SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL MV18220)

COMPANY: F. Hoffman-La Roche LTD. NAME OF FINISHED PRODUCT: FUZEON® (enfuvirtide) NAME OF ACTIVE SUBSTANCE(S): enfuvirtide	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A 24 week, open label single arm study to evaluate the safety and efficacy of switching a toxicity causing antiretroviral (ARV) to enfuvirtide (ENF) and to assess resolution or improvement of ARV toxicities in patients with current, historical treatment-limiting toxicities Report No. [redacted], April 2007.		
INVESTIGATORS / CENTERS AND COUNTRIES	28 centers in Germany, Spain, Italy, Canada, Poland and Romania.		
PUBLICATION (REFERENCE)	Stoll M, Muller M, Staszewski S, Gorgolas M, Portilla J, Streinu-Cercel A, Rowell L, Labriola-Tompkins, Waalberg E and Salgo M. Switching a Toxicity-Causing Antiretroviral (ARV) to Enfuvirtide (ENF) in Patients with Treatment-Limiting Toxicities. 8th International Congress on Drug Therapy in HIV-1 Infection. Glasgow, 12-16 November 2006 (Poster P56).		
PERIOD OF TRIAL	Dec 21, 2004 – Oct 23, 2006	CLINICAL PHASE	IV
OBJECTIVES	**Primary:** To assess the resolution and change in severity of the primary offending ARV toxicity over 24 weeks, after the toxicity-causing ARV was switched to enfuvirtide at baseline. **Secondary:** 1. To assess the safety and tolerability of an enfuvirtide-based regimen over 24 weeks after the toxicity-causing ARV was switched to enfuvirtide at baseline. 2. To assess the maintenance of efficacy of an enfuvirtide-based regimen at 24 weeks after the toxicity-causing ARV was switched to enfuvirtide at baseline. 3. Adherence: 4-day recall questionnaire		
STUDY DESIGN	Open-label, single-arm, multicenter study		
NUMBER OF SUBJECTS	300 patients were planned and 91 were enrolled (65 males and 26 females).		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Human immunodeficiency virus type 1 (HIV-1) infected patients with prior experience and/or prior documented resistance to each of the 3 classes of approved ARV agents. All patients were experiencing treatment-limiting toxicity to a component of their ARV regimen.		
TRIAL DRUG / STROKE (BATCH) No.	[redacted]		
DOSE / ROUTE / REGIMEN / DURATION	90 mg twice daily by subcutaneous injection for 24 weeks		
REFERENCE DRUG / STROKE (BATCH) No.	Not applicable		

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CRITERIA FOR EVALUATION	
SAFETY:	1. Change from baseline in ARV-associated toxicities 2. Treatment-emergent adverse events (AEs) 3. Acquired immunodeficiency syndrome (AIDS)-defining events 4. Abnormal laboratory tests 5. Deaths 6. Changes from baseline in vital signs 7. Discontinuations due to injection-site reaction (ISRs) or other AEs
EFFICACY:	1. Proportion of patients who maintained or improved viral load response from baseline to Week 24 2. Proportion of patients who maintained or improved their CD4 counts from baseline to Week 24
OTHER:	1. Mean score changes from baseline in MOS-HIV scores 2. Adherence to enfuvirtide and the background ARV regimen 3. Relationship between improvement/resolution in the primary ARV-associated toxicity and 1) adherence or 2) Medical Outcomes Study (MOS)-HIV scores
STATISTICAL METHODS	All data from this study were summarized descriptively using numbers and percentages of patients for categorical variables and mean, median, standard deviation, median, minimum and maximum for continuous variables. No statistical hypothesis testing was performed.

METHODOLOGY:

Primary and non-primary ARV-associated toxicities were identified at baseline and followed for changes in severity during the study. Although graded using the same severity scales as for AEs, ARV-associated toxicities were tracked and analyzed separately from AEs.

SAFETY RESULTS:

Of the 91 enrolled patients, 38 (42%) had no change in the primary ARV-associated toxicity, while 26 (29%) had resolution, 24 (26%) had improvement and 3 (3%) had worsening. Compared with primary ARV-associated toxicities, non-primary ARV-associated toxicities were more likely to remain unchanged during the study. However, it should be noted that non-primary ARV associated toxicities may have been due to an ARV medication other than the medication that was switched to enfuvirtide at baseline; thus some patients continued taking ARV medications that were causing non-primary toxicities. Of the 60 non-primary ARV-associated toxicities at baseline, 41 (68%) had no change in the toxicity, while 16 (27%) had resolution, 2 (3%) had improvement and 1 (2%) had worsening.

A total of 58 patients (64%) experienced AEs during the study. The only individual AEs reported in more than 3 patients were nasopharyngitis (10 patients [11%]), ISR (6 patients [7%]) and diarrhea (4 patients [4%]).

No treatment-emergent laboratory abnormalities were serious adverse events (SAEs) or resulted in

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discontinuation from the study.

Six patients were discontinued from the study for ISRs. For 5 patients, the primary reason for withdrawal was noted as "injection-site reaction," and for 1 patient, the primary reason was noted as "adverse event."

There were no deaths and only one treatment-related SAE (exacerbation of chronic bronchitis considered remotely related).

There were no treatment-emergent AIDS-defining events that met the protocol-specified reporting criteria.

There were no clinically relevant changes in vital signs.

EFFICACY RESULTS:

Overall, 66% of patients maintained or improved their viral load category (< 50, ≥ 50 but < 400 or ≥ 400 copies/mL) and 73% of patients maintained or improved their CD4 count category (< 50, ≥ 50 and < 100, ≥ 100 and < 200 or ≥ 200 cells/mm^3) during the study. Eleven patients shifted to a higher viral load category during the study, and 3 patients shifted to a lower CD4 count category.

Stability or improvement in virological and immunologic parameters was demonstrated by stable HIV-1 ribonucleic acid (RNA) levels (-0.08 [1.38] log_{10} copies/mL at Week 24) and increases in CD4 counts (18.87 cells/mm^3 at Week 24).

OTHER RESULTS:

Mean increases were observed during the study for all MOS-HIV scale scores, indicating improvement in health-related quality of life. Quality of life improvements were similar at Weeks 12 and 24, indicating that perceived increases in quality of life were maintained throughout the treatment period.

Most patients reported excellent adherence to the background regimen (91.21% of patients reported ≥ 95% adherence). Reported adherence to enfuvirtide was somewhat lower (79.12% of patients reported ≥ 95% adherence and 85.71% reported ≥ 90% adherence).

There was no notable difference in adherence to enfuvirtide by outcome of the primary ARV-associated toxicity (improvement/resolution vs. no change/worsening). Adherence to the background regimen was lower among patients who had no change or worsening in the primary toxicity (85.37% had ≥ 95% adherence) compared with patients who had improvement or resolution (96.00% had ≥ 95% adherence).

For all MOS-HIV scales except cognitive functioning, the mean increases from baseline at Weeks 12 and 24 were greater among patients with improved or resolved toxicity compared with those who had no change or worsening toxicity.

CONCLUSIONS:

Results of this open-label, single-arm study in HIV-infected patients experiencing treatment-limiting toxicity to a component of their ARV regimens demonstrate that switching from the toxic ARV medication to enfuvirtide improves or resolves toxicities in a majority of patients over a 24-week treatment period. Safety and tolerability results were favorable, and efficacy (virological and immunological response and quality of life) was similar to or improved over baseline. Overall, the results support a favorable risk/benefit ratio for enfuvirtide.