

24-WEEK SAFETY AND EFFICACY OF ENFUVIRTIDE AS PART OF AN OPTIMIZED
ANTIRETROVIRAL REGIMEN IN CHILDRENWiznia A¹, Church J², Emmanuel P³, Eppes S⁴, Rowell L⁵, Evans C⁵, Bertasso A⁶ and the T20-310 Study Group¹Jacobi Medical Center, Bronx, NY, USA; ²Childrens Hospital Los Angeles, CA, USA; ³All Children's Hospital, St. Petersburg, FL, USA; ⁴Alfred I. DuPont Hospital for Children, Wilmington, DE, USA; ⁵Roche, Welwyn, UK; ⁶Roche, Nutley, NJ, USAAndrew Wiznia, MD
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Introduction

- Enfuvirtide (T-20, FUZEON®) is the only approved member of the new class of antiretroviral agents called fusion inhibitors that inhibit viral binding or fusion to host target cells.
- Enfuvirtide (ENF) was approved in the US in March 2003 for HIV-infected adults and children 6 years of age or older for use in combination with other antiretroviral drugs in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy.¹
- An early pediatric study (T20-204) in children 3–12 years of age indicated that a 24-week regimen of ENF 30 mg/m² or 60 mg/m² *bid* subcutaneously (sc) in HIV-1-infected children was well tolerated.² Activity against HIV-1 virus in children was also demonstrated.² Children receiving the 60 mg/m² sc dose achieved target 12-hour ENF trough levels of > 1000 ng/mL.³
- Preliminary investigations in T20-204 also demonstrated the safety and tolerability of ENF over the first 7 days of treatment in both children and adolescents.
- T20-310 is an ongoing Phase I/II pharmacokinetic, safety and efficacy study of ENF in combination with an optimized background (OB) over 48 weeks in HIV-1-infected children (3–11 years) and adolescents (12–16 years).
- In this trial, intensive pharmacokinetic investigations of ENF at a dose of 2 mg/kg *bid* (maximum dose of 90 mg/dose), delivered sc, in HIV-1-infected children and adolescents produces drug exposure comparable to that seen in adults following 90 mg sc *bid* dosing.^{4,5}
- This presentation reports primary 24-week safety and efficacy results from T20-310 in children (5–11 years). Data from adolescents (12–16 years) were presented previously.⁵

Methods

Study design and patients

- T20-310 is an ongoing multicenter, open label, non-randomized, non-comparative study of ENF dosed at 2 mg/kg sc *bid* (up to a maximum 90 mg/dose).
- All patients had prior treatment experience with at least two antiretroviral drug classes for at least 3 months and baseline HIV-1 RNA \geq 5000 copies/mL.
- Assessments for efficacy and safety parameters, including HIV-1 RNA change from baseline, change in absolute CD4 cell number and percentage, change from baseline CD4 cell number and percentage, CD4 percentages, clinical and laboratory adverse events, injection site reactions (ISRs), and adherence were performed monthly through week 24 and bimonthly thereafter.
- Adherence was assessed at each study visit using three methods: returned used vials; an adherence questionnaire completed by each patient or parent/legal guardian that inquired as to the number of ENF doses missed in the 4 days preceding the visit; and the average of the results from the preceding two methods.
- Data presented here are from the children stratum (5–11 years of age).

- All subjects who received at least one dose of study medication are included in the present analysis.

Results

Patient demographics

- 24, vertically infected, children 5–11 years of age were enrolled in the study. Baseline demographics and disease characteristics are shown in **Table 1**.

Table 1. Demographic and baseline characteristics: children stratum

| | |
|--|---------------------|
| Total number of children patients enrolled | 24 |
| Age (years) | |
| Median (range) | 9.0 (5.0–11.0) |
| Sex, n (%) | |
| Male | 9 (37.5) |
| Female | 15 (62.5) |
| Race, n (%) | |
| White | 8 (33.3) |
| Black | 15 (62.5) |
| Other | 1 (4.2) |
| Ethnicity, n (%) | |
| Hispanic | 6 (25.0) |
| Non-Hispanic | 17 (70.8) |
| Missing | 1 (4.2) |
| HIV classification, n (%) | |
| No signs/symptoms (N) | 2 (8.3) |
| Mild signs/symptoms (A) | 6 (25.0) |
| Moderate signs/symptoms (B) | 3 (12.5) |
| Severe signs/symptoms (C) | 13 (54.2) |
| Median number of prior ARVs | 10 (6–14) |
| Median duration of prior therapy (months) | 85 (11.9–138.3) |
| Baseline HIV-1 RNA (log ₁₀ copies/mL), median (range) | 4.9 (4.0–6.0) |
| Baseline CD4 count (cells/mm ³), median (range) | 370.5 (6.0–2007.0)* |
| Baseline CD4 cell percentage, median (%) | 16.9% (0.7%–50.1%)* |
| Tanner staging, n (%) | |
| 1 | 17 (70.8) |
| 2 | 5 (20.8) |
| 3 | 1 (4.2) |
| Missing | 1 (4.2) |
| Genotypic sensitivity score at baseline (%)** | |
| 0–1 | 10 (41.7) |
| 2–3 | 13 (54.2) |
| 4–5 | 1 (4.2) |

* n = 20

** Defined as the number of antiretrovirals in a patient's OB regimen to which the patient's viral isolate was sensitive based on the results of genotypic resistance testing (ViroLogic, South San Francisco, CA)

Patient disposition at 24 weeks

- 22 patients (91.7%) completed 24 weeks of treatment with ENF
- Two patients (8.3%) discontinued the study by week 24*
 - One patient discontinued for safety reasons unrelated to ENF (multi-organ failure and metabolic disorder)**
 - One patient refused continued therapy.
- One additional patient discontinued at the week 24 visit for non-safety reasons (refused treatment). Since this patient completed 24 weeks of therapy, she is not included here as a discontinuation
- Case history for this patient: VL at baseline = 809,213 copies/mL HIV-1 RNA; CD4 at baseline = 59 cells/mm³ (3.7%). Interstitial pneumonia active at baseline. Background regimen consisted of didanosine, lopinavir/ritonavir and saquinavir (Invirase). The only concomitant medication was Prozac. On study Day 8, the patient was hospitalized for interstitial pneumonia. Blood culture was negative. The patient was treated with antibiotics. The event resolved on study Day 25. On study Day 29 she was hospitalized due to multi-organ failure and mitochondrial toxicity which were treated with supportive measures. She discontinued all antiretroviral treatment, including ENF, the day of hospitalization (study Day 29). She succumbed on study Day 34.

Adherence

- Adherence results are summarized in **Table 2**. Mean adherence was calculated from the average of the results of the adherence questionnaire and the number of returned used vials.

Table 2. Summary of adherence to enfuvirtide over 24 weeks (n = 24)

| *Level of adherence | Returned used vials n (%) | Adherence questionnaire n (%) | Mean adherence n (%) |
|---------------------|---------------------------|-------------------------------|----------------------|
| \geq 85% | 12 (50) | 23 (96) | 17 (71) |
| \geq 80% | 16 (67) | 23 (96) | 18 (75) |
| \geq 75% | 17 (71) | 23 (96) | 18 (75) |
| \geq 65% | 18 (75) | 24 (100) | 21 (88) |

* Categories are not exclusive

Safety over 24 weeks

- 24 patients (100%) reported an adverse event (AE) over the 24 weeks. The most common AEs (\geq 3 patients) are shown below. The majority of the AEs were mild to moderate in intensity.
 - Upper respiratory tract infection (n = 10; 41.7%)
 - Nasopharyngitis (n = 5; 20.8%)
 - Pyrexia (n = 5; 20.8%)
 - Vomiting (n = 5; 20.8%)
 - Otitis media (n = 4; 16.7%)
 - Loose stools (n = 4; 16.7%)
 - Oral candidiasis (n = 4; 16.7%)
 - Cough (n = 4; 16.7%)
 - Gastroenteritis (n = 3; 12.5%)
 - Nasal congestion (n = 3; 12.5%)
 - Mouth ulceration (n = 3; 12.5%)

AEs considered related to ENF

- Five patients (21%) reported a total of six AEs considered by the investigator to be related to ENF. They included:
 - fatigue
 - pyrexia
 - upper respiratory tract infection
 - neurodermatitis
 - hypocalcaemia
 - diminished appetite.

Serious adverse events (SAEs)

- Five patients (21%) reported an SAE (1 for pneumonia) through week 24.
- None of the SAEs were considered by the investigator to be related to ENF.
- One patient discontinued treatment due to multi-organ failure and metabolic disorder and subsequently died; the death was considered unrelated to ENF (see details above).

Injection site reactions (ISRs)

- ISRs were reported by 21 patients (88%). Of these 21 patients, ISR questionnaires were completed by 17 (81%). 94% (16/17) of patients reported the worst pain/discomfort grade as mild or moderate.
- The most common signs/symptoms reported were:
 - induration (75%; 67% of those reported \leq grade 2)
 - nodules and cysts (58%; 86% \leq grade 2)
 - erythema (50%; 75% \leq grade 2).

Laboratory abnormalities

- Treatment-emergent grade 3 laboratory abnormalities were reported for AST, GGT [n = 2 each; 8.3% (different patients)], ALT, and amylase (n = 1 each; 4.2%).
- Treatment-emergent grade 4 laboratory abnormalities were reported for platelets, neutrophils and amylase (n = 1 each; 4.2%).

Efficacy of ENF over 24 weeks: Comparison with responses seen in adolescents

- Overall, the median change from baseline in plasma HIV-1 RNA was -1.53 log₁₀ copies/mL (n = 22) in the children. This decrease was greater than previously observed in adolescents [-0.59 log₁₀ copies/mL (n = 18)] also enrolled as part of the T20-310 trial.⁵
- The categorical responses seen in the younger patients also appeared to be better than those observed in the adolescent patients with one-third of children reaching < 400 copies/mL over the 24 weeks (**Table 3**), compared to 10.7% of the adolescent patients.⁵

Table 3. Efficacy results (ITT) at 24 weeks (n = 22)

| HIV-1 RNA (copies/mL) | n (%) |
|---|---------|
| < 50 | 6 (25) |
| < 400 | 8 (33) |
| \geq 1.0 log ₁₀ decrease from baseline | 12 (50) |

- Immunological responses in both the children and adolescent groups were clinically relevant with changes from baseline in CD4 count of +182 cells/mm³ (n = 18, baseline values for 2 patients were unavailable) and +139 cells/mm³ (n = 15), respectively. In the children group the median CD4 cell percentage change from baseline was 4.5% (n = 18).

Discussion

- The present study demonstrates that ENF together with an OB regimen appears to have a favorable safety profile and is well tolerated in heavily pretreated HIV-1-infected children (5–11 years).
- Responses in the children appeared better than those previously reported in adolescent patients⁵ also enrolled as part of the T20-310 trial. This could be related to the greater reported adherence in the younger patients.
- Nevertheless, both patient groups displayed decreases in HIV RNA load and clinically meaningful increases in CD4 over 24 weeks.

Conclusion

- ENF provided a clinically meaningful immunologic response together with potent antiviral activity in this difficult-to-treat HIV-1-infected patient population.

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