2. SYNOPSIS

Name of Sponsor/Company: Roche S.p.A. **Name of Finished Product:** Fuzeon® **Name of Active Ingredient(s):** Enfuvirtide	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Study title:	Evaluation of the viral burden decrease rate in HIV naïve patients treated by enfuvirtide, in comparison to the standard therapy	
Investigators:	[redacted]	
Centers:	[redacted]	
Publication (reference): -		
Clinical phase:	II	
Study period:	initiation date (first patient enrolled): 17 May 2005 completion date (last patient completed): 6 November 2007	
Objectives: *Primary objective*: To characterize the viral slope in HIV positive patients treated after the first drug administration and to determine the amount of change in viral burden compared to baseline in HIV-1 positive patients treated for 12 weeks with the following therapeutic regimens: - **A_1**: enfuvirtide+lamivudine+zidovudine - **B_1**: lopinavir/ritonavir+lamivudine+zidovudine		

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Secondary objectives:
To determine the efficacy and safety, as well as the patient quality of life (QoL) and the compliance to enfuvirtide treatment in comparison to the standard therapy.
The following parameters were assessed:
- Time to reach a HIV-RNA < 400 copies/mL and CD4+ > 200 cells/mL
- HIV-RNA plasma concentrations
- Proviral DNA
- Duration of initial suppression of viral burden
- Proportion of patients with a viral burden <50 or ≥ 50 - <400 copies/mL
- CD4+ cell count
- CD8+ cell count
- Time to virological failure: viral burden > 400 copies/mL
- env (arm A) and pol (arms A and B) sequence mutations
- systemic tolerability
- MOS-HIV questionnaire
- Assessment of the local safety to ENF treatment
- Assessment of the degree of satisfaction from investigator and patient
- Assessment of the best long term therapeutic strategy (48 weeks)

Experimental design:	multi-centre, randomized, parallel groups, open label, pilot study.
Number of patients:	Planned: 30 patients. Randomized: 31 Completed: 17
Diagnosis:	HIV positive, naïve patients.

Inclusion criteria:
The patients had to meet the following inclusion criteria at the screening and before starting the study treatment:
- Written informed consent
- Age > 18 years
- Naïve HIV positive patients
- HIV-RNA plasma concentration >10.000
- Patients with advanced illness and/or symptomatic HIV infection with CD4+ <200 cells/mL or with diagnosis of AIDS defining events (opportunistic infections) with whichever CD4+ count
- Patients capable to comply with study procedures

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Exclusion criteria:
- Patients with severe concomitant illnesses
- ALT and/or AST > 5 x ULN
- Previous ENF treatment
- Patients not capable to self inject the treatment (exceptions: family Doctor or caregiver may provide injections to the patient for the whole study duration)
- Evidence of opportunistic infection, undercurrent illnesses or any condition that may prevent patient to take the antiretroviral therapy
- Pregnancy, breast feeding, or women who planned to become pregnant during the study period
- Alcohol or drug abuse that could render the patient not reliable in following the study procedures
- Other previous evidence of patient not reliable in following the study procedures
- History of psychological disturbances or conditions interfering with the patient capability to understand the study requirements
- Patients who had taken a new investigational drug within the last 4 weeks

Study drug acute treatment

Study drugs	Enfuvirtide (ENF) +lamivudine+zidovudine
Routes	Enfuvirtide: injectable solution; Lamivudine+zidovudine: oral tablets
Dosage schedules	Enfuvirtide: 1 ampoule (90 mg) BID; Lamivudine+zidovudine: 1 tablet (150 mg + 300 mg) BID
Batch No.	[redacted]

Maintenance treatment

Study drugs	abacavir+lamivudine+zidovudine
Routes	Oral
Dosage schedules	1 tablet (300 mg + 150 mg + 300 mg) BID

Treatment duration	phase I (acute) 14 weeks; phase II (maintenance) 34 weeks

Reference drugs acute + maintenance treatment

Reference drugs	Lopinavir/ritonavir +lamivudine+zidovudine
Route	Oral
Dosage schedule	Lopinavir/ritonavir: 3 soft gelatin capsules (133.3 mg + 33.3 mg) BID Lamivudine+zidovudine: 1 tablet (150 mg + 300 mg) BID

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Assessment criteria:

The primary efficacy variable was the assessment of the viral slope. The baseline blood values of viral burden have been determined before starting the antiviral treatment. The viral burden was determined by means of PCR.

Blood samples were drawn at 24, 48, and 96 hours after the first dose of the study drugs. The changes in the viral burden were calculated by means of the following indices:

- Area under concentration/time curve (AUC_{0-96})
- Evaluation of nadir levels
- Change from baseline
- Viral slope

Secondary efficacy variables included:

- HIV-RNA viral burden in blood after 1, 2, 4, 8, 12, 24, 36 and 48 weeks of treatment.
- In case of viral blip the resistances were studied by HIV genotyping assay.

At the same time points the following parameters were also evaluated:

- Proviral DNA
- CD4+ and CD8+ cell pools
- Proportion of patients with a viral burden <50 or ≥ 50 - <400 copies/mL
- Time to failure (virological, immunological, clinical)

Both in the acute induction phase, before the complete viral suppression, and in the occasion of any viral blip (increase of blood viral burden >50 c/mL even in a single determination) genotypic mutations in the HIV viral sequence of *env* and *pol* were tested by means of automatic sequencing. After the 12th week the genotyping resistance assay was performed only in patients with measurable viral burden or in case of viral blip.

- Assessment of the best therapeutic strategy at long term (48 weeks). That evaluation was performed in a descriptive way on the basis of viral course and of CD4+ and CD8+ count.
- Quality of Life (QoL) was assessed after 24 and 48 weeks by means of MOS-HIV questionnaire.

Safety parameters:

The local tolerability in terms of injection site reactions (ISR) to ENF was assessed for the whole treatment duration; the systemic safety profile was assessed during the whole study period at 1, 2, 4, 8, 12, 24, 36 and 48 weeks, by means of Adverse Events (AEs) recording and by performing the following laboratory examinations:

- Blood tests and chemistry
- HbsAG, anti-HCV Ab
- Lipid profile
- Urinalysis (pH, RBC, proteins, glucose, chetones, leukocyte esterase)

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Statistical methods:
All analysis was presented by initial treatment arm (A1 or B1).
Complete descriptive analysis of patients' disposition, including number of screened patients, randomized patients, no. of patients who completed the study, no. of discontinued patients and primary reason of the discontinuation.
Demographic and screening/baseline characteristics as well as treatment exposure and compliance were described for the safety population. The primary efficacy analysis was performed on both the ITT and OT population, secondary efficacy analysis on ITT population. Safety analysis on the safety population.
In general terms, for continuous variables the following statistics were calculated: mean, standard deviation (SD), median, inter-quartile range (IQR), minimum and maximum values. For categorical variables absolute and relative frequencies were presented. 95% CI were also provided, whenever indicated.
Before performing any univariate statistical test on continuous variables, the assumptions of normality and variance homogeneity were checked.

<u>Primary efficacy data</u>
Two primary objectives have been performed:
- the analysis of kinetics variables considering the time points 0 (baseline), 24, 48, and 96 hours after the first dose. The slope was computed for each subject by fitting a linear regression of HIV-RNA measurement at 24, 48 and 96 hours, separated by treatment. The slope was next summarized by treatment and differences were investigated by two sample t-Test or by Mann-Whitney test. Time profile of median change over baseline of HIV-RNA value at each scheduled visit was graphically described.
- the change over baseline of HIV-RNA level at week 12. An analysis of covariance model (ANCOVA, main effects) was applied considering the change versus baseline of the HIV-RNA level at week 12 as dependent variable and including treatment as fixed effect, the viral load value at baseline as covariate. Both the LOCF approach and the prevalence approach were used.

<u>Secondary efficacy data</u>
The following variables were summarized by visit and by treatment group:
- CD4 and change vs. baseline of CD4 value;
- CD8 and change vs. baseline of CD8 value;
- CD4/CD8 rate and change vs. baseline of CD4/CD8 value;
- HIV-DNA (if available), and change vs. baseline of HIV-DNA value.
An analog ANCOVA model as for the primary efficacy variable was used for evaluating the change versus baseline of HIV-DNA level, CD4+ and CD8+ cells. The baseline value of the relevant test, together with the baseline value of HIV-RNA level, was used as covariates in the models.

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Time to viral decay (HIV-RNA < 400 copies/mL and CD4+ cells > 200 cells/mL) was graphically displayed by Kaplan-Meier method, overall by treatment groups and stratified by different levels of:
HIV-RNA at baseline (<100000 / ≥100000 copies/mL)
CD4 at baseline (<100 / ≥100 cell/mm3)
CD4% at baseline (< / ≥ median value)
The difference between two treatment groups on time to viral decay was evaluated by means of log rank test.
Concerning the MOS-HIV questionnaire, the composite questions (i.e. the multiple item questions – no. 4, 8, 9, 10, 11) were reversed in the score order, if needed, to give the same significance to items (e.g. the higher the score, the better the patient's condition). In case of missing data, the mean of all non-missing items was entered in the relevant subscale.
Patient's and physician's evaluation were compared among treatment arms at 24 and 48 weeks by chi-square test, using in SAS the CMH option for the 'Row mean score differ' statistic.
Duration of treatment in days and compliance was described by summary statistics for continuous variables.

Safety data
Adverse events were described by standard method. Summary tables were produced for all vital signs, hematological and blood chemical parameters showing the number of observations at each time point, the mean, median, standard deviation, inter-quartile range and the lowest and highest values. In addition, for each parameter a 4x4 transition table (where the forth category is for missing data) was produced to describe patients with normal values, or below/above the normal ranges, on treatment vs. baseline. After treatment start patients was classified as abnormal if a value outside the normal range was reported at least once on study. If multiple abnormalities were reported for the relevant parameter within patients, only the first occurrence was taken into account with the corresponding classification (below / above the normal limits).

Determination of sample size:
The sample size was based on feasibility criteria without any formal statistical hypothesis; 15 patients per group ensure a power of 80% to detect an effect size of 1.1 with a two-tailed significance level of 5%.

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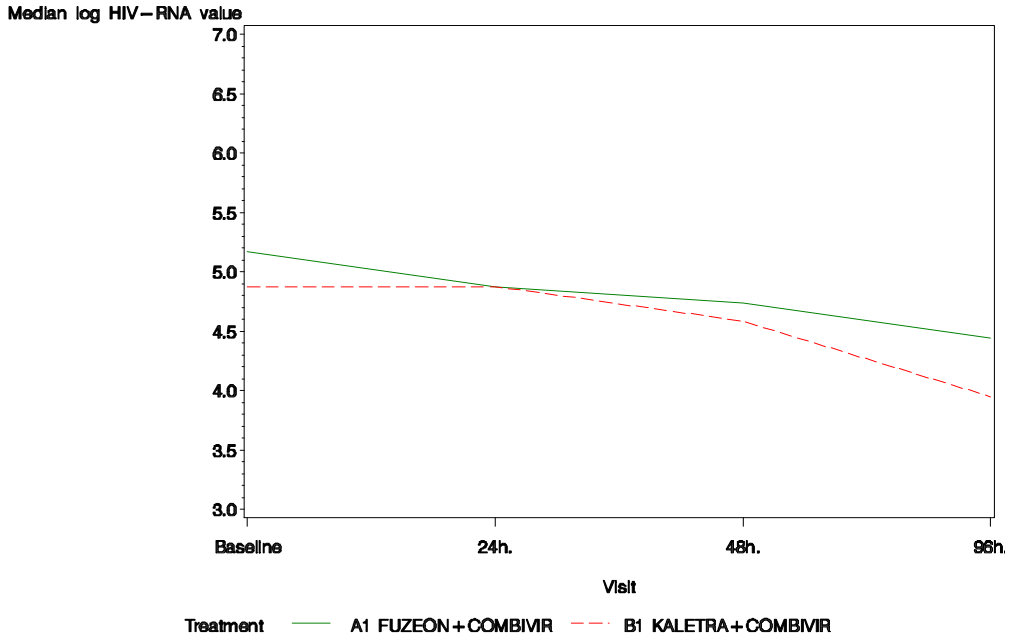
Results
Efficacy:

Analysis of primary efficacy variables

Viral slope of HIV-RNA level (0, 24, 48, 96 hours)
Baseline median values differed between the two treatment groups, with a higher value for Fuzeon group (5.2 vs. 5.0 copies/mL). From baseline to time point 24 hour after treatment, the RNA-HIV level remained approximately steady in the Kaletra group while decreased in Fuzeon group to the level of Kaletra. From this point on the RNA-HIV levels decreased in both treatment groups, more markedly in Kaletra group.

Figure: Median log HIV-RNA value (copies/mL) at baseline 24, 48 and 96 hours by treatment (ITT-population)



The slope was obtained by fitting a linear regression by patient at the aforementioned time points. The mean slope resulting from this analysis was very similar between treatments (-0.010 in the Fuzeon group vs. -0.009 in the Kaletra one) and the t-test result did not reject the hypothesis of no difference between treatments. However, the slope was significantly different from zero for both treatment groups (95% CI: -0.013 LL / -0.007 UL for Fuzeon; -0.013 LL / -0.006 UL for Kaletra). The analysis in the OT population confirmed the results.

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Descriptive statistics of slope by treatment and t-test results – ITT population

	A1 FUZEON+COMBIVIR (N=15)		B1 KALETRA+COMBIVIR (N=12)		
	Slope	**Standard Error**	**Slope**	**Standard Error**	**p-value**
N	15.0000	15.0000	12.0000	12.0000	
Mean	-.01010	0.00231	-.00952	0.00313	
SD	0.00547	0.00141	0.00574	0.00238	
Median	-.01104	0.00196	-.01066	0.00266	
Q1	-.02308	0.00034	-.01840	0.00029	
Q2	-.00196	0.00540	0.00137	0.00955	
Min	-.01410	0.00161	-.01356	0.00163	
Max	-.00648	0.00326	-.00681	0.00407	
T-test on slope among treatments: p-value (2-tailed, alpha 0.05)					0.7890

HIV-RNA change vs. baseline at week 12

A decrease from baseline of about the same magnitude was observed for both treatments at week 12. In both the ITT and OT analyses, the decrease vs. baseline was slightly greater in the Kaletra group but not statistically significant (p=0.3944 in the ITT population, p=0.6143 in the OT population), when controlling for the baseline value.

Analyses of secondary efficacy variables

The mean values of AUC0-96, Nadir and Cmax values were comparable among treatment groups, the differences being not statistically significant. Similar results were obtained in the OT population. On a descriptive way, the three parameters, reported as the natural logarithms of HIV-RNA values, were on average slightly higher in the Fuzeon group, than in the Kaletra group.

A mean increase in CD4 cells was observed at week 12 for both treatment groups, (mean absolute change: 4.80 in the Fuzeon group, 4.10 in the Kaletra group) and a mean decrease in CD8 cells (mean absolute change: -2.6 in the Fuzeon group, -6.0 in the Kaletra group). None of these differences between treatment groups was statistically significant, as was the difference in the mean absolute change of HIV-DNA level (copies/mL): - 41 in the Fuzeon group, -127 in the Kaletra group.

No statistical difference between treatment groups was detected for the time to viral decay, with median values of 169 days in the Fuzeon group and 85 days in the Kaletra group. Eleven patients out of 15 reached a viral decay in the Fuzeon group, 10 patients out of 12 had a viral decay in the Kaletra group.

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In the analysis stratified by classes of HIV-DNA and CD4 cells, no statistical difference between treatment groups was detected for any combination except for the comparison within the class of patients with CD4% cells below the median value at baseline: patients treated in the Kaletra group showed a significant shorter time to decay than patients in the Fuzeon group.
In general, for both treatment groups, time to viral decay was shorter in patients with better conditions at baseline: HIV-RNA >/= 100000 copies or CD4 cells > 100/mm3 or CD4% cells > median value.
No statistical difference between treatments was detected for any of the MOS-HIV questionnaire items.
Patients and physicians' evaluations at week 24 and 48 were comparable among treatments, with most of responses being 'good'.

Safety:
The incidence of adverse events was comparable between treatment groups, 81.3% in the Fuzeon group vs. 86.7% in the Kaletra group.
More serious adverse events were observed in the Kaletra group (5 patients, 33.3%) than in the Fuzeon group (2 patients, 12.5%).
A higher percentage of patients suffered from drug related adverse events in the Fuzeon group (75.0%) than in the Kaletra group (33.3%).
All serious adverse events were experienced each by 1 patient.
All serious events occurred in the Fuzeon group were judged as not related or unlikely related by the investigator. Two serious adverse events reported in the Kaletra group were drug-related (probable relationship): asthenia and nausea both complained of by patient [redacted], site [redacted].
The most represented system organ classes were in both treatment groups general disorders and administration site, the most frequent adverse events were injection site reaction and pyrexia in the Fuzeon group, pyrexia, diarrhea and oral candidiasis in the Kaletra group.
The most frequent drug-related adverse events were: injection site in the Fuzeon group, leading to drug discontinuation for two patients; nausea, vomiting, and hypertriglyceridaemia in the Kaletra group.
Laboratory parameters gave the following results: among the blood and lymphatic system disorders, anemia (2 patients) and eosinophilia (1 patient) were reported as adverse events in the Fuzeon group, anemia (2 patients), lymphopenia (1 patient), and neutropenia (1 patient) were reported as adverse events in the Kaletra group. All of these events were not serious, but anemia (grade 3) experienced by one patient in the Kaletra group.
Among investigations, blood lactate dehydrogenase increase (1 patient), hemoglobin decrease (1 patient) and transaminase increase (1 patient) were reported as adverse events, all in the Fuzeon group and none serious.

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Urine resulted as positive, at least once after treatment start, for leukocytes in 7 patients in both treatment groups, and for proteins in 7 in the Fuzeon group and in 10 in the Kaletra group.
Concerning the evaluation of local tolerability in the Fuzeon group at week 12 with respect to week 1, an improvement was observed for general evaluation, inflammation and hardening. No relevant changes for itch, nodule and cysts and dose adjustments. A worsening was noted for average duration of lesions, number of evident single lesions at visit 12, bruise and concomitant therapy due to reaction on injection site.

Conclusions:
This was a multi-centre, randomized, parallel groups, open label, pilot study on viral slope, in 31 HIV naïve patients, to assess the efficacy and safety of enfuvirtide, given at the dose of 90 mg BID s.c. in combination with lamivudine and zidovudine for 14 weeks in the acute phase, compared to a standard treatment with lopinavir/ritonavir in combination with lamivudine and zidovudine. The acute phase was followed by a maintenance phase of 34 weeks, in which the group A was given abacavir in combination with lamivudine and zidovudine, while the group B received lopinavir/ritonavir in combination with lamivudine and zidovudine.
The analysis of the primary and secondary efficacy parameters confirmed similar efficacy of the two treatment regimens, with an overall safety profile that was also similar or better for enfuvirtide. In conclusion, the study objective that the therapy with enfuvirtide would save 2 classes of drugs (PI, NNRTI) in HIV naïve patients is confirmed.

Date of report: 06.02.2009