CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-481

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-481
APPLICANT:	Hoffmann-La Roche Inc., Trimeris
NAME OF DRUG:	Fuzeon® (Enfuvirtide)
INDICATION:	Treatment of HIV Infection
TYPE OF REVIEW:	Clinical
DOCUMENTS REVIEWED:	Volumes 73, 74
STATISTICAL REVIEWER:	Thomas Hammerstrom, (HFD-725)
TEAM LEADER:	Greg Soon, PhD, (HFD-725)
MEDICAL INPUT:	Melisse Baylor, M.D. (HFD-530)
PROJECT MANAGER:	Virginia Yoerg, (HFD-530)
SUBMISSION DATE:	Sept. 16, 2002

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-481

0. Executive Summary

The applicant has conducted two trials to test the efficacy of Fuzeon. Both trials were conducted in patients who had at least 6 months experience with, or resistance to, drugs in all three classes: NRTI's, PI's, and NNRTI's. (One trial required resistance to at least 2 PI's, the other to only 1 PI.) The other difference between the trials was that one was recruited in North and South America, the other in Europe and Australia.

An optimized background (OB) regimen was identified by genotypic and phenotypic testing. Subjects were randomly assigned in a 2:1 ratio to get 90 mg Fuzeon or nothing in addition to their background regimen. No blinding or placebo was used because Fuzeon is administered by subcutaneous injection and almost all subjects have an injection site reaction.

Fuzeon (+OB) was statistically and clinically significantly superior to OB alone in both trials with respect to the protocol specified primary endpoint of mean change from baseline in HIV RNA, with respect to the endpoint more commonly used in contemporary anti-HIV NDA's, percent of subjects with sustained viral suppression to below LOQ [redacted], and with respect to change from baseline in CD4 count.

The findings on the primary endpoint were robust to handling of missing data. They were also robust to sensitivity analyses intended to explore the possibility of biased drop-out by nonblinded subjects and of deliberate non-compliance by nonblinded control subjects.

There was no suggestion of treatment-covariate interactions in any of the subgroups studied. There is no evidence about the efficacy of this drug in less experienced populations.

1. Background

The applicant submitted two randomized, controlled clinical trials with Enfuvirtide (Fuzeon or T-20) for this supplement: trial 301 and trial 302.

2. Trials 301 and 302

2.1 Objectives in Trials

The primary objective of both studies was to compare the efficacy of Fuzeon at a dose of 90 mg by subcutaneous injection (SCI) bid added to an individualized optimized background (OB) regimen to that of OB alone. The OB regimen was selected based on the patient's antiretroviral (ARV) history and on genotypic and phenotypic resistance testing. The primary efficacy endpoint was change from baseline in log HIV RNA level. The study population was HIV-1 infected patients with at least 6 months experience with (or documented resistance to) all three classes of ARV drugs: NRTI's (nucleoside reverse transcriptase inhibitors), NNRTI's (non-nucleoside RTI's), and PI's (protease inhibitors). Specifically, patients in trial 301 were required to have experience with, or resistance to, >=1 NRTI, >= 2 PI's, and >= 1 NNRTI while patients in trial 302 were required to have experience with, or resistance to, >=1 NRTI, >= 1 PI's, and >= 1 NNRTI. They were also required to have confirmed viral load of at least [redacted] in both trials.

2.2 Summary of Study Design

The studies were open-label, randomized, two-arm, parallel, untreated controlled, multi-center trials. Trial 301 was conducted at 47 centers in the US, Canada, Mexico, and Brazil. Trial 302 was conducted at 64 centers in Australia, Belgium, France, Germany, Italy, the Netherlands, Spain, Switzerland, Sweden, and the UK.

In both trials, subjects were randomly assigned in a 2:1 ratio to 90 mg SCI bid Fuzeon + OB or OB alone. The randomization was stratified by baseline viral load ([redacted] .

copies/mL), number of newly approved or investigational ARV's in the OB (0, 1, or 2), and geographical region. The only new or investigational ARV's seen in the studies were Kaletra, used by 35% of subjects in trial 301, and tenofovir, used by 2% of subjects in trial 301.

2.3 Patient Accounting and Baseline Characteristics

501 patients were randomized in trial 301. Of these, 6 patients never started treatment. Of the 495 eligible patients who started treatment, 65 withdrew before the end of the study. The subjects were enrolled at 47 centers on North and South America. The exact distribution of patients and sites by country is given in table 2.3 A.

TABLE 2.3 A
PATIENTS BY COUNTRY, TRIAL 301

Country	Patients	Country	Patients
USA	404	Mexico	16
Canada	66	Brazil	9

512 patients were randomized in trial 302. Of these, 4 patients never started treatment. Of the 508 eligible patients who started treatment, 74 withdrew before the end of the study. The subjects were enrolled at 65 centers in Europe and Australia. The exact distribution of patients and sites by country is given in table 2.3 C.

TABLE 2.3 C
PATIENTS, SITES BY COUNTRY, TRIAL 302

Country	Patients	Country	Patients
Australia	58	Belgium	25
France	127	Germany	60
Italy	61	Netherlands	14
Spain	89	Switzerland	22
Sweden	3	UK	49

In trial 301, the study population was 92% male with a mean age of 42 years. They were 83% white and 12% black. The mean CD4 count at baseline was 117 cells/mm^3; the mean HIV RNA level

was 5.1 logs. 86% of patients had prior AIDS defining events.

In trial 302, the study population was 87% male with a mean age of 42 years. They were 95% white and 3% black. The mean CD4 count at baseline was 149 cells/mm^3; the mean HIV RNA level was 5.1 logs. 77% of patients had prior AIDS defining events.

Phenotypic and genotypic sensitivity scores (PSS and GSS) were defined as the number of drugs in the OB to which the patients viral samples showed phenotypic or, respectively, genotypic sensitivity. In the analysis phase, missing PSS and GSS were set equal to half the number of drugs in the OB. The baseline distributions of PSS and GSS are given in table 2.3 E. Prior ARV experience is given in table 2.3 F and composition of the OB is given in table 2.3 G.

TABLE 2.3 E
BASELINE PHENOTYPIC, GENOTYPIC SENSITIVITY SCORES

	Trial 301		Trial 302	
	PSS	GSS	PSS	GSS
0	26%	15%	32%	18%
1-2	43%	53%	45%	58%
3-4	25%	27%	18%	20%
>=5	1%	3%	2%	2%
Missing	1%	1%	3%	2%

TABLE 2.3 F
PRIOR ARV EXPERIENCE

	Trial 301		Trial 302	
	T-20+OB	OB	T-20+OB	OB
Mean Number of Prior ARV's	12.3	11.9	12.1	12.0
Mean Duration of ARV Use	7.1	7.3	7.6	7.7
Prior NRTI Experience				
3-4 Drugs	21%	27%	16%	10%
>=5 Drugs	79%	70%	84%	90%
Prior PI Experience				
1-2 Drugs	10%	10%	7%	8%
3-4 Drugs	40%	50%	41%	39%
>=5 Drugs	49%	39%	52%	54%
Prior NNRTI Experience				
1 Drug	45%	47%	43%	41%
2 Drugs	45%	41%	50%	52%
3 Drugs	9%	11%	6%	7%
Kaletra Experience	39%	28%	61%	52%
Tenofovir Experience	1%	0%	5%	2%

TABLE 2.3 G
COMPOSITION OF THE OB

	Trial 301		Trial 302	
	T-20+OB	OB	T-20+OB	OB
Number of Drugs				
3	31%	32%	39%	42%
4	37%	35%	39%	31%
5	30%	33%	20%	24%
New ARV's Used				
None	20%	21%	29%	26%
Kaletra	62%	62%	36%	42%
Tenofovir	8%	7%	18%	14%
Both	10%	10%	17%	18%
Number of PI's				
1-2	91%	95%	86%	85%
3-4	6%	2%	5%	4%
Number of NRTI's				
1-2	67%	69%	62%	66%
3-4	32%	30%	38%	33%
Number of NNRTI's				
0	69%	72%	74%	75%
1	31%	28%	26%	25%

Table 2.3 H summarizes the primary reasons for discontinuation from study 301 and from double blind treatment. Subjects who had a viral failure on OB alone are subdivided into those who switched to Fuzeon and those who did not switch. Table 2.3 I gives the same summary for trial 302.

TABLE 2.3 H
PATIENT STATUS, TRIAL 301

	Fuzeon+OB	OB		
Randomized	332	169		
In Treated ITT	328	167		
No Follow-Up	2	2		
Non-Failure	190	59		
Completed	170	51		
Withdrew	20	8		
Safety	17	5		
LTFU	3	3	OB Only	
			Switched	No Switch
Viral Failure	136	106	81	25
Completed	119	90	75	15
Withdrew	17	16	6	10
Safety	8	8	3	5
LTFU	9	8	3	5

TABLE 2.3 I
PATIENT STATUS, TRIAL 302

	Fuzeon+OB	OB		
Randomized	341	171		
In Treated ITT	338	170		
No Follow-Up	3	1		
Non-Failure	170	39		
Completed	147	37		
Withdrew	23	2		
Safety	18	1		
LTFU	5	1	OB Only	
			Switched	No Switch
Viral Failure	165	130	114	16
Completed	131	115	105	10
Withdrew	34	15	9	6
Safety	16	8	7	1
LTFU	18	7	2	5

2.4 Summary of Methods of Assessment

2.4.1 Schedule of Measurements

Patients had CD4 counts taken at week 0, monthly to month 6, and every 2 months thereafter to month 11. HIV RNA was measured at weeks 0, 1, 2, every 2 weeks to week 16, every 4 weeks to week 24, and every 8 weeks to week 48. Plasma samples were assessed by the [redacted] assay. HIV RNA levels [redacted] were remeasured by the [redacted] assay.

The patients were queried about the number of pills or injections missed in the four days preceding each study visit. Adherence was computed as the lowest among all assigned drugs of the percentages of doses not missed.

2.4.2 Criteria for Switching Regimen

Viral failure was defined as any of the following:
1) confirmed viral load > baseline - .5 logs with first such measurement at week 6 or later,
2) confirmed viral load > baseline - 1.0 logs with first such measurement at week 14 or later, or
3) confirmed viral load < baseline - 2.0 logs followed by confirmed viral load > nadir + 1.0 logs with first such measurement at week 6 or later.

In these criteria, confirmation = consecutive measurements covering at least 2 weeks and nadir = average of two lowest measurements.

Patients in the OB arm who were viral failures were allowed to revise their OB and add Fuzeon to their therapy. Patients in the Fuzeon arm who were viral failures were allowed to revise their OB.

Patients who experienced toxicity associated with drugs in the OB were allowed to substitute a drug of the same class. If there was class toxicity, patients were allowed to substitute a PI for an NNRTI and vice versa. Patients were also allowed to interrupt treatment for up to 28 days to deal with toxicities. Longer interruptions constituted discontinuation from the study.

2.4.3 Assessment of Treatment Effects

The protocol specified primary endpoint at week 24 was change from baseline in log HIV RNA level. The final value in this computation was the mean of the week 24 value and the preceding value for subjects not failing before week 24. For subjects failing before week 24, the final value was the mean of the two values constituting the initial and confirmatory failure observations. For subjects lost to follow-up, the final value was the mean of the last two values before loss.

Four secondary viral endpoints were also used. Three were percent successful with success defined as [redacted], [redacted] or [redacted] or <baseline-1 log copies/mL. Loss to follow-up counted as failure. The fourth endpoint was time to the earlier of viral failure and loss to follow-up.

2.5 Summary of Statistical Analysis

The planned primary analysis was an analysis of covariance (ANCOVA) on change from baseline with the following predictor variables: treatment, stratum, treatment-by-stratum interaction, and baseline PSS. In the analysis, the stratum was defined differently than in the randomization. Geographic region was not included and use of investigational or newly approved ARV's was binary (yes or no) rather than ternary (0, 1, or 2).

2.6 *Summary of Applicant's Results*

The results for trials 301 and 302 are given in table 2.6 A. This table gives the least squares mean computed from the primary analysis ANCOVA and the sample size for each of the two arms together with the 95% confidence interval for the difference in the means. Results are given for all subjects. Results subdivided by a number of covariates, including gender, race, age, and baseline HIV RNA, CD4 count, and gp41 level, are given in section 5 below for both trials pooled together. The primary analysis found enfuvirtide plus OB to be superior to OB alone with a p-value < .001.

TABLE 2.6 A
HIV RNA RESULTS
CHANGE IN LOG FROM BASELINE

	Fuzeon+OB	OB	95% Interval
Trial 301	-1.67 (326)	-.76 (165)	(-1.27, -.59)
Trial 302	-1.43 (335)	-.65 (169)	(-1.07, -.49)

The applicant also conducted a sensitivity analysis in which subjects who were lost to follow-up before week 24 were imputed a week 24 value of HIV RNA equal to baseline. The results of this sensitivity analysis were compatible with those of the LOCF analysis. The results are compared in table 2.6 B.

TABLE 2.6 B
SENSITIVITY ANALYSES ON CHANGE IN LOG HIV RNA

Missing Values	Fuzeon+OB	OB	95% Interval
Trial 301			
LOCF	-1.67 (326)	-.76 (165)	(-1.27, -.59)
Return to Baseline	-1.64	-.75	(-1.24, -.54)
Trial 302			
LOCF	-1.43 (335)	-.65 (169)	(-1.07, -.49)
Return to Baseline	-1.36	-.64	(-1.02, -.43)

The applicant also showed that the observed difference of approximately .9 log copies/ml appeared by week 2 and remained fairly constant through week 24.

The applicant also included three efficacy analyses based on

categorical endpoints, in which subjects lost to follow-up before week 24 were classified as failures. Success corresponded to week 24 HIV RNA [redacted] or <1 log below baseline. Results with these three endpoints are summarized in table 2.6 C below. The table includes the percent successful on each arm by each definition together with the 95% confidence interval for the odds ratio of success, Fuzeon relative to control. (Odds ratios > 1 are favorable to Fuzeon.) These analyses were also done with loss to follow-up counted as censored rather than failed. The results are close enough to those in table 2.6 C (LTFU=failed) that they need not be reported separately.

TABLE 2.6 C
BINARY ENDPOINTS

Week 24 HIV RNA	Fuzeon+OB	OB	95% Interval for Odds Ratio
Trial 301			
< [redacted]	64/326 = 20%	12/165 = 7%	(1.7, 6.4)
<	121/326 = 37%	27/165 = 16%	(2.0, 5.1)
< 1 log below base	169/326 = 52%	48/165 = 29%	(1.8, 4.0)
Trial 302			
< [redacted]	41/335 = 12%	9/169 = 5%	(1.2, 5.6)
< [redacted]	95/335 = 28%	23/169 = 14%	(1.6, 4.6)
< 1 log below base	143/335 = 43%	35/169 = 21%	(1.9, 4.7)

Table 2.6 D shows the breakdown of the withdrawals in each arm by cause, as provided in the applicant's dataset. The data for withdrawals during the period 0-24 weeks are slightly different from those reported in the applicant's text and repeated in tables 2.3 H and I above. This table also includes the withdrawals later than 24 weeks. (LOE means lack of efficacy.)

TABLE 2.6 D
REASONS FOR WITHDRAWALS BY TRIAL AND ARM

		TRIAL_301		TRIAL_302	
Period	Reason	OB	Fuzeon	OB	Fuzeon
0-24 Weeks	AE	13	26	7	33*
	DEATH	0	0	2	2
	LOE	3	4	6	14
	LTFU	10	9	3	11
> 24 Weeks	AE	6	11	4	7
	DEATH	0	3	1	1
	LOE	4	4	7	10
	LTFU	11	10	5	12

* includes one lab abnormality

3. Summary of Applicant's Conclusions

The applicant concluded that the use of 90 mg SCI bid enfuvirtide in conjunction with an optimized background regimen resulted in significant decrease in viral load at 24 weeks in highly experienced HIV patients, compared to optimized background alone.

4. Statistical Reviewer's Comments and Analyses

4.1 Sensitivity Analyses on Change from Baseline

The statistical reviewer concurs with the applicant that both trials have demonstrated statistically significant improvements in the primary endpoint of change in viral load from baseline to week 24, with the protocol specified adjustments for subjects switching therapy for lack of efficacy. These results were robust to treating missing data as either LOCF or return to baseline. Here all HIV RNA measurements after switching off assigned treatment are missing. (HIV RNA measurements may have been made after such switch but these are not measurements on the assigned therapy; the latter are necessarily missing after switch.)

The FDA statistical reviewer also two performed additional sensitivity analyses intended to explore the possibility that the open label nature of the trial may have resulted in biased conclusions. First, all missing HIV RNA values from subjects discontinuing assigned therapy were imputed in an asymmetric fashion. Subjects on OB were given the more favorable of LOCF and return to baseline; subjects were given the less favorable of LOCF and return to baseline for their missing observations at week 24.

A second possible concern is that subject's not given Fuzeon would have an incentive to not take their assigned OB therapy. This stratagem would allow them to fail early and then add Fuzeon to their regimen without losing viral sensitivity to any of the drugs in their OB. (They would be putting themselves at risk of disease progression by doing this.) If they used this stratagem, one would also expect them to lie about compliance so the measurement of self-reported compliance would not assure a reviewer that this wasn't occurring.

However, one would expect that subjects not taking any drugs would not experience any viral decline. Therefore, as a sensitivity analysis, the primary analyses were repeated twice,

first excluding all control subjects who had a nadir > baseline - .25 log copies and then excluding all control subjects who had a nadir > baseline - .5 log copies.

The results of these sensitivity analyses are given in tables 4.1 A and B.

TABLE 4.1 A
CHANGE FROM BASELINE IN TRIAL 301
SENSITIVITY ANALYSES

	Fuzeon		OB			95% Limit	
OB Group Excluded	Mean	N	Mean	N	Diff	Lower	Upper
Both Arms LOCF							
None	-1.81	328	-.94	167	.86	.62	1.10
Nadir>Base-.25	-1.81		-1.24	120	.56	.29	.84
Nadir>Base-.5	-1.81		-1.35	97	.46	.16	.76
Both Arms Back to Base							
None	-1.73	328	-.88	167	.85	.61	1.09
Nadir>Base-.25	-1.73		-1.16	120	.58	.30	.85
Nadir>Base-.5	-1.73		-1.28	97	.46	.16	.76
OB Arm Favorable							
None	-1.72	328	-1.02	167	.70	.47	.94
Nadir>Base-.25	-1.72		-1.29	120	.43	.17	.70
Nadir>Base-.5	-1.72		-1.39	97	.33	.04	.62

One can see that in trial 301, all of the sensitivity analyses result favor fuzeon and result in 95% confidence intervals for difference between change from baseline under fuzeon and change from baseline on OB which exclude zero. I.e. the results even in the most stringent analysis were statistically significantly in favor of fuzeon. This even included analyses which excluded those 70 of the 167 OB patients who had the worst response and which treated missing data in a manner which favors the OB arm. These results were supported by the p-values from ANCOVA which used treatment, baseline HIV RNA stratum, geographic region, and baseline PSS as covariates. The nine p-values corresponding to the analyses in table 4.1 A were all < .0012.

TABLE 4.1 B
CHANGE FROM BASELINE IN TRIAL 302
SENSITIVITY ANALYSES

OB Group Excluded	Fuzeon Mean	N	OB Mean	N	Diff	95% Limit Lower	Upper
Both Arms LOCF							
None	-1.42	337	-.67	170	.75	.52	.98
Nadir>Base-.25	-1.42		-.92	116	.50	.23	.77
Nadir>Base-.5	-1.42		-1.14	86	.28	-.03	.59
Both Arms Back to Base							
None	-1.32	337	-.58	170	.75	.52	.97
Nadir>Base-.25	-1.32		-.78	116	.54	.27	.81
Nadir>Base-.5	-1.32		-.99	86	.33	.01	.64
OB Arm Favorable							
None	-1.3	337	-.75	170	.56	.34	.78
Nadir>Base-.25	-1.3		-.96	116	.35	.08	.61
Nadir>Base-.5	-1.3		-1.17	86	.14	-.17	.44

The results from the sensitivity analyses in trial 302 are only slightly less favorable than those in trial 301. All of the analyses produced results in fuzeon subjects had greater mean decrease from baseline than did OB subjects. Only the analyses which excluded the 84 worst performing OB subjects produced results in which fuzeon was not statistically significantly superior to OB. P-values from ANCOVA using the same predictor variables as for trial 301 confirmed the patterns in table 4.1 B.

It is a reasonable conclusion that the physician's and patient's knowledge of which treatment they were assigned did not bias behavior by an amount sufficient to explain the observed superiority of fuzeon. The primary finding of superiority for fuzeon is robust.

4.2 Times to Loss of Viral Suppression to BLQ

These trials did not use as its primary endpoint the time until confirmed rebound of viral load to above LOQ after confirmed achievement of BLQ levels. Because this endpoint has been common in most other recent NDA's for drugs indicated for HIV infection, the results are given as a secondary analysis.

The applicant's calculations reported in table 2.6 C above counted subjects as viral failures if they qualified to switch treatments, even if they did not switch. In the FDA computation reported here, only actual regimen switches contributed to viral failure. Both trials are pooled together for this secondary endpoint because the inclusion/exclusion criteria are nearly the same. Only geographic region differs between the trials.

These trials had results that were somewhat unusual compared to other trials in less ART experienced populations. Specifically, many subjects first achieved confirmed viral levels <50 copies/mL at later times than commonly seen. The number of subjects first achieving levels [redacted] and [redacted] at times later than 197 days (= end of 24 week window) are given in table 4.2 A.

TABLE 4.2 A
TIMES OF FIRST CONFIRMED VIRAL SUPPRESSION
BOTH TRIALS POOLED TOGETHER

LOQ = [redacted]

Arm	Status at Week 48	Time 1st BLQ	Number Pats
OB	Suppressed	Before Day 197	23 (7%)
		After Day 197	5 (1.5%)
	Not Suppressed	Before Day 197	17 (5%)
		After Day 197	0
		Never	292 (87%)
T-20	Suppressed	Before Day 197	112 (17%)
		After Day 197	15 (2.3%)
	Not Suppressed	Before Day 197	69 (10%)
		After Day 197	3 (0.5%)
		Never	466 (70%)

LOQ = 400 copies/ml			
OB	Suppressed	Before Day 197	46 (14%)
		After Day 197	1 (0.3%)
	Not Suppressed	Before Day 197	32 (9%)
		After Day 197	0
		Never	258 (77%)
T-20	Suppressed	Before Day 197	213 (32%)
		After Day 197	5 (0.8%)
	Not Suppressed	Before Day 197	107 (16%)
		After Day 197	0
		Never	340 (51%)

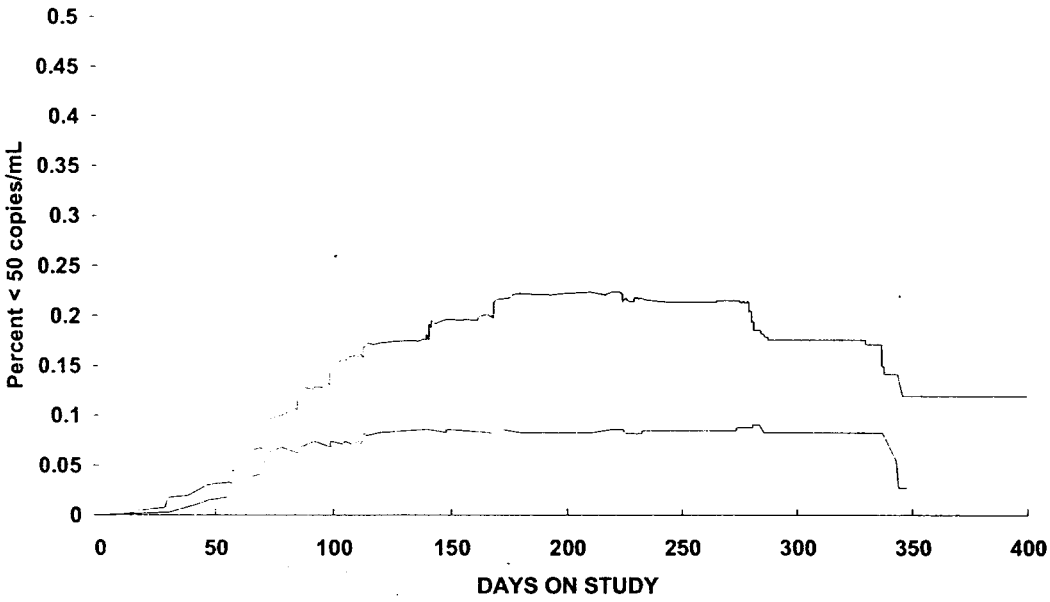
Table 4.2 B summarizes results for viral suppression by week 24. The table gives the percent BLQ on each arm for LOQ = _____ together with the Fuzeon BLQ rate minus the OB rate and 95% confidence limits for this difference. In this table subjects who have not achieved the first of two consecutive visits with viral load BLQ by day 197 are counted as failures, even if they became suppressed afterwards and would have been counted as virally suppressed at week 48. The table also contains results for percent of subjects who had HIV RNA level at least 1 log below baseline at the week 24 visit.

TABLE 4.2 B
VIRAL SUPPRESSION BY WEEK 24
BOTH TRIALS POOLED

	Fuzeon		OB			95% Limit		
LOQ	%BLQ	N	%BLQ	N	Diff	Lower	Upper	P-value
50 copies	.22	665	.08	337	.14	.09	.18	<.0001
400 copies	.37		.16		.21	.15	.26	<.0001
>=1 log drop	.55		.30		.25	.19	.31	<.0001

Figure 4.2 shows the time course of % below 50 copies/mL out to the end of the trial. Subjects administratively censored while still suppressed are not counted as failures in this plot.

PERCENT WITH VIRAL SUPPRESSION
BOTH TRIALS POOLED TOGETHER



APPEARS THIS WAY
ON ORIGINAL

4.3 Results with CD4 Counts

Table 4.3 A gives mean CD4 count in both arms at week 24 and mean change from baseline to week 24. In both cases, missing data were replaced by LOCF. (Recall that data recorded after switching regimens are missing.) The table also gives the estimate and 95% confidence limits for Fuzeon - OB and the p-value for the difference.

TABLE 4.3 B
MEAN CD4 COUNT, MEAN CHANGE IN CD4 COUNT
BY ARM AND TRIAL

	Fuzeon		OB			95% Limit		
Endpoint	Mean	N	Mean	N	Diff	Lower	Upper	P-value
CD4 Count								
301	200	328	155	165	-45	-72	-18	.0011
302	217	337	184	170	-33	-66	0	.0493
Change in CD4 Count								
301	79	328	45	165	-33	-48	-19	<.0001
302	66	337	36	167	-30	-47	-13	.0007

There was a statistically significant increase in CD4 count of about 30 more cells with Fuzeon than with OB in both trials. With 95% confidence there was an improvement of at least 10-20 cells.

4.4 Analyses of Bacterial Infection Rates

The FDA clinical reviewer noted that there was an apparent increase in the incidence of bacterial infections in the Fuzeon arm and the Switch arm (i.e. OB patients subsequent to adding Fuzeon) relative to the OB (specifically, OB patients prior to adding Fuzeon). Certain specific bacterial infections, namely pneumonia and sepsis, showed even higher apparent increases in incidence. Table 4.4 A shows the numbers and percents of subjects on each of the three arms with any bacterial infection (as identified by the FDA clinical reviewer), pneumonia, pneumonia or bronchopneumonia, and sepsis. Because the trial designs were similar, both trials were pooled together. In these tables, subjects assigned to the OB arm often appear twice. They are always counted as in the OB arm. If they later add Fuzeon, without having an infection, they are also counted in the Switch arm. Subjects who have an infection while still on OB were not included in the Switch arm, even if they added Fuzeon after the infection.

TABLE 4.4 A
NUMBERS OF SUBJECTS WITH BACTERIAL INFECTIONS
BOTH TRIALS POOLED

Infection	Arm	Infected	Not Infected	Percent	Rate/100 P-yr
Any	OB	39	298	11.6%	25.5
	T20	161	505	24.2%	23.7
	SW	46	162	22.1%	19.3
Bronchopneumonia & Pneumonia	OB	4	333	1.2%	2.44
	T20	45	621	6.8%	5.84
	SW	9	218	4.0%	3.18
Pneumonia	OB	4	333	1.2%	2.44
	T20	42	624	6.3%	5.44
	SW	9	218	4.0%	3.18
Sepsis	OB	1	336	.3%	.61
	T20	11	655	1.7%	1.38
	SW	4	225	1.7%	1.39

The apparent increase shown in this table in the percentage of subjects with infections does not accurately reflect the smaller exposure of the OB patients. The rightmost column of the table gives the incidence rate per 100 person years of exposure, a more reliable measure of the risk in the three groups.

As another method of adjusting for the differences of duration of exposure, the FDA statistical reviewer plotted Kaplan-Meier curves for time to first bacterial infection and time to first pneumonia. These curves are given in figures 4.4 A and 4.4 F, respectively. Figures 4.4 B, C, D and E give the 95% confidence intervals for the difference in infection rates, Fuzeon - OB and Switch - OB and the 95% confidence intervals for the log hazard ratios of OB/Fuzeon and OB/Switch. The log hazard plots give information as to whether the risk is increasing or decreasing over time. Figures 4.4 G-J give the confidence bands for differences in percent infected and log hazard ratios for time to first pneumonia.

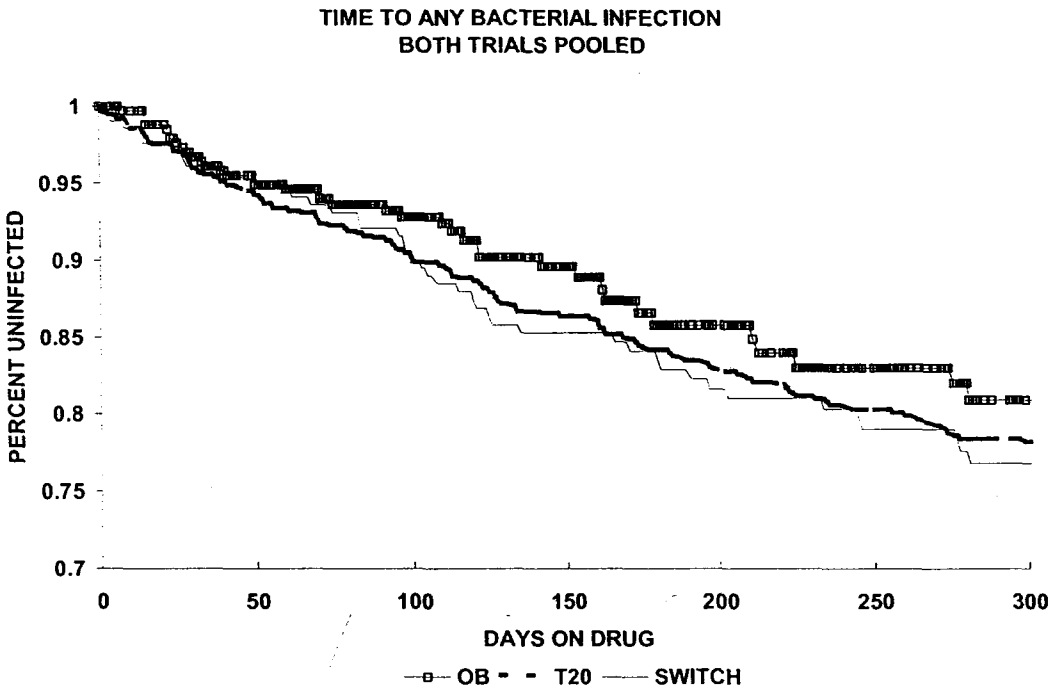


Figure 4.4 A

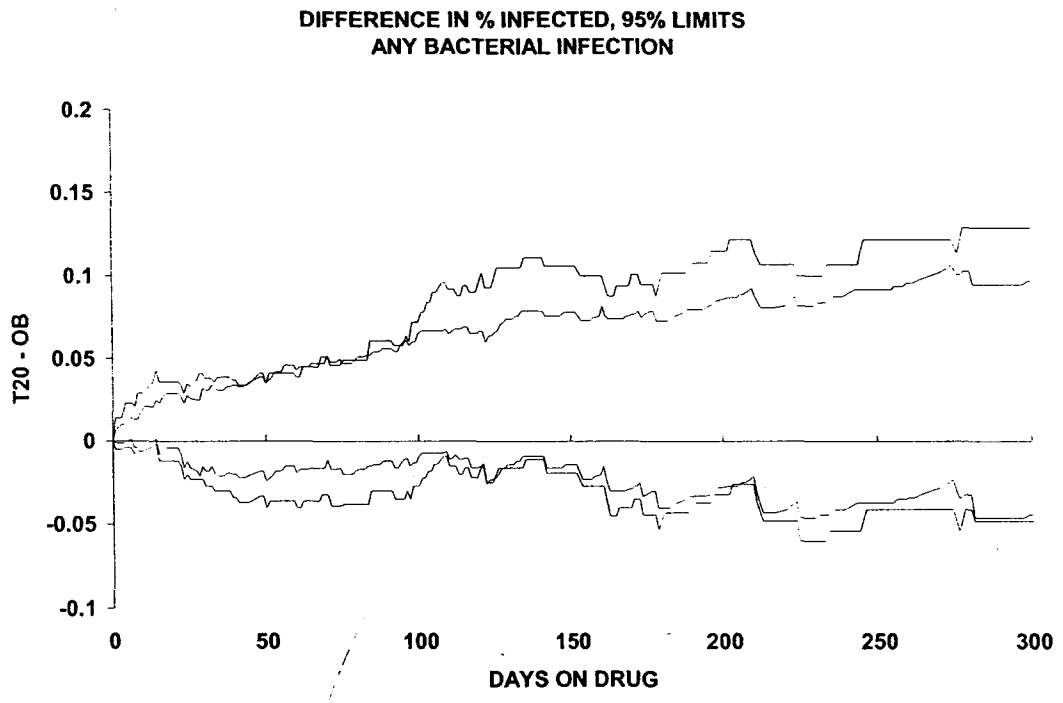


Figure 4.4 B

APPEARS THIS WAY
ON ORIGINAL

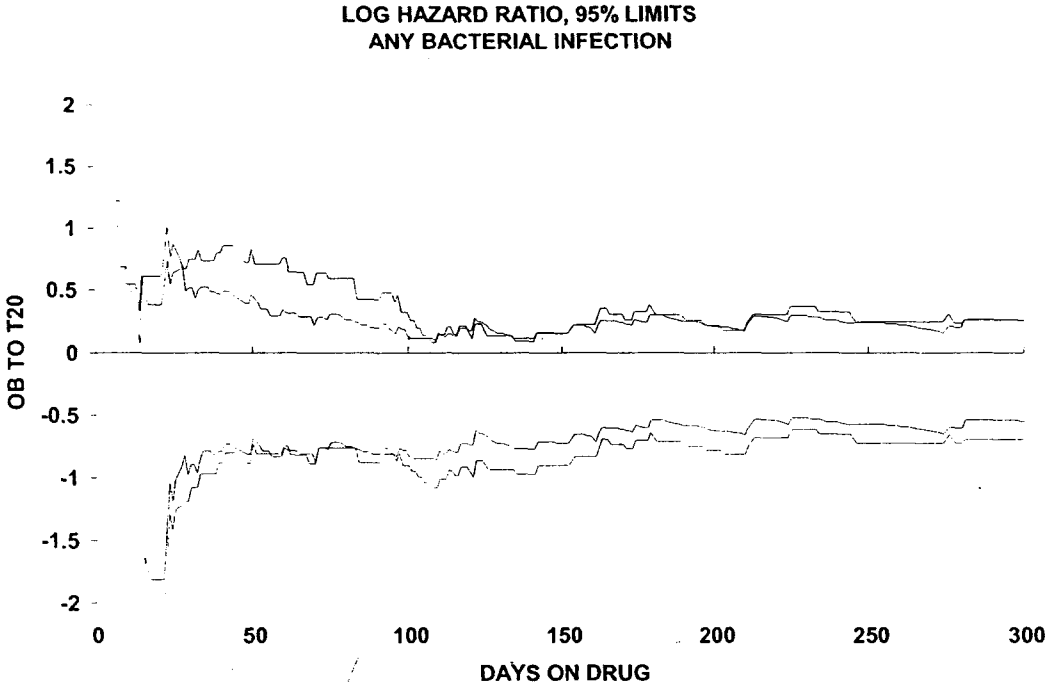


Figure 4.4 C

APPEARS THIS WAY
ON ORIGINAL

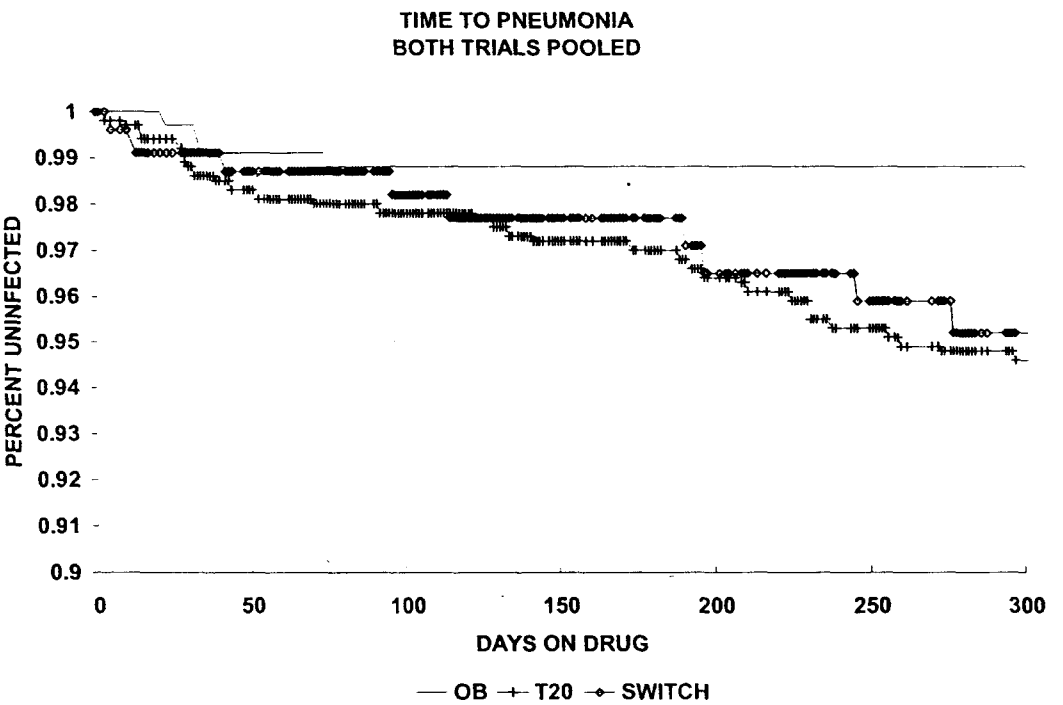


Figure 4.4 D

APPEARS THIS WAY
ON ORIGINAL

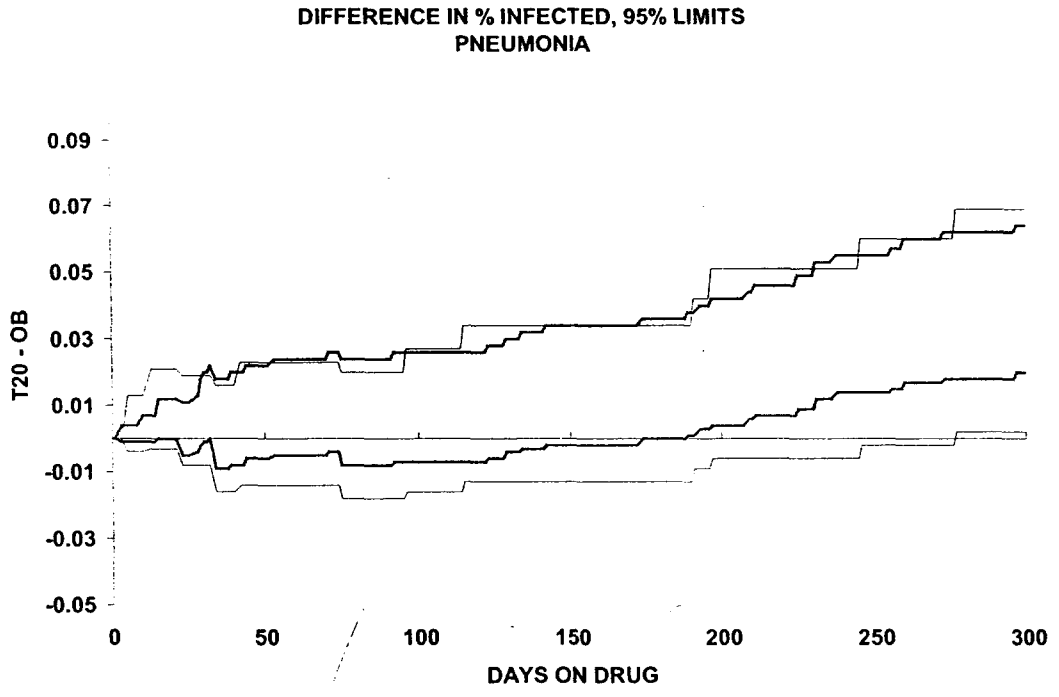


Figure 4.4 E

APPEARS THIS WAY
ON ORIGINAL

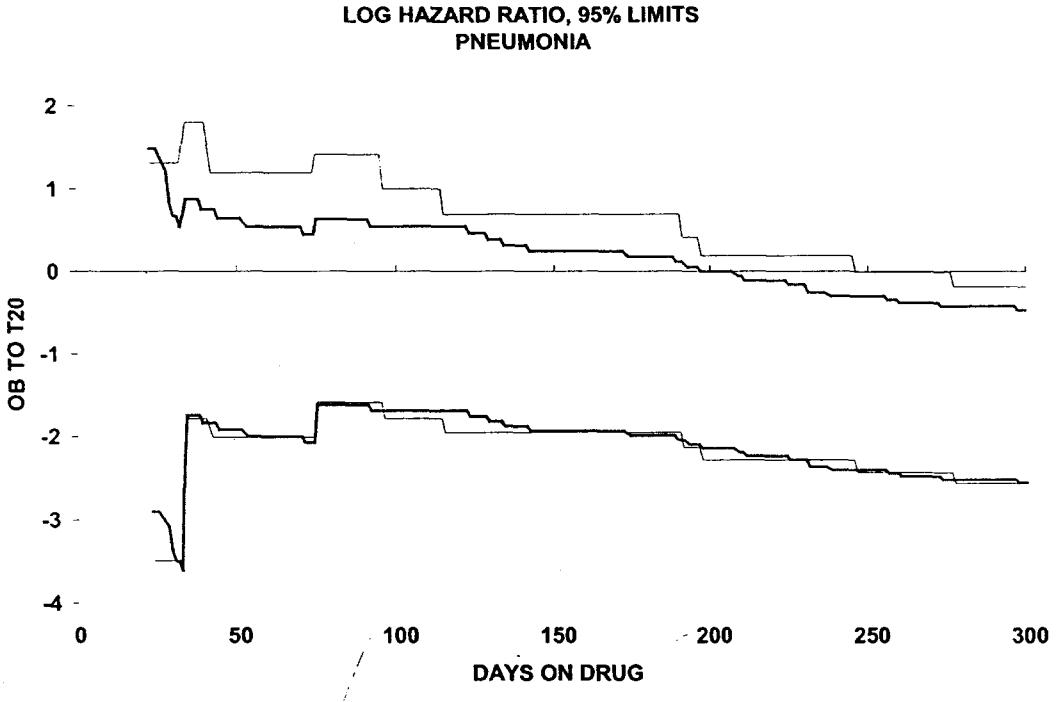


Figure 4.4 F

APPEARS THIS WAY
ON ORIGINAL

One can see from figures 4.4 B and C and from the rightmost column of table 4.4 A that there is no statistically convincing difference in the incidence rates of first bacterial infection. Because this is a safety endpoint rather than an efficacy endpoint, there is some cause for concern about the signal that appears in these plots. One can see from figures 4.4 D and E that the log hazard ratios remain inside confidence bands that do not appear to increase or decrease over the first 300 days of observation.

One can see from table 4.4 A that the incidence per person-year of exposure for pneumonia and for sepsis are both about twice as high for subjects on Fuzeon as for subjects on OB. Switch subjects had incidence rates for sepsis comparable to Fuzeon subjects but incidence rates for pneumonia comparable to OB subjects. Figures 4.4 G and H show that there is a statistically significant increase in the rate of pneumonias after about 150-200 days on trial. Figures 4.4 I and J also show a suggestion of a decreasing hazard ratio (higher risk for Fuzeon or Switch arms relative to OB) at later times periods. One will notice that it is possible to draw a horizontal line through the confidence bands for OB/Fuzeon log hazard ratio. This means that one cannot assert that the decreasing hazard ratio is statistically significant. (Sepsis was rare enough that Kaplan-Meier curves for this endpoint were uninformative.)

In interpreting the above data, one needs to be aware of several reasons for caution. First, there is a clinical caution: because bacterial infections and pneumonia were not efficacy endpoints, they were not adjudicated formally. Second, there is a statistical caution: there is informative censoring with respect to this endpoint. Bacterial infections are a safety endpoint, not an efficacy endpoint. Subjects were initially randomized to the two arms but they were withdrawn from the OB arm and switched to Fuzeon on the basis failure with respect to the efficacy endpoint, HIV load. Consequently, the sickest patients in the OB arm were switched to Fuzeon without waiting to see if they got pneumonia or other bacterial infection. One would reasonably expect that these switched patients would be those at higher risk of opportunistic infection. If the withdrawal of these patients from the OB arm is treated as if it

were random censoring, as the Kaplan-Meier analysis does, then one would underestimate the risk of bacterial infection in the OB arm at later time periods. Furthermore, the rates in the Switch would over-estimate the risk from Fuzeon.

The FDA statistical reviewer also explored the possibility that some of the observed differences in infection rates may be explicable by other covariates. The reviewer performed Cox proportional hazards regressions on times to first bacterial infection and first pneumonia, using as covariates 1) treatment arm, 2) baseline CD4 count, 3) average change in CD4 count from baseline to time of infection or censoring, 4) baseline HIV RNA, 5) average change in HIV RNA, 6) age, 7) sex, and 8) viral failure or not. Statistically insignificant covariates were discarded. One should note that three of the covariates are treatment emergent covariates, not baseline covariates. (The clinical reviewer also suggested prophylactic antibiotic use as a ninth covariate. However, dates of starting and ending use were missing for over half of the antibiotics reported as concomitant meds.)

These analyses may be briefly summarized in table 4.4 B. This table give the hazard ratio for all covariates used in the final model. It also gives the 95% upper and lower confidence limits and the p-value. In this table, the Fuzeon and Switch arms were pooled together.

TABLE 4.4 B
COX REGRESSIONS ON TIMES TO INFECTION
BOTH_TRIALS_POOLED

	Hazard Ratio	95% Limits Lower	Upper	p-value	
ANY_BACTERIAL_INFECTION					
Trt	1.23	0.87	1.76	0.2459	
Baseline_cd4/100	0.86	0.77	0.96	0.0076	*
TAD_cd4/100	0.63	0.51	0.76	0.0000	*
Baseline_log_hiv_rna	1.45	1.15	1.82	0.0016	*
TAD_log_hiv_rna	1.30	1.10	1.55	0.0025	*
Sex	0.63	0.43	0.92	0.0173	*
Viral_failure	0.45	0.29	0.71	0.0007	*
PNEUMONIA					
Trt	2.79	0.99	7.87	0.0528	?
Baseline_cd4/100	0.58	0.43	0.78	0.0003	*
TAD_cd4/100	0.53	0.35	0.81	0.0032	*

One can see that there is a small (23%) and statistically insignificant elevation in risk of any bacterial infection with Fuzeon. There is a larger (179%) increase in the risk of pneumonia with Fuzeon. This might not be real (the lower bound of the hazard ratio is .99) but a p-value of .053 with a safety endpoint is generally enough to raise concerns.

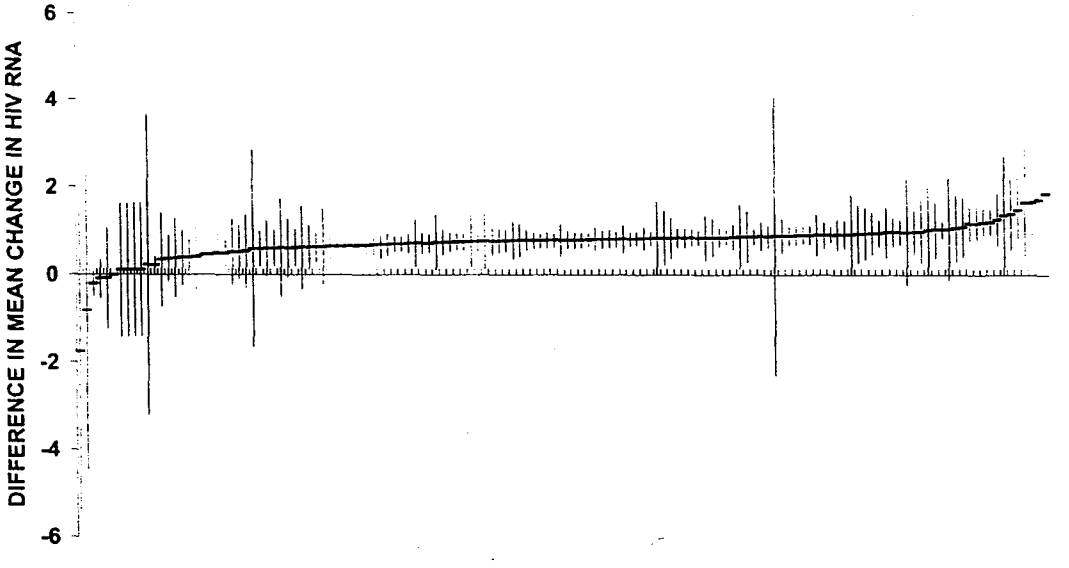
It is difficult to reach a definitive conclusion with respect to this issue. The increased risk is most noticeable with respect to pneumonia; there is no clear evidence that bacterial infections in general are more likely with Fuzeon. Discussion with clinical reviewers has suggested no mechanism by which only pneumonia risk would be elevated. The increase in risk of pneumonia attains statistical significance only after substantial non-random loss of subjects from the control arm. The subjects withdrawn from the control arm were sicker than those retained on the OB. (When an ITT analysis was done, counting subjects started on OB as still in the OB even after adding Fuzeon, a statistically significant difference between the arms occurred only after day 300; when subjects started on OB were considered censored after adding Fuzeon, a statistically significant difference between the arms occurred after day 150.)

The most reasonable conclusion is that users should be aware of the possibility of increased risk of pneumonia but that the evidence is insufficient to warrant considering the drug unsafe.

5. Results in Special Populations

There was no evidence of interactions between treatment and any interesting covariates. Fuzeon appeared to be roughly equally effective in both sexes, both races, at all levels studied for age, baseline HIV RNA, baseline CD4 count, baseline gp41 level, baseline genotypic sensitivity score (GSS), baseline phenotypic sensitivity score (PSS), risk factor, previous AIDS diagnosis, geographic region, reason discontinued, type of OB therapy, prior mutations, or concurrent disease (including cardiovascular, diabetes, or hepatitis B or C). Figure 5 A shows a plot of estimated difference between Fuzeon and OB in mean change from baseline in HIV RNA levels, together with 95% confidence intervals for the difference, for all the 140 subgroups created by subdivision according to any of the above covariates. (Very small subgroups have been deleted.)

FUZEON - OB MEAN CHANGE IN RNA
WITH 95% CONFIDENCE LIMITS



7

APPEARS THIS WAY
ON ORIGINAL

The mean differences in this plot looks just like what one would expect if one took 140 observations from a normal distribution with expected value of .75. Thus, the plot supports the contention that there were no identifiable sub-populations in which Fuzeon was not effective. Tables 5 A, 5 B, 5 C, and 5 D give differences in mean effect between Fuzeon and OB. (The difference is always computed so that positive numbers correspond to Fuzeon benefit.) The tables also give 95% confidence limits for those differences, mean effects on OB and on Fuzeon, sample sizes on OB and on Fuzeon, and p-values for the treatment differences for 4 endpoints for subgroups based on sex, race, age, baseline HIV RNA, CD4 count, and Gp41, GSS, and PSS. The four endpoints are change from baseline to week 24 in HIV RNA (with missing data imputed as back to baseline), percentage of subjects with viral load [redacted] percentage of subjects with viral load [redacted] and change from baseline to week 24 in CD4 count. For the primary endpoint, table 5 A also includes results subdivided by previous AIDS diagnoses, geographic reason, risk factor for HIV infection, reason discontinued, and structure of optimized background regimen.

TABLE 5 A

WEEK 24 CHANGE FROM BASELINE IN HIV RNA

BOTH TRIALS POOLED

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	T-20	OB	T-20	OB	P-value
SEX								
Female	0.52	-0.10	1.14	-1.58	-1.06	68	34	.098
Male	0.83	0.66	1.00	-1.52	-0.69	597	303	<.0001
RACE								
White	0.82	0.64	0.99	-1.52	-0.70	594	298	<.0001
Non-White	0.63	0.11	1.15	-1.56	-0.93	71	39	.017
AGE								
<37	0.40	-0.02	0.82	-1.35	-0.95	149	62	.06
37-40	0.77	0.44	1.09	-1.51	-0.74	167	85	<.0001
41-46	0.95	0.63	1.27	-1.59	-0.64	161	92	<.0001
>=47	0.97	0.67	1.26	-1.63	-0.66	188	98	<.0001
Baseline CD4								
<23	0.74	0.44	1.04	-1.19	-0.45	185	87	<.0001
23-100	0.65	0.32	0.97	-1.30	-0.66	165	86	.0001
101-232	1.21	0.91	1.51	-1.99	-0.78	174	111	<.0001
>=233	0.47	0.05	0.88	-1.65	-1.18	141	53	.027
Baseline log HIV RNA								
<=4.6	0.67	0.38	0.97	-1.50	-0.83	146	83	<.0001
4.6-5.1	0.92	0.60	1.25	-1.64	-0.71	172	83	<.0001
5.1-5.5	0.63	0.27	0.98	-1.44	-0.82	179	88	.0006
>5.5	0.97	0.63	1.31	-1.53	-0.56	168	83	<.0001

TABLE 5 A (cont.)
WEEK 24 CHANGE FROM BASELINE IN HIV RNA
BOTH TRIALS POOLED

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	T-20	OB	T-20	OB	P-value
Baseline GP41								
	0.54	-0.30	1.38	-1.54	-0.99	28	28	.20
Negative	0.98	-0.24	2.20	-1.39	-0.42	8	4	.12
Positive	0.87	0.68	1.06	-1.56	-0.69	491	229	<.0001
Non-quant	0.65	0.29	1.00	-1.41	-0.76	138	76	.0004
GSS								
0	0.68	0.45	0.90	-0.76	-0.09	113	54	<.0001
1	0.88	0.61	1.15	-1.31	-0.43	194	95	<.0001
2	0.88	0.55	1.21	-1.84	-0.97	184	93	<.0001
3	0.60	0.19	1.02	-1.74	-1.14	112	65	.0045
4	1.03	0.38	1.67	-2.24	-1.21	62	30	.0017
PSS								
0	0.80	0.60	0.99	-0.92	-0.12	192	100	<.0001
1	0.91	0.60	1.22	-1.40	-0.49	163	68	<.0001
2	0.92	0.56	1.27	-1.89	-0.97	138	82	<.0001
3	0.46	-0.01	0.92	-1.97	-1.51	103	53	.054
4	0.94	0.33	1.55	-2.12	-1.18	69	34	.0024
DGAIDSEV								
No	1.17	0.78	1.57	-1.89	-0.71	138	49	<.0001
Yes	0.70	0.52	0.88	-1.43	-0.73	527	288	<.0001
PREVADE								
None	1.17	0.78	1.57	-1.89	-0.71	138	49	<.0001
CUR	0.67	-0.05	1.39	-1.55	-0.88	34	23	.067
PRE	0.70	0.52	0.89	-1.42	-0.72	493	265	<.0001

TABLE 5 A (cont)
WEEK 24 CHANGE FROM BASELINE IN HIV RNA
BOTH TRIALS POOLED

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	T-20	OB	T-20	OB	P-value
REGION								
Netherlands	1.85	0.82	2.88	-2.28	-0.44	9	5	.0004
Switzerland	1.65	0.40	2.90	-2.23	-0.58	12	10	.0099
Belgium	1.02	0.02	2.02	-2.00	-0.98	16	9	.045
Italy	0.97	0.38	1.55	-1.32	-0.35	41	19	.0012
Australia	0.74	0.11	1.38	-1.52	-0.78	37	21	.022
Spain	0.72	0.17	1.26	-1.34	-0.62	60	29	.0095
Britain	0.64	-0.23	1.51	-1.50	-0.86	32	17	.15
France	0.59	0.18	1.01	-0.96	-0.37	86	41	.005
Germany	0.40	-0.25	1.04	-0.94	-0.55	41	19	.23
Brazil	1.71	0.05	3.37	-2.12	-0.41	6	3	.043
Southern Cal	1.66	0.89	2.42	-1.95	-0.30	23	10	<.0001
Smoky Mount	1.39	0.57	2.20	-2.10	-0.72	27	13	.0008
Mexico	1.36	0.00	2.72	-1.80	-0.45	11	5	.051
Southeast	0.99	0.26	1.73	-1.90	-0.90	37	20	.0081
Canada	0.94	0.26	1.61	-2.05	-1.12	45	21	.0067
Great Lakes	0.93	0.03	1.84	-1.61	-0.67	23	12	.044
Northern Cal	0.84	0.01	1.68	-1.55	-0.70	28	15	.048
Southwest	0.63	-0.33	1.58	-1.53	-0.90	19	11	.20
Mid-Atlantic	0.61	-0.08	1.30	-1.38	-0.77	38	19	.081
Western	0.61	-0.51	1.74	-1.24	-0.62	12	7	.28
Northwest	0.41	-0.47	1.30	-1.83	-1.42	23	12	.36
Metropolitan	0.35	-0.74	1.44	-1.26	-0.91	17	9	.53
New England	-0.08	-1.25	1.08	-1.68	-1.77	19	10	.89

TABLE 5 A (cont)
WEEK 24 CHANGE FROM BASELINE IN HIV RNA
BOTH TRIALS POOLED

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean Change T-20	Mean Change OB	N T-20	N OB	P-value
RISK								
Bisexual	0.60	-0.05	1.25	-0.99	-0.39	27	16	.07
Transfusion	1.04	-0.13	2.22	-1.55	-0.51	21	5	.082
Heterosexual	0.78	0.39	1.18	-1.45	-0.67	117	66	.0001
Homosexual	0.75	0.55	0.96	-1.55	-0.80	435	224	<.0001
IV Drug	1.27	0.66	1.88	-1.88	-0.61	46	23	<.0001
Other	1.48	0.73	2.22	-1.30	0.17	17	2	.0001
REASON DISCONTINUED								
Complete	1.03	0.83	1.22	-1.91	-0.89	509	255	<.0001
AE	0.22	0.01	0.44	-0.29	-0.07	77	30	.045
Death	0.38	-0.53	1.29	-0.70	-0.32	6	3	.42
LOE	-0.20	-0.50	0.09	-0.02	-0.22	32	20	.18
LTFU	-0.09	-0.55	0.37	-0.31	-0.41	41	29	.69
OB REGIMEN								
NRTI+NNRTI+PI	0.80	0.42	1.17	-1.69	-0.90	154	75	<.0001
NRTI+NNRTI	0.87	0.13	1.61	-1.32	-0.45	29	14	.021
NRTI+PI	0.78	0.58	0.97	-1.49	-0.72	459	235	<.0001
NNRTI+PI	0.89	-2.30	4.08	-2.40	-1.51	6	2	.58
NRTI Only	1.09	0.40	1.78	-1.11	-0.02	14	10	.0019

TABLE 5 B

PERCENT — COPIES/ML AT WEEK 24

BOTH TRIALS POOLED

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	T-20	OB	T-20	OB	P-value
SEX								
Female	.09	-.09	.27	.32	.24	68	34	.34
Male	.16	.11	.20	.24	.08	597	303	<.0001
RACE								
White	.15	.10	.19	.25	.08	594	298	<.0001
Non-White	.08	-.06	.23	.21	.13	71	39	.25
AGE								
<37	.08	-.03	.19	.22	.15	149	62	.18
37-40	.11	.02	.20	.22	.11	167	85	.018
41-46	.15	.06	.24	.25	.10	161	92	.0011
>=47	.24	.16	.32	.30	.06	188	98	<.0001
Baseline CD4								
<23	.04	-.03	.11	.11	.07	185	87	.27
23-100	.10	.02	.18	.17	.07	165	86	.013
101-232	.27	.18	.36	.38	.11	174	111	<.0001
>=233	.19	.06	.32	.36	.17	141	53	.0037
Baseline log HIV RNA								
<=4.6	.32	.21	.43	.44	.12	146	83	<.0001
4.6-5.1	.20	.10	.30	.32	.12	172	83	.0001
5.1-5.5	.04	-.04	.13	.16	.11	179	88	.33
>5.5	.07	.01	.13	.11	.04	168	83	.025
GSS								
0	.07	.02	.12	.07	.00	113	54	.0035
1	.16	.09	.23	.21	.04	194	95	<.0001
2	.22	.12	.31	.34	.12	184	93	<.0001
3	.07	-.06	.20	.27	.20	112	65	.30
4	.24	.05	.42	.40	.17	62	30	.011
PSS								
0	.13	.08	.17	.12	.00	192	100	<.0001
1	.16	.08	.24	.21	.04	163	68	.0001
2	.24	.13	.35	.38	.15	138	82	<.0001
3	.09	-.05	.24	.32	.23	103	53	.21
4	.13	-.04	.30	.30	.18	69	34	.14

TABLE 5 C

PERCENT ——— COPIES/ML AT WEEK 24

BOTH TRIALS POOLED

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	T-20	OB	T-20	OB	P-value
SEX								
Female	.07	-.12	.27	.40	.32	68	34	.47
Male	.23	.17	.28	.37	.15	597	303	<.0001
RACE								
White	.22	.16	.28	.37	.15	594	298	<.0001
Non-White	.10	-.06	.27	.31	.21	71	39	.22
AGE								
<37	.07	-.06	.20	.32	.24	149	62	.27
37-40	.21	.10	.31	.37	.16	167	85	.0002
41-46	.23	.12	.33	.38	.15	161	92	<.0001
>=47	.30	.20	.39	.42	.12	188	98	<.0001
Baseline CD4								
<23	.14	.06	.22	.21	.07	185	87	.0005
23-100	.17	.07	.27	.28	.12	165	86	.0007
101-232	.34	.24	.45	.52	.18	174	111	<.0001
>=233	.15	.00	.31	.51	.36	141	53	.054
Baseline log HIV RNA								
<=4.6	.28	.16	.41	.55	.27	146	83	<.0001
4.6-5.1	.26	.15	.37	.42	.17	172	83	<.0001
5.1-5.5	.16	.06	.26	.32	.16	179	88	.0024
>5.5	.17	.09	.25	.23	.06	168	83	<.0001
GSSCOVR								
0	.11	.05	.16	.11	.00	113	54	.0003
1	.25	.16	.33	.33	.08	194	95	<.0001
2	.26	.14	.37	.49	.24	184	93	<.0001
3	.18	.03	.32	.46	.28	112	65	.015
4	.27	.07	.47	.50	.23	62	30	.0085
PSSCOVR								
0	.19	.13	.24	.19	.00	192	100	<.0001
1	.22	.11	.33	.36	.13	163	68	.0001
2	.31	.19	.43	.53	.22	138	82	<.0001
3	.13	-.04	.29	.50	.38	103	53	.13
4	.20	.01	.39	.43	.24	69	34	.036

TABLE 5 D

WEEK 24 CHANGE FROM BASELINE IN CD4 COUNT

BOTH TRIALS POOLED

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	T-20	OB	T-20	OB	P-value
SEX								
Female	-5	-55	45	80	85	66	32	.84
Male	35	23	46	71	37	583	294	<.0001
RACE								
White	32	20	45	72	40	579	289	<.0001
Non-White	19	-10	47	76	57	70	37	.19
AGE								
<37	0	-33	33	66	66	146	58	.995
37-40	21	1	42	69	48	165	83	.041
41-46	40	17	62	81	41	157	89	.0004
>=47	52	32	71	73	21	181	96	<.0001
Baseline CD4								
<23	27	14	40	52	25	178	82	.0001
23-100	40	24	56	75	35	160	84	<.0001
101-232	42	19	65	98	57	172	108	.0004
>=233	17	-22	56	64	47	139	52	.40
Baseline log HIV RNA								
<=4.6	22	-3	47	53	31	143	80	.083
4.6-5.1	46	24	68	85	39	168	79	<.0001
5.1-5.5	14	-5	33	65	51	175	86	.15
>5.5	40	14	65	84	44	163	81	.0023
GSS								
0	36	16	56	47	11	109	51	.0005
1	34	15	54	68	33	188	93	.0006
2	37	14	60	88	51	182	90	.0017
3	16	-16	47	64	49	112	63	.33
4	26	-10	62	103	77	58	29	.15
PSS								
0	45	29	60	59	15	188	98	<.0001
1	34	12	55	66	33	159	65	.0022
2	18	-12	48	84	65	135	78	.23
3	16	-17	49	78	62	101	52	.35
4	42	13	71	93	51	66	33	.0045

6. Statistical Reviewer's Summary

The applicant has conducted two trials to test the efficacy of Fuzeon. Both trials were conducted in patients who had at least 6 months experience with, or resistance to, drugs in all three classes: NRTI's, PI's, and NNRTI's. (One trial required resistance to at least 2 PI's, the other to only 1 PI.) The other difference between the trials was that one was recruited in North and South America, the other in Europe and Australia.

An optimized background (OB) regimen was identified by genotypic and phenotypic testing. Subjects were randomly assigned in a 2:1 ratio to get 90 mg Fuzeon or nothing in addition to their background regimen. No blinding or placebo was used because Fuzeon is administered by subcutaneous injection and almost all subjects have an injection site reaction.

Fuzeon (+OB) was statistically and clinically significantly superior to OB alone in both trials with respect to the protocol specified primary endpoint of mean change from baseline in HIV RNA, with respect to the endpoint more commonly used in contemporary anti-HIV NDA's, percent of subjects with sustained viral suppression to below LOQ [redacted] and with respect to change from baseline in CD4 count.

The findings on the primary endpoint were robust to handling of missing data. They were also robust to sensitivity analyses intended to explore the possibility of biased drop-out by nonblinded subjects and of deliberate non-compliance by nonblinded control subjects.

There was no suggestion of treatment-covariate interactions in any of the subgroups studied. There is no evidence about the efficacy of this drug in less experienced populations.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:
Archival NDA #21-481
HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Dr. Baylor
HFD-530/Dr. Gitterman
HFD-530/Ms. Yoerg
HFD-725/Dr. Hammerstrom
HFD-700/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Ms. Robinette

APPEARS THIS WAY
ON ORIGINAL

APPENDIX: Variations in Calculated Numbers

The FDA reviewer and the applicant often obtain slightly different results for derived values such as Percent with one log drop in HIV RNA levels at week 24 or time averaged change from baseline in log HIV RNA. These discrepancies arise from minor differences in the algorithms used. For example, 1) should a few subjects discontinuing study after one dose be included in the dataset? 2) should one log drop in HIV RNA be based on a snapshot view nearest to week 24 or should two confirming observations be required? 3) should missing data for subjects lost to follow-up be set equal to baseline at week 24 only or at every visit from time of loss to week 24? 4) should time averaged change be computed with time in days or time rounded off to nearest week?

As long as the same algorithm is followed for all arms on the trial, none of these differences are of practical importance. One can easily see that any differences between the FDA reviewers calculations and those used by the applicant in the label do not change the estimate of the efficacy of the drug.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Hammerstrom
4/11/03 04:41:13 PM
BIOMETRICS

Greg Soon
4/14/03 10:15:43 AM
BIOMETRICS

Mohammad Huque
4/15/03 11:03:21 AM
BIOMETRICS