drug regimen would then serve as the experimental arm of the proposed COG Phase III trial. In this study, 4 of the first 8 patients had DLTs. The DLTs were bone marrow aplasia (2 patients), increased lipase (1 patient), and increased bilirubin (1 patient). For 3 of the 4 patients with DLTs, the DLT occurred after the patient received clofarabine, etoposide, and cyclophosphamide but before receipt of any vincristine or PEG-asparaginase. These events are expected for clofarabine and do not represent a new safety signal. However, the frequency of DLTs met the criteria for stopping the study, and the study was closed. Because of the toxicity profile observed during this pilot study, the COG determined that the doses of clofarabine, etoposide, and/or cyclophosphamide in the 3-drug backbone should be modified for their upcoming AALL1131 randomized Phase III trial. Specifically, the dose of clofarabine for that study will be reduced to 30 mg/m2. Data from the current study, as well as from the CLO21800205 study, suggest that further investigation of the 3-drug backbone (clofarabine, etoposide, and cyclophosphamide) warrants careful consideration of the patient eligibility criteria and study drug doses.

Rapporteur's Overall Conclusion AND RECOMMENDATION

- **Overall conclusion**

Clofarabine is approved in the EU 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 is 52 mg/m^2 of body surface area administered in monotherapy, by intravenous infusion over 2 hours daily for 5 consecutive days.

Phase I study CLO08808 was designed to assess safety and tolerability of a 5-drug regimen (clofarabine, etoposide, cyclophosphamide, vincristine, PEG-asparaginase) for patients with relapsed or refractory ALL. The results were to inform the design of an upcoming phase III trial in first line treatment of newly diagnosed very high risk ALL in paediatric patients (AALL1131).

Patients ranged from 4 to 23 years old (mean 11.0, SD 7.09). In the frame of a report on a paediatric study, submitted in accordance with Article 46 of regulation (EC) N01901/2006, the MAH should have presented results specifically in the paediatric population.

The primary outcome of study CLO08808 was the incidence of DLTs during 1 cycle of the 5-drug regimen. The study was closed due to occurrence of 4 dose-limiting toxicities (DLTs) among 8 included patients, meeting the protocol-specified criterion for stopping the study (> 3 DLTs for 9 patients). Three of the 4 DLTs occurred while patients had only received the 3-drug backbone association (clofarabine + etoposide + cyclophosphamide) but before receipt of the two complementary drugs (vincristine and PEG-asparaginase). Four patients had one SAE. Seven patients experienced AE, Grade 4 or 5. Five patients had a treatment- emergent worsening to Grade 3 or Grade 4 lipase.

Overall, safety results from study CLO08808 are consistent with results from study CLO21800205 (please refer to Evoltra P46 – Paediatric Article 46 Follow Up Measure 033 AR), showing a high – toxicity profile of the 3-drug backbone combination (Recommended Phase 2 Doses (RP2Ds) : Clofarabine 40mg/m² + Etoposide 100mg/m² + Cyclophosphamide 440 mg/m²), let alone the 5-drug combination.

In the dose-escalation study CLO21800205, safety results showed that the combined regimen at the RP2Ds is associated with a very high toxicity as evidenced by the 80.0% patients who experienced at least 1 related SAE and 3 cases of veno-occlusive disease reported in the phase II study. Last patient completed study drug in November 2009. Hence, it is unclear why the same R2PD, known to induce

high toxicity, was used in a 5-drug regimen in study CLO08808 (First Patient Consented: January 2010).

No efficacy conclusions could be drawn from CLO08808 study due to the small number of patients included.

With respects to these findings, further investigations with both drug combinations (3 or 5 drugs) are needed but require particular caution, especially for the upcoming AALL1131 phase III trial. Even if dosing of clofarabine will be reduced from 40 to 30mg/m² for this trial, as mentioned by the MAH, safety and tolerability of clofarabine in drug combinations remain a key issue to be closely monitored. The high toxicity profile of the combinations can only be balanced by a clear efficacy benefit that remains to be shown in the studied (first relapse) and targeted (first line) populations.

- **Recommendation**

☒ **Fulfilled –**

However, within the next PSUR, the MAH should provide detailed information concerning:

- the four censored patients,

- the two patients who received post-study allogeneic bone marrow transplant, with follow-up data.

ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable