Poster L-108

14th Conference on Retroviruses and Opportunistic Infections (CROI)
Los Angeles, US

February 25–28, 2007

ENFUVIRTIDE DOES NOT REQUIRE DOSE-ADJUSTMENT IN PATIENTS WITH CHRONIC RENAL FAILURE: THE RESULTS OF A PHARMACOKINETIC STUDY OF ENFUVIRTIDE IN HIV-1-INFECTED PATIENTS WITH IMPAIRED RENAL FUNCTION (NP17586)

Tebas P[1], Bellos N[2], Lucasti C[3], Richmond G[4], Godofsky E[5], Patel I[6], Buss N[7], Chiu Y-Y[6], Rowell L[8] and Salgo M[6]

[1]University of Pennsylvania, Philadelphia, PA; [2]Southwest Infectious Disease, Dallas, TX; [3]South Jersey Infectious Disease, Somers Point, NJ; [4]North Broward Hospital District, Ft Lauderdale, FL; [5]Bach & Godofsky, Bradenton, FL; [6]Roche, Nutley, NJ; [7]Roche, Basel, Switzerland; [8]Roche, Welwyn, UK

Background

- Renal failure is common among HIV-infected patients.[1,2]
- Dosage adjustments for antiretrovirals (ARVs) in HIV-infected patients with renal failure is often based on clinical judgement rather than the results of clinical trials.
- Enfuvirtide (ENF, FUZEON®) is the only approved drug in the class of ARVs known as HIV-1 fusion inhibitors.
- ENF is a 36 amino acid peptide with a high bioavailability (84%), small volume of distribution (5.5 L), low systemic clearance (1.4 L/h) and moderately high protein binding (92%).[3] Being a peptide, ENF is primarily catabolized to its constituent amino acids and has been shown to have a low potential for drug–drug interactions.[4–6]
- Study NP17586 is the first study to investigate the effect of chronic renal failure on the pharmacokinetics of ENF.

Methods

- The study was designed as three parallel groups of 8 HIV-positive patients with stable renal function (creatinine clearance [CLcr] calculated using the Cockcroft-Gault equation):
  1. Group A: patients with severe renal impairment (CLcr of 11 to 35 mL/min)
  2. Group B: patients with end-stage renal disease (ESRD) requiring hemodialysis (CLcr ≤10 mL/min)
  3. Group C: patients with normal renal function (CLcr > 80 mL/min).
- Patients in Groups A and C received a single subcutaneous (SC) dose of ENF (90 mg) while patients in Group B received a single SC dose of ENF on two occasions separated by a minimum washout period of 1 week (a single dose on a dialysis and non-dialysis day).
- Blood samples for ENF pharmacokinetics were collected prior to each single dose and at 1, 2, 3, 4, 6, 8, 10, 12, 24, 32 and 48 hours following each dose.
- Bioanalysis was conducted using High Performance Liquid Chromatography (HPLC) with tandem mass spectrometric detection.
- Pharmacokinetic parameters for ENF were estimated using model independent methods and included maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the plasma concentration–time profile from time zero to infinity (AUC_∞), apparent clearance (CL/F) and the terminal elimination half life ($t_{1/2}$).
- Dialysis clearance of ENF and the ENF extraction ratio was estimated by measurement of samples collected simultaneously from the lines entering and leaving the dialysis chamber.
- Drug exposure in the present study was compared to six other studies conducted by the study sponsor.[7]
- ANOVA was used to compare AUC_∞ and C_{max} estimates for all patients with sufficient data. Ninety percent confidence intervals were computed for estimates of AUC_∞ and C_{max} and estimates for groups A and B were compared to the reference group (Group C).

Results

Demographics

- Recruitment into Group A (severe renal impairment) was found to be problematic and enrolment was limited to 4 patients. Thus, in total, 20 subjects were enrolled into the study (**Table 1**).

Table 1. Summary of patient demographics

Demographics	Group A* (n = 4)	Group B§ (n = 8)	Group C‡ (n = 8)
Sex			
Male	3 (75%)	7 (87%)	7 (87%)
Race			
Caucasian	1 (25%)	--	5 (62%)
Black	3 (75%)	8 (100%)	3 (38%)
Mean age (year)	53.8 ± 12.2	48.8 ± 7.7	44.8 ± 6.8
Mean weight (kg)	72.5 ± 21.5	85.1 ± 25.2	83.7 ± 15.6
Mean height (cm)	165.1 ± 15.0	175.9 ± 11.1	169.5 ± 11.6
Mean BMI (kg/m²)	26.5 ± 5.9	27.3 ± 7.0	28.0 ± 4.2
Mean CLcr (mL/min)**	24.3 ± 6.1	13.3 ± 5.8	133 ± 30.1

*Group A severe renal impairment (CLcr 11–35 mL/min)
§Group B end-stage renal disease required dialysis (CLcr ≤ 10 mL/min)
‡Group C normal renal function, (CLcr > 80 mL/min)
** A number of the patients in Group B had baseline creatinine clearance outside the range specified in the protocol. These patients were included in the study as they were undergoing dialysis and therefore had a slightly improved apparent creatinine clearance.

Pharmacokinetics

- Pharmacokinetic parameters are summarized in **Table 2** and plasma concentration–time profiles are presented in **Figure 1**.

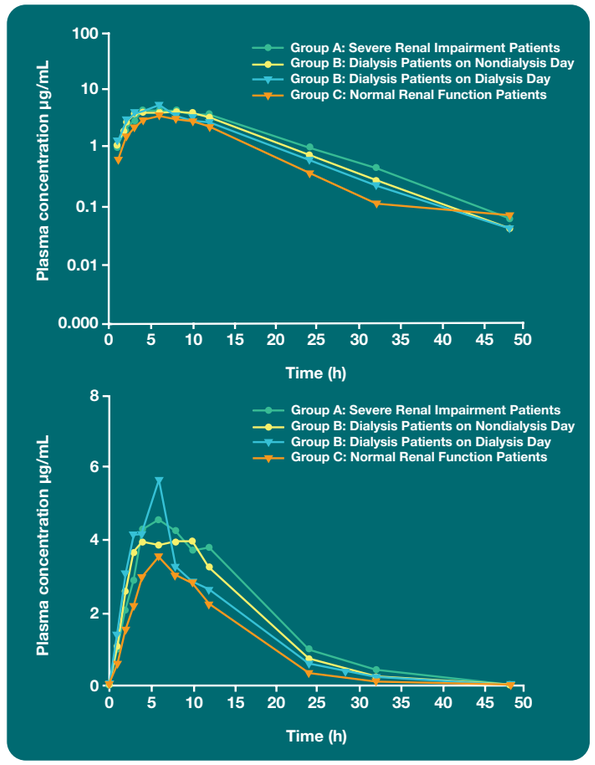
Table 2. Mean ± SD ENF pharmacokinetic parameters following administration in patients with or without renal impairment

Group (creatinine CLcr)	N	C_{max} (μg/mL)	T_{max} (h)	AUC_∞ (μg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
A (11–35 mL/min)	4	5.7 ± 1.8	7.0 ± 3.5	80.3 ± 17.3	4.9 ± 1.2	1.2 ± 0.3
B (≤10 mL/min) non-dialysis day	8	5.3 ± 2.4	7.3 ± 3.0	71.1 ± 20.6	5.6 ± 1.3	1.4 ± 0.4
B (≤10 mL/min) dialysis day	7*	6.3 ± 3.1	5.6 ± 1.1	66.9 ± 30.9	6.1 ± 2.1	1.6 ± 0.7
C (> 80 mL/min)	8	3.8 ± 1.2	6.8 ± 1.5	49.6 ± 9.9	6.2 ± 5.3	1.9 ± 0.4

*One subject failed to provide complete PK samples

- In patients with severe renal impairment exposure to ENF was greater and clearance lower (AUC_∞ 80.3 μg·h/mL; C_{max} 5.7 μg/mL; CL/F 1.2 L/h) than for patients with normal renal function (AUC_∞ 49.6 μg·h/mL; C_{max} 3.8 μg/mL; CL/F 1.9 L/h).
- Patients with ESRD had a higher ENF exposure (AUC_∞ 71.1 μg·h/mL; C_{max} 5.3 μg/mL) and lower ENF clearance (CL/F 1.4 L/h) on the non-dialysis PK day, than patients with normal renal function.
- On the day patients received dialysis, C_{max} and CL/F were increased slightly (6.3 μg/mL and 1.6 L/h, respectively), and AUC_∞ reduced (66.9 μg·h/mL) compared to values for the non-dialysis day.
- The mean dialysis plasma clearance was 3.0 ± 4.7 L/h at midpoint of the dialysis procedure and 2.0 ± 2.7 L/h at endpoint. The extraction ratio was 0.13 ± 0.20 at midpoint and 0.09 ± 0.10 at the endpoint.

Figure 1. Mean enfuvirtide plasma concentration–time profiles following SC administration of enfuvirtide to patients with or without renal impairment



- Using ANOVA none of the 90% confidence intervals for any pairwise comparison for C_{max} and AUC_∞ were within the 80–125% bioequivalence range (**Table 3**).

Table 3. Results of ANOVA: 90% confidence interval for C_{max} and AUC_∞

Parameter	Ratio*	90% Confidence Interval	
		Lower Bound	Upper Bound
C_{max}	A*/C = 1.53	105	223
	B/C = 1.37	101	187
	B§/B = 1.18	91.2	154
AUC_∞	A/C = 1.62	125	210
	B/C = 1.41	114	174
	B§/B = 0.90	70.9	114

*Group A severe renal impairment (CLcr 11–35 mL/min)
Group B end-stage renal disease on non-dialysis day (CLcr ≤10 mL/min)
§Group B end-stage renal disease on dialysis day (CLcr ≤10 mL/min)
Group C (normal renal function), CLcr > 80 mL/min

Comparison to historical data from subjects with normal renal function

- Data range (minimum-maximum) for C_{max} and AUC from 6 previous studies were compared to the data from the present study (**Tables 4-5**)
- Because body weight is known to affect the pharmacokinetics of ENF and mean body weights differed between the present and historical studies pharmacokinetic parameters were normalized to a body weight of 70 kg

Table 4. Comparison of data range for C_{max} and AUC between the present study and historical data in patients with normal renal function

Parameter	Historical data§	Group A	Group B (non dialysis day)	Group B (dialysis day)	Group C
C_{max} (μg/mL)	2.24 – 16.0	4.25 – 8.30	2.75 – 10.4	3.76 – 12.8	4.25 – 8.30
AUC (μg·h/mL)	24.6 – 128	56.2 – 93.6	44.3 – 111	31.7 – 116	36.6 – 64.1

§ Data from 6 studies (Roche data on file)
Group A severe renal impairment (CLcr 11–35 mL/min)
Group B end-stage renal disease on non–dialysis day (CLcr ≤10 mL/min)
Group B end-stage renal disease on dialysis day (CLcr ≤10 mL/min)
Group C normal renal function, (CLcr > 80 mL/min)

Table 5. Comparison of data range for normalized C_{max} and AUC between the present study and historical data in patients with normal renal function

Weight normalized parameter*	Historical data§	Group A	Group B (non dialysis day)	Group B (dialysis day)	Group C
C_{max} (μg/mL)	2.49 – 21.8	3.96 – 7.80	3.61 – 8.42	4.31 – 9.84	2.98 – 6.44
AUC (μg·h/mL)	24.4 – 124	52.4 – 136	53.8 - 143	45.2 – 90.8	43.4 – 87.1

* Parameters normalized to a body weight of 70 kg
§ Data from 6 studies (Roche data on file)
Group A severe renal impairment (CLcr 11–35 mL/min)
Group B end-stage renal disease on non–dialysis day (CLcr ≤10 mL/min)
Group B end-stage renal disease on dialysis day (CLcr ≤10 mL/min)
Group C normal renal function, (CLcr > 80 mL/min)

- For all patients (Groups A, B, and C) in the present study, drug exposure based on both C_{max} and AUC were within the range seen in the historical studies.
- For all patients in the present study, drug exposure based on weight normalized C_{max} were within the range seen in the historical studies.
- For patients in the present study with severe renal impairment (Group A) and end-stage renal disease (Group B on non-dialysis days) the highest weight normalized overall exposure (AUC) was modestly higher than the highest value seen in the historical studies.
- The AUC exposures seen in subjects with severe renal impairment and hemodialysis subjects were within the range seen in the patients in the two pivotal Phase III TORO trials (25 to 125 μg·h/mL, n=628)[5]. Therefore, the safety and efficacy profiles for ENF in patients with a creatinine clearance below 35 mL/min are expected to be similar to those documented for patients in the TORO trials.

Safety

- No subject died, had a serious adverse event or had an adverse event leading to withdrawal from the study.

Adverse Events

- One subject in Group A, 3 subjects in Group B and 1 subject in Group C had an adverse event during the study.
- Adverse events in Groups A and C included an upper respiratory tract infection and local swelling, respectively. Neither event was judged by the investigator as related to ENF.
- Adverse events in Group B included headache, injection site paresthesia, pain in extremity, body temperature increased, nausea, and vomiting. Headache and injection site paresthesia were judged by the investigator as related to ENF.
- All adverse events were mild or moderate in severity.
- No local injection site reactions (ISRs) were reported by the subjects in Groups A or C. Four of the 8 subjects in Group B had a local ISR. Each of the local ISRs were associated with grade 1 induration at the injection site and all lasted less than 1 day. Three of these subjects had no pain associated with their reactions. One subject reported mild tenderness at the injection site within 1 hour of ENF injection (grade 1 on immediate pain), but this did not persist for longer than 1 hour following injection (grade 0 on reactive pain).

Laboratory Parameters

- Five subjects had marked laboratory abnormalities. With the exception of one subject, each marked abnormality was an isolated occurrence. One subject with high glucose and glycosuria, had the preexisting condition of diabetes.

Vital Signs

- One subject in Group A (elevated blood pressure), one subject in Group B (elevated body temperature), and no subjects in Group C had an abnormal vital sign during the study.

Discussion

- Although ANOVA showed that none of the 90% confidence intervals for any pairwise comparison between groups for C_{max} and AUC_∞ were within the 80–125% bioequivalence range, the present study was not powered to test equivalence between patients with normal renal function and patients who were renally impaired.
- Exposure to ENF in patients with severe renal impairment was higher than in patients with normal renal function.
- This increased exposure to ENF in patients with severe renal impairment is accompanied by a 35% lower ENF clearance compared to patients with normal renal function.
- Patients on hemodialysis had a 14% (dialysis day) or 28% (non-dialysis day) lower clearance; and 34% (dialysis day) or 43% (non-dialysis day) higher ENF exposure, compared to study patients with normal renal function.
- Dialysis had a minimal impact on the pharmacokinetics of ENF, with approximately 13% of the ENF being removed during the dialysis procedure which supported the observation of similar pharmacokinetic parameters between the non-dialysis and dialysis days.
- ENF clearance increased by 19.1% and AUC_∞ was reduced by 5.9% on the dialysis day compared to the non-dialysis day.
- ENF was generally well tolerated in each of the three groups with no apparent differences in adverse events, laboratory parameters or vital signs.

Conclusion

- C_{max} and AUC exposures observed in subjects with normal renal function were slightly lower than those observed in renally impaired (creatinine clearance < 35 mL/min) subjects whose C_{max} and AUC exposures are within the historical ranges from six studies in subjects with normal renal function. Mean AUC exposures seen in subjects with creatinine clearance less than 35 mL/min are within the range seen in subjects in the two pivotal Phase III TORO studies. Safety and efficacy profiles for subjects with creatinine clearance below 35 mL/min should be similar to what is documented for subjects in the TORO trials.
- Therefore, ENF does not require dosage adjustment in patients with severe renal impairment, end-stage renal disease or in patients receiving hemodialysis.
- **ENF does not require dosage adjustment in patients receiving hemodialysis.**

References

1. Rao TK. *Infect. Dis. Clin. North Am.* 2001; **15**:833–850
2. Franceschini N. *et al. Kidney International*. 2005 ; **67**:1526–1531
3. Zhang X, *et al. CPT* 2002; **72**:10–19
4. Boyd MA, *et al. J. Clin. Pharmacol*. 2003; **43**:1382–1391
5. Zhang X, *et al. CPT* 2004; **75**:558–568
6. Ruxrungtham K, *et al. J. Clin. Pharmacol*. 2004; **44**:793–802
7. Roche data on file.

14th Conference on Retroviruses and Opportunistic Infections (CROI)
Los Angeles, US
February 25–28, 2007

ENFUVIRTIDE DOES NOT REQUIRE DOSE-ADJUSTMENT IN PATIENTS WITH CHRONIC RENAL FAILURE: THE RESULTS OF A PHARMACOKINETIC STUDY OF ENFUVIRTIDE IN HIV-1-INFECTED PATIENTS WITH IMPAIRED RENAL FUNCTION (NP17586)

Tebas P[1], Bellos N[2], Lucasti C[3], Richmond G[4], Godofsky E[5], Patel I[6], Buss N[7], Chiu Y-Y[6], Rowell L[8] and Salgo M[6]

[1] University of Pennsylvania, Philadelphia, PA;
[2] Southwest Infectious Disease, Dallas, TX;
[3] South Jersey Infectious Disease, Somers Point, NJ;
[4] North Broward Hospital District, Ft Lauderdale, FL;
[5] Bach & Godofsky, Bradenton, FL;
[6] Roche, Nutley, NJ;
[7] Roche, Basel, Switzerland;
[8] Roche, Welwyn, UK