CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-548

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-548
NAME OF DRUG:	Lexiva™ (Fosamprenavir)
INDICATION:	Treatment of HIV Infection
APPLICANT:	GlaxoSmithKline
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STATISTICAL REVIEW AND EVALUATION

NDA#: 21-548

1. Executive Summary

The applicant has demonstrated in one clinical trial with ART naive patients that lexiva at 1400 mg bid, when added to a background regimen of two NRTI's, produces a statistically and clinically significant reduction in viral load, including a significant increase in the proportion of patients whose viral load is undetectable by the Amplicor or the Ultrasensitive assay. This clinical benefit is sustained to at least 48 weeks. A second clinical trial in this same population demonstrated a similar statistically and clinically significant reduction in viral load for lexiva at 1400 mg qd, boosted by ritonavir at 200 mg qd. Both trials showed the lexiva effects by comparison to a nelfinavir control.

The trials were conducted across several continents within a diverse adult population. There was no convincing evidence that the observed clinical benefit is reduced in any of the racial, gender, or age categories examined.

The applicant has also conducted one clinical trial with patients who have already failed at least regimen containing a PI comparing lexiva at 700 mg bid boosted with ritonavir at 100 mg bid to Kaletra (lopinavir at 400 mg bid plus ritonavir at 100 mg bid), when each regimen was added to a background regimen of two NRTI's. The estimated reduction in viral load in the bid boosted lexiva arm and the Kaletra arm were nearly equal, particularly as measured by proportion of patients with undetectable viral load at week 48. Although the confidence limits were too wide to permit direct conclusion of statistical equivalence between bid boosted lexiva and Kaletra, meta-analysis supports the inference that boosted bid lexiva would have been statistically significantly superior to placebo with respect to these endpoints.

A second arm in this trial used lexiva at 1400 mg qd boosted by ritonavir at 200 mg qd. This arm performed at a statistically and clinically significantly inferior level to both the bid boosted lexiva and the Kaletra control. One should conclude that ART experienced patients should be treated with the bid boosted lexiva regimen rather than the qd regimen.

Again, there was no convincing evidence in this experienced population that boosted lexiva effects differed consequentially among racial, gender, or age categories.

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2. Background

The applicant submitted three randomized, controlled phase III clinical trials with lexiva for this application: trials 30001, 30002 and 30003.

3. Applicant's Statistical Evaluation

3.1 Objectives in Trials

The primary objective of study 30001 was to compare the efficacy of lexiva (LEX) at a dose of 1400 mg bid to that of nelfinavir (NFV) at 1250 mg bid in treatment naive patients. The comparator drugs in both arms were added to a background regimen of two other drugs: 3TC at 150 mg bid and abacavir (ABC) at 300 mg bid.

The primary objective of study 30002 was to compare the efficacy of lexiva (LEX) at a dose of 1400 mg qd plus ritonavir at 200 mg qd (LEX/r) to that of nelfinavir (NFV) at 1250 mg bid in treatment naive patients. The comparator drugs in both arms were added to a background regimen of two other drugs: 3TC at 150 mg bid and abacavir (ABC) at 300 mg bid.

In trials 30001 and 30002, the primary efficacy endpoint was percent of subjects achieving sustained viral load below 400 copies/mL through 48 weeks. The study populations in both trials were HIV-1 infected patients with no prior experience to anti-retroviral therapy (ART). They were also required to have confirmed viral load of at least 5000 copies/mL in trial 30001 and of at least 1000 copies/mL in trial 30002.

The primary objective in trial 30003 was to compare the efficacy of two boosted lexiva regimens: LEX at a dose of 1400 mg qd plus ritonavir at 200 mg qd (LEX/r qd) or LEX at a dose of 700 mg bid plus ritonavir at 100 mg bid (LEX/r bid) to that of lopinavir at 400 mg bid plus ritonavir at 100 mg bid (LPV/r) in PI (protease inhibitor) experienced patients. The comparator drugs in both arms were added to a background regimen of two NRTI's.

In trial 30003, the primary efficacy endpoint was change from baseline in log HIV RNA level. The study population was HIV-1 infected patients with prior failure to a protease-inhibitor (PI) containing highly active anti-retroviral therapy (HAART). They were also required to have confirmed viral load of at least 1000 copies/mL.

3.2 Summary of Study Design

Trial 30001 was an open-label, randomized, two-arm, parallel, active controlled, multi-center trial, conducted at 29 sites, 24 in the US, 3 in Puerto Rico, and 1 each in Panama and South Africa. Subjects were randomly assigned in a 2:1 ratio to 1400 mg bid lexiva + background or 1250 mg NFV bid + background. Randomization was stratified by baseline HIV RNA level (5-10K, 10-100K, or > 100K copies/mL).

Trial 30002 was an open-label, randomized, two-arm, parallel, active controlled, multi-center trial, conducted at 101 centers in North America (44 centers), western Europe (42 centers), eastern Europe (8 centers), and Africa/Asia/Australia (7 centers). Subjects were randomly assigned in a 1:1 ratio to 1400/200 mg qd lexiva/ritonavir + background or 1250 mg bid nelfinavir + background. The randomization was stratified by baseline HIV RNA level (1-10K, 10-100K, or > 100K copies/mL).

Trial 30003 was an open-label, randomized, three-arm, parallel, active controlled, multi-center trial, conducted at 103 centers in North America (55 centers), western Europe (38 centers), Latin America (2 centers), and Australia (8 centers). Subjects were randomly assigned in a 1:1:1 ratio to 1400/200 mg qd lexiva/ritonavir + background, 700/100 mg bid lexiva/ritonavir + background or 400/100 mg bid lopinavir/ritonavir + background. The randomization was stratified by baseline HIV RNA level (1-10K, 10-100K, or > 100K copies/mL).

3.3 Patient Accounting and Baseline Characteristics

251 patients were randomized in trial 30001. Of these, 2 patients never started treatment. Of the 249 eligible patients who started treatment, 87 discontinued treatment before week 48. Table 3.3 A summarizes the primary reasons for discontinuation from study 30001 and from treatment.

TABLE 3.3 A
PATIENT STATUS, TRIAL 30001

	LEX		NFV	
Randomized	168		83	
In Treated ITT	166		83	
Completed	116	(70%)	45	(54%)
Withdrew by Week 48	49	(30%)	38	(46%)
AE	9		6	
LTFU	27		15	
LOE	13		17	
Withdrew after Week 48	1		0	
LTFU	1		0	

In trial 30001, the study population was 69% male with a median age of 37 years. They were 44% Latino, 24% white, and 32% black. (This classification ignores the fact that Latino is a language group, not an ethnic group.) 7% were current or former IV drug users. The median CD4 count at baseline was 212 cells/mm^3; the median HIV RNA level was 4.83 logs. 20% of patients had prior AIDS defining events. 5% were positive for hepatitis B and 14% were reactive for hepatitis C.

The subjects were enrolled at 29 sites, 24 in the US, 3 in Puerto Rico, and 1 each in Panama and South Africa. Subjects were randomly assigned in a 2:1 ratio to 1400 mg bid lexiva + background or 1250 mg NFV bid + background. Randomization was stratified by baseline HIV RNA level (5-10K, 10-100K, or > 100K copies/mL). The exact distribution of patients by continent is given in table 3.3 B.

TABLE 3.3 B
PATIENTS BY CONTINENT, TRIAL 30001

Continent	Pats
N America	230
Other	21

660 patients were randomized in trial 30002. Of these, 11 patients never started treatment. Of the 649 eligible patients who started treatment, 176 discontinued treatment before week 48. Table 3.3 C summarizes the primary reasons for discontinuation from study 30002 and from treatment.

TABLE 3.3 C
PATIENT STATUS, TRIAL 30002

	LEX/r	NFV
Randomized	329	331
In Treated ITT	322	327
Completed	231 (72%)	242 (74%)
Withdrew by Week 48	91 (28%)	85 (26%)
AE	28	16
LTFU	62	42
LOE	1	27

In trial 30002, the study population was 73% male with a median age of 36 years. They were 8% Latino, 53% white, and 36% black. 14% were current or former IV drug users. The median CD4 count at baseline was 170 cells/mm^3; the median HIV RNA level was 4.81 logs. 22% of patients had prior AIDS defining events. 8% were positive for hepatitis B and 18% were reactive for hepatitis C.

The subjects were enrolled at 101 centers in North America (44 centers), western Europe (42 centers), eastern Europe (8 centers), and Africa/Asia/Australia (7 centers). Subjects were randomly assigned in a 1:1 ratio to 1400/200 mg qd lexiva/ritonavir + background or 1250 mg bid nelfinavir + background. The randomization was stratified by baseline HIV RNA level (1-10K, 10-100K, or > 100K copies/mL). The exact distribution of patients by continent is given in table 3.3 D.

TABLE 3.3 D
PATIENTS BY CONTINENT, TRIAL 30002

Continent	Pats
N America	283
Europe	276
Other	101

320 patients were randomized in trial 30003. Of these, 5 patients never started treatment. Of the 315 eligible patients who started treatment, 38 discontinued treatment before week 24. Table 3.3 E summarizes the primary reasons for discontinuation from study 30003 and from treatment.

TABLE 3.3 E
PATIENT STATUS, TRIAL 30003

	LEX/r qd	LEX/r bid	LPV/r
Randomized	107	107	106
In Treated ITT	105	107	103
Completing Week 48	78	79	85
Withdrew by Week 48	27	28	18
AE/Death	2	6	8
LTFU	13	10	9
LOE	12	12	1

The subjects were enrolled at 103 centers in North America (55 centers), western Europe (38 centers), Latin America (2 centers), and Australia (8 centers). The exact distribution of patients and sites by country is given in table 3.3 F.

TABLE 3.3 F
PATIENTS BY CONTINENT, TRIAL 30003

Continent	Pats
Europe	110
N America	178
Other	32

In trial 30003, the study population was 84% male with a

median age of 41 years. They were 9% Latino, 67% white and 24% black. 11% were current or former IV drug users. The median CD4 count at baseline was 263 cells/mm^3; the median HIV RNA level was 4.14 logs. 33% of patients had prior AIDS defining events. 5% were positive for hepatitis B and 16% were reactive for hepatitis C.

The background of two RTI's included lamivudine (3TC), tenofovir (TFV), didanosine (DDI), abacavir (ABC), stavudine (D4T), and zidovudine (ZDV). The exact percentages in each combination are given in table 3.3 F.

TABLE 3.3 F
COMPOSITION OF THE NRTI BACKGROUND, TRIAL 30003

	LEX/r qd	LEX/r bid	LPV/r
3TC/TFV	11%	21%	14%
DDI/TFV	15%	14%	14%
ABC/TFV	15%	10%	14%
D4T/TFV	11%	13%	12%
ABC/D4T	10%	5%	8%
D4T/DDI	8%	5%	3%
3TC/ZDV	3%	<1%	8%

3.4 Summary of Methods of Assessment

3.4.1 Schedule of Measurements

Patients had HIV RNA and CD4 counts was measured at weeks 0, 1, 2, 4, every 4 weeks to week 24, and every 8 weeks thereafter. Plasma samples were assessed by the Roche Ultrasensitive assay. HIV RNA levels > 75 K copies/mL were remeasured by the Roche Amplicor assay.

3.4.2 Criteria for Switching Regimen

Subjects in trial 3001-3 were allowed to substitute one background NRTI for another if toxicity to the original NRTI was observed. The number of such switches is given in table 3.4 A.

TABLE 3.4 A

SWITCHES IN NRTI BACKGROUND, TRIAL 30002

No. NRTI's Switched	LEX/r	NFV
1	30 (9%)	28 (9%)
2	1 (<1%)	3 (<1%)

3.4.3 Assessment of Treatment Effects

In trials 30001 and 30002, the protocol specified primary endpoint at week 48 was percent of subjects with sustained viral load below 400 copies/mL. Subjects were considered to have experience viral rebound to above 400 copies if lost to follow-up. Two secondary viral endpoints were also used. These were percent <50 copies/mL and time averaged change from baseline.

In trial 30003, the protocol specified primary endpoint at week 24 was time averaged change from baseline in log HIV RNA level. The applicant conducted analyses using last observation carried forward (LOCF) to replace missing data and using baseline values to replace missing data. Three secondary viral endpoints were also used. These were percent successful with success defined as <50 copies/mL, <400 copies/mL, or at least a 1 log drop from baseline. Loss to follow-up counted as failure.

3.5 Summary of Statistical Analysis

Analyses were stratified by baseline HIV RNA levels as in the random assignment. Inferences were based on stratified Student t- statistics and their corresponding confidence intervals. Lower confidence bounds above -10% for difference from an active control in percent BLQ were considered evidence of superiority to placebo. Upper confidence bounds below .5 log copies for difference in time averaged difference from baseline were considered evidence of superiority to placebo.

3.6 Summary of Applicant's Results

The results for trial 30001 are given in tables 3.6 A and B. Table 3.6 A gives the numbers and percentages of subjects with viral load sustained below 400 copies/mL on the LEX 400 mg and control arms on all three trials. It also gives the 95% confidence intervals for the differences between percent successful on LEX and control. Table 3.6 B gives the same results for the endpoint using 50 copies/mL. In these tables, large negative values of the lower confidence limit would be evidence that LEX may not work as well as the control arm.

TABLE 3.6 A
PERCENT < 400 COPIES, TRIAL 30001, WEEK 48

Stratum	LEX	NFV	95% CI for LEX-NFV
Pooled	109/166 = 66%	42/83 = 51%	2%, 28%
5-10 K	11/15 = 73%	3/8 = 38%	-4%, 76%
10-100 K	49/78 = 63%	26/38 = 68%	-24%, 13%
>100 K	49/73 = 67%	13/37 = 35%	13%, 51%

TABLE 3.6 B
PERCENT < 50 COPIES, TRIAL 30001, WEEK 48

Stratum	LEX	NFV	95% CI for LEX-NFV
Pooled	92/166 = 55%	34/83 = 41%	2%, 27%
5-10 K	11/15 = 73%	3/8 = 38%	
10-100 K	41/78 = 53%	22/38 = 58%	
>100 K	40/73 = 55%	9/37 = 24%	

The results for this trial using change from baseline in log HIV RNA, out to week 48, are given in table 3.6 C. This table gives the observed mean change from baseline at week 48, ignoring subjects lost to follow-up; the sample size for this single visit value; and the 95% confidence interval for the difference between the arms in the time averaged change from baseline (TAD).

In the confidence intervals in this table, negative values for Log HIV are evidence of superiority of LEX to control. Large positive upper limits are evidence that LEX may not work as well

as the control. For CD4 count, positive values in the confidence limits are evidence of LEX superiority.

TABLE 3.6 C
TRIAL 30001
CHANGE FROM BASELINE TO WEEK 48 IN LOG HIV

Variable	LEX	NFV	95% CI for LEX-NFV
Log HIV	-2.41 (163)	-2.32 (79)	-.33, .17
CD4 Count	140	139	

The results for trial 30002 are given in tables 3.6 D and E. Table 3.6 D gives the numbers and percentages of subjects with viral load sustained below 400 copies/mL on the LEX/r 400 mg and control arms on all three trials. It also gives the 95% confidence intervals for the differences between percent successful on LEX/r and control. Table 3.6 E gives the same results for the endpoint using 50 copies/mL. In these tables, large negative values of the lower confidence limit would be evidence that LEX/r may not work as well as the control arm.

TABLE 3.6 D
PERCENT < 400 COPIES, TRIAL 30002, WEEK 48

Stratum	LEX/r	NFV	95% CI for LEX/r-NFV
Pooled	221/322 = 69%	221/327 = 68%	-6%, 8%
1-10 K	22/30 = 73%	23/33 = 70%	
10-100 K	115/167 = 69%	114/161 = 71%	
>100 K	84/125 = 67%	84/133 = 63%	

TABLE 3.6 E
PERCENT < 50 COPIES, TRIAL 30002, WEEK 48

Stratum	LEX/r	NFV	95% CI for LEX/r-NFV
Pooled	177/322 = 55%	173/327 = 53%	-6%, 10%
1-10 K	21/30 = 70%	21/33 = 64%	
10-100 K	99/167 = 59%	92/161 = 57%	
>100 K	57/125 = 46%	60/133 = 45%	

The results for this trial using change from baseline in log

HIV RNA, out to week 48, are given in table 3.6 F. This table gives the observed mean change from baseline at week 48, ignoring subjects lost to follow-up; and the sample size for this single visit value. Because these were secondary endpoints, no 95% confidence intervals for the difference between the arms were computed. In this table, negative values for Log HIV are evidence of superiority of LEX/r to control. Large positive upper limits are evidence that LEX/r may not work as well as the control. For CD4 count, positive values are evidence of LEX/r superiority.

TABLE 3.6 F
TRIAL 30002
CHANGE FROM BASELINE TO WEEK 48 IN LOG HIV

Variable	LEX/r	NFV
Log HIV	-2.52 (317)	-2.52 (324)
CD4 Count	124	137

The reported results in trial 30003 are given in tables 3.6 G and H. Table 3.6 G gives, for the two Lexiva arms and the Kaletra (LPV/r) arm, the mean change from baseline for all observed subjects at week 24 for log HIV RNA. Three methods of analysis are used: observed only (discontinued subjects not included), missing values for discontinued subjects replaced by baseline, and LOCF for discontinued subjects, together with the N's on which those are based. 97.5% confidence intervals are given for the difference between each LEX/r arm and the LPV/r arm in time averaged change from baseline. The 97.5% intervals were used to adjust for the multiple comparison of two LEX/r doses to control.

TABLE 3.6 G

MEAN CHANGE FROM BASELINE AT WEEK 24, TRIAL 30003

	LEX/r qd	LEX/r bid	LPV/r
N	104	105	103
LOG HIV RNA (Observed)			
Mean	-1.49	-1.53	-1.76
Interval	-.017, .551	-.047, .536	
LOG HIV RNA (Discontinue = Baseline)			
Mean	-1.42	-1.46	-1.67
Interval	-.049, .553	-.083, .533	
LOG HIV RNA (LOCF)			
Mean	-1.48	-1.53	-1.77
Interval	-.007, .590	-.044, .557	

The overall results are consistent across methods of handling data: both LEX/r doses were about .25 log copies worse than LPV/r and with 95% confidence, adjusted for two comparisons, they were at most approximately .55 log copies worse than LPV/r.

The results for the secondary endpoints, percent sustained BLQ, with LOQ=400 and =50, and for percent with at least 1 log drop from baseline, in trial 30003 are given in tables 3.6 H and I. Table 3.6 H gives the results at week 24, table 3.6 I gives the results at week 48. We include both tables for these endpoints because the differences between TLR/r and LPV/r change more between weeks 24 and 48 than do the results for TAD. A full evaluation of the comparative efficacy is easier if the 24 week results are included. In these computations, subjects lost to follow-up are considered failures. The table gives the fraction and percentage successful and 95% confidence intervals for the difference between LEX/r and LPV/r. Unlike table 3.6 G, these confidence intervals are not adjusted to 97.5% to allow for two comparisons.

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TABLE 3.6 H

PERCENT BLQ AT WEEK 24, TRIAL 30003

Arm	LEX/r qd	LEX/r bid	LPV/r
	%<400		
N	61/105	64/107	71/103
%	= 58%	= 60%	= 69%
Interval	-24%, 2%	-21%, 4%	
	%<50		
N	42/105	45/107	49/103
%	= 40%	= 42%	= 48%
Interval	-21%, 6%	-17%, 9%	
	>1 Log Drop from Baseline		
N	65/105	67/107	75/103
%	= 62%	= 63%	= 73%
Interval	-23%, 2%	-22%, 3%	

The overall results are similar across all three endpoints and both doses of LEX/r: LEX/r is estimated to be about 10% worse than LPV/r and with 90% confidence, adjusting for two comparisons, could be more than 20% worse than LPV/r.

TABLE 3.6 I

PERCENT BLQ AT WEEK 48, TRIAL 30003

Arm	LEX/r qd	LEX/r bid	LPV/r
	%<400		
N	52/105	62/107	63/103
%	= 50%	= 58%	= 61%
Interval	-25%, 2%	-15%, 11%	
	%<50		
N	39/105	49/107	52/103
%	= 37%	= 46%	= 50%
Interval	-27%, 0%	-17%, 10%	

The pattern among the three arms is different from what was seen at week 24. By week 48, the inferiority of LEX/r qd to LPV/r has been confirmed: it remains about 10% worse and was statistically significantly inferior to LPV/r with respect percent <50. However, percent BLQ on LEX/r bid remained nearly constant between weeks 24 and 48 while declining enough on LPV/r to make the estimated superiority of LPV/r to LEX/r bid decrease

from 10% to 3-4%. (One will notice that 7 subjects actually achieved viral loads <50 for the first time between weeks 24 and 48.) Based on the week 48 findings, the bid LEX/r is clearly superior to qd LEX/r and is close enough to LPV/r to be clearly superior to placebo.

Table 3.6 J gives median change from baseline to weeks 24 and 48 in CD4 count for all three arms.

TABLE 3.6 J
MEDIAN CHANGE FROM BASELINE, TRIAL 30003

	LEX/r qd	LEX/r bid	LPV/r
CD4 Count, Week 24			
N	95	86	91
Median	72	62	63
Week 48			
N	81	79	85
Median	61	81	91

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3.7 Summary of Applicant's Conclusions

The applicant concluded that the antiviral efficacy in treatment naive subjects of 1400 mg bid lexiva and of 1400 mg qd lexiva boosted with 200 mg qd of ritonavir were both similar to that of nelfinavir when added to a background regimen of two NRTI's.

The applicant also concluded that 700 mg bid lexiva boosted with 100 mg bid ritonavir had demonstrable antiviral efficacy in treatment experienced subjects. This conclusion was based on estimates of virological success and change in viral load that were comparable to the results found in the LPV/r arm of the trial and were with acceptably high confidence not sufficiently worse than LPV/r to be comparable to placebo. The same claim of efficacy in treatment experienced patients could not be made for 1400 mg qd lexiva boosted with 200 mg qd ritonavir.

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4. Statistical Reviewer's Comments and Analyses

4.1 Problems with the Applicant's Analysis

The applicant's analyses with time averaged differences (TAD) in the trial with experienced patients (30003) are deficient in several ways. The first difficulty is that TAD is not the parameter on which conclusions of efficacy are generally based. Even in highly ART experienced populations, clinically fractions of the treated population achieve below quantitation, either at LOQ = 400 or LOQ = 50, depending on the assay. Consequently, the FDA reviewer considers an analysis based on percent of subjects BLQ to be primary. This analysis will be given in section 4.2 below.

A second, very serious deficiency with the TAD was the applicant's assumption that an inferiority to an effective control drug of no more than .5 log copies/mL constituted evidence of efficacy. The protocol and the NDA submission contain no justification for this tolerance limit. One may presume that it was chosen because the limit of assay variability is approximately .5 log copies/mL. This is mistaken reasoning. A clinically meaningful difference may well be smaller than the limit of assay variability. Assay variability is a statement about the assay, not about the disease process. Furthermore, group means can readily be established to greater precision than the variability of a single assay measurement. This is the most serious of the three deficiencies because it lends itself to false assertions of superiority to an imputed placebo control.

The other two deficiencies concern the applicant's concern the method of calculation. Because these problems may affect both LEX/r and control arms, these deficiencies may be less consequential. The first of these two additional deficiencies is that the applicant made the unrealistic assumption that about missing data for subjects lost to follow-up. The applicant imputed these missing data by last observation carried forward. The evidence from previous experience is that viral loads return to baseline once drug treatment is discontinued. The applicant's

mistake tends to bias the results in favor of the arm with more loss to follow-up.

Finally, the applicant used an approximation by assuming all subjects had their viral load on the same day and that mean difference between the arms on TAD could be approximated by a suitably weighted average of mean differences at the scheduled time of each visit.

There is also a problem with the applicant's analyses of percent BLQ. The applicant neglected to collect the exact dates on which subjects started new drugs to replace the assigned lexiva or control protease inhibitor. This was an unprofessional omission since those dates are important to correct computation of time of failure of assigned regimen. The applicant did record an approximation to the dates of interest, namely the date of discontinuation of the assigned protease inhibitor. In accordance with other NDA reviews, the FDA statistical reviewer has used those dates as the dates of starting a new drug. The applicant, in contrast, conducted a sequence of analyses in which the start of a new drug was imputed to occur on the day of discontinuation or on that day plus one, two, three, four, etc. days. The applicant selected a four day post discontinuation window as their approximation to the day of starting new drug. This appears to have been selected so as to give a slightly larger apparent benefit from lexiva. In practical terms, the conclusion that lexiva is an effective drug against HIV when used with at least two NRTI's in either treatment naive or treatment experienced patients is unchanged and the magnitude of the estimated difference in response between lexiva and control is quite small. The choice of how long after drug discontinuation one waits before imputing start of new drug has slightly larger effect on the response rate in each arm (both lexiva and control get higher responses). The exact magnitude of the effect of imputed date of starting drug will be given in tables below.

The FDA reviewers have examined all the subjects who had a failure before week 48 using the applicant's recorded stop date and who did not have such a failure using the applicant's recorded stop date plus four days as the days imputed to the start of a new drug. All of these subjects appear to have had

still controlled viral load before and immediately after the stop date. This may be taken as supporting the later date for start of a new drug. The FDA statistical reviewer is uncomfortable with modifications of the algorithm for computing success or failure that are based on case by case examination of the response profiles after knowing the results, particularly when the success/failure decision is made on an individual basis by judges knowing the treatment assignments. Therefore, in what follows, results will be reported using the pre-specified choice of stop date. Results using the stop date plus four days are compared to the results using the stop date in table 4.7 A below.

The FDA reviewer considers that cross trial comparisons should be made only with extreme caution and with regard to the risk of confounding the effects of different drugs with the effects of different enrolled samples. With this caveat in mind, the FDA reviewer will use the day of discontinuation as the day of starting new drug in order not to give lexiva an undeserved advantage in cross trial comparisons.

4.2 Results with Percent BLQ in Experienced Patients

Table 4.2 A summarizes the differences between lexiva and Kaletra and the 95% confidence intervals for the three viral load endpoints in trial 30003 with experienced patients as calculated by the FDA statistical reviewer. Only the results for the more favorable lexiva arm, the bid dosing, are included. Nevertheless, the 95% confidence intervals are computed to include adjustment for the second, qd dosing, lexiva arm.

TABLE 4.2 A
VIRAL LOAD ENDPOINTS IN TRIAL 30003
DIFFERENCES BETWEEN LEXIVA BID AND KALETRA

	Means			Adjusted 95% Limits	
Endpoint	Lex/r	Kal	Difference	Lower	Upper
%<400	58%	61%	-3.2%	-18.4%	12.0%
%<50	46%	50%	-4.7%	-20.2%	10.8%
TAD	-1.40	-1.67	.27	-.044	.584

In all three cases, the potential inferiority of lexiva to the active control (18.4% and 20.2% worse on percent BLQ, .584 log copies worse on time averaged difference from baseline) is large enough to require further examination.

In active controlled trials, if one wishes to conclude efficacy by getting a confidence limit within a pre-specified delta, the choice of delta must take into account established limits of superiority of the control to placebo. The applicant's use of a delta based on the limits of the assay is irrelevant. There are two possible ways to use the data in active control trial 30003 to estimate whether LEX/r would have shown superiority to placebo in experienced patients. The first method is to combine the treatment estimates in trial 30003 with those from trials in the Kaletra NDA to get an estimate of the difference between LEX/r and placebo. The second method is to survey previous NDA's with 2 drug controls to determine a range of reasonably credible values for the treatment response of subjects treated with 2 antiretrovirals and compare that with the estimated effect of LEX/r plus 2 antiretrovirals.

The first of these two methods proceeds as follows. In trial 30003, the data provide an estimate of the difference in efficacy of LEX/r and LPV/r, together with a standard error of that estimate. Two trials from the NDA for LPV/r (Kaletra®) provide data relevant to estimating the difference between LPV/r and placebo. These were trials 863 and 888. Each can be used, in a different manner, to estimate the difference between LEX/r and placebo.

Trial 888 is the more comparable of the two LPV/r trials to trial 30003. Trial 30003 used patients who were PI failures with baseline log HIV RNA = 4.1 copies/mL and baseline CD4 count = 263; trial 888 used patients who were PI and NRTI experienced but NNRTI naive with a baseline log HIV RNA of 4.1 and baseline CD4 count = 322. Trial 30003 added a background of two NRTI's to each; trial 888 added a background of nevirapine (NVP), an NNRTI plus two NRTI's. Trial 888 also had an active control: the control arm had a PI selected by genotypic/phenotypic analysis. However, the trial showed statistically and clinically significant superiority of LPV/r over the select PI. Thus, if

trial 30003 shows that LEX/r was inferior to LPV/r by a smaller a margin than was the control PI in trial 888, that would support a claim of superiority of LEX/r to placebo.

In order to estimate the difference in efficacy of LEX/r and placebo, one must combine the results from all trials 30003 and 888. An outline of the computation required is given in table 4.2 B.

TABLE 4.2 B
COMPARISON OF LEX/r TO OTHER PI, USING % <400
USING TRIALS 30003 AND 888

Observed Data

Source	Arm1	Arm2	Mean1	Mean2	Difference	SEE
LEX NDA						
Tr 30003	LEX/r	LPV/r	62/107=58%	63/103=61%	-3.2%	6.88%
LPV/r NDA						
Trial 888	LPV/r	PI	84/148=57%	46/140=33%	24%	5.69%

Imputed

Arm1	Arm2	Difference	SEE
LEX/r	PI	-3.2+24% = 20.8%	$\sqrt{.0688^2+.0569^2}$ = 8.92%

The estimates from trials 30003 and 888 from the LEX/r and the LPV/r NDA's were added to get an estimated difference between LEX/r and control. The result of this combination gives an estimated difference of 24% more subjects sustained <400 copies at 24 weeks than with a selected PI control. However, the tentative 95% confidence interval is 0.8% to 40.8%. (This confidence interval includes a multiple comparison adjustment for the presence of two lexiva arms in trial 30003.) In other words, LEX/r might credibly produce anything from a 1% to a 41% improvement over the other PI control. The FDA statistical reviewer regards this as sufficient demonstration of efficacy of lexiva in the experienced population, even without an attempt to estimate the difference between a selected PI plus 2 ART drugs and placebo plus same 2 ART drugs. Similarly, one may dispense with inferences based on the other trial in the LPV/r NDA, which enrolled patients who were ART naive.

Table 4.2 C gives a summary of the estimated differences

with multiple comparison adjusted confidence intervals for LEX/r and various controls, including sensitivity analyses intended to give a feeling for the uncertainty due to pooling data from different trials.

TABLE 4.2 C
DIFFERENCES IN PERCENT <400, LEX/r AND CONTROLS

Control	Diff	Adjusted 95% Limits	Source	Population
LPV/r	-3.2%	-18.4%, 12.0%	Trial 30003	ART experienced
PI	20.8%	0.8%, 40.8%	Imputed: 03, 888	Experienced
	20.8%	-3.2%, 44.8%	**	
	16.6%	-7.4%, 40.6%	****	

** same trial with SEE inflated 20%

****same trial with Diff deflated 20% and SEE inflated 20%

One can see that LEX/r is observed, using data from a randomized clinical trial with ART experienced patients, to be equivalent to LPV/r but with sufficient statistical uncertainty as to leave open the possibility that it is clinically significantly inferior to LPV/r. Based on comparing results in two different trials, both with ART experienced patients, LEX/r is estimated to be statistically and clinically superior to an investigator selected PI in the same sort of population. With nominal 95% confidence adjusted for multiple comparisons, it appears to be at worst 1% better than the selected PI, and possibly, as much as 41% better. This statistical significance disappears in a sensitivity analysis in which the standard error is inflated by 20% to compensate for the differences among trial populations but the lexiva benefit was still confidently estimated to be no more than 3.2% worse than the active control. In the most extreme of the sensitivity analyses, when both the standard error was inflated by 20% and the lexiva benefit was deflated by 20%, lexiva was confidently estimated to be no more than 7.4% worse than an active control.

The FDA statistical reviewer would summarize these analyses by concluding that there is reasonably convincing evidence that LEX/r makes a positive contribution to the two NRTI background in PI experienced patients when assessed by proportion with

sustained viral suppression.

The second method for determining what, if anything, LEX/r added to the 2 drug background regimen, is to survey other NDA's with 2 drug arms. A graphical presentation of such a survey is given in figure 4.2 below.

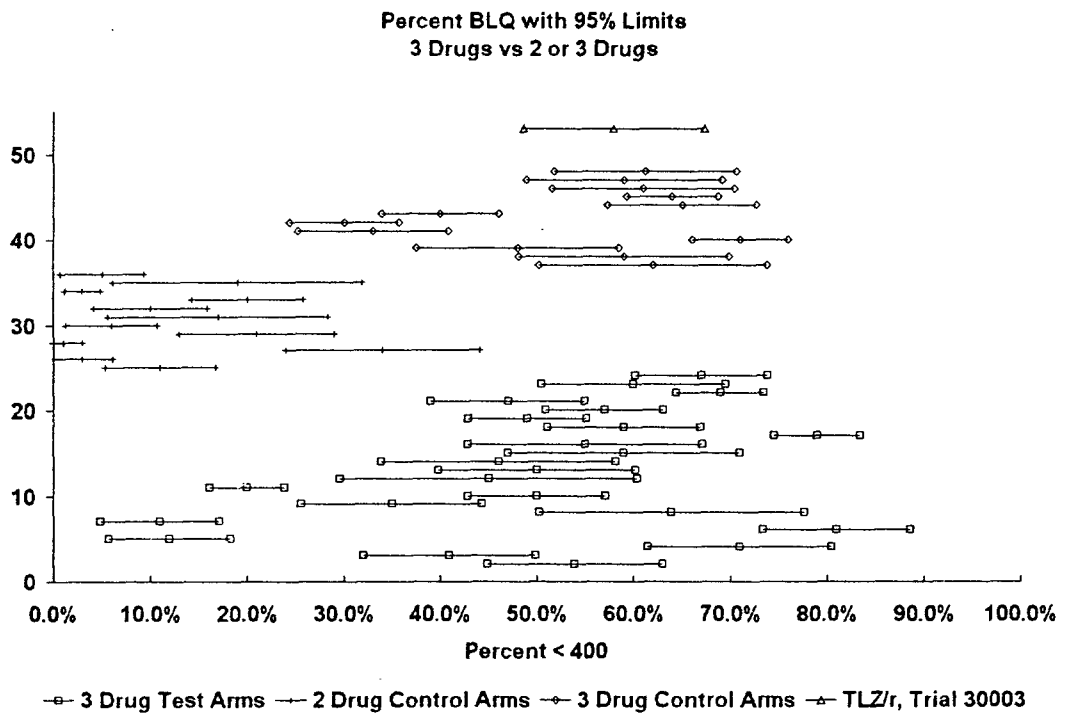

Figure 4.2 plots the observed value and the 95% confidence intervals for percent of subjects with sustained BLQ viral load for test drug and for control drug for 12 trials comparing a test drug to placebo and for 11 trials comparing a test drug to an active control. In all trials, both arms had a two drug background. The percent BLQ is given on the horizontal axis, the vertical axis is a stacking of the trials. The top interval, marked by triangles is the 95% confidence interval for LEX/r in trial 30003. Below that, marked by diamonds are the intervals for 3 drug control arms. Below, those, marked by plus signs are the intervals for two drug control arms. At the bottom, marked by squares, are the intervals for 3 drug test arms. (All the test drugs were ultimately approved.) The percent BLQ was not always measured at the same time; various trials had data at weeks 16, 24, or 48. Generally, the later the time point, the lower the percent BLQ.

The further to the right the interval is, the better that regimen performed. One can clearly see that the LEX/r arm in trial 30003 is comparable to many of the three drug arms and is clearly to the right of all of the two drug arms.

An overall conclusion from this survey of other trials is that LEX/r plus two NRTI's produced a rate BLQ reasonably convincingly higher than the rate seen in any of the trial arms with only 2 active drugs. The results support the conclusion that LEX/r is effective in the experienced population of trial 30003, even though it might not be the first choice as PI in an experienced population.

4.3 Results with Time Averaged Difference

One can repeat both methods presented in section 4.2 for comparing LEX/r to an imputed placebo, using TAD (time averaged difference) instead of percent sustained BLQ as the response variable.

Tables 4.3 A and B contain the computations for method 1, comparing LEX/r to placebo by way of intermediate results from the LPV/r (Kaletra) NDA. TAD results from trial 888, which

compared LPV/r to investigator selected PI, each added to a background of two NRTI's is outlined in table 4.3 A. Recall that negative values of TAD are better. In the computed differences throughout this section, a negative difference indicates superiority of LEX/r to control, a positive difference indicates superiority of the control to LEX/r.

TABLE 4.3 A
COMPARISON OF LEX/r TO PLACEBO, USING TAD
USING TRIALS 30003, 888

Observed Data

Source	Arm1	Arm2	Mean1	Mean2	Difference	SEE
LEX NDA						
Tr 30003	LEX/r	LPV/r	-1.40	-1.67	.27	.140
LPV/r NDA						
Trial 888	LPV/r	PI	-.972	-.867	-.104	.078

Imputed

Arm1	Arm2	Difference	SEE
LEX/r	PI	.27-.104 = .166	$\bullet\bullet .140^2+.078^2 = .160$

$\bullet\bullet$ PI selected by geno/phenotypic analysis

The final result gives an estimated difference of .166 (a .166 log copies lesser average reduction with LEX/r than with a selected PI) with a tentative 95% confidence interval (adjusted for comparison with 2 lexiva arms in trial 30003) of -.193 to .525. In other words, LEX/r might credibly produce anything from a .193 log copy reduction compared to an optimized PI to a .525 log copy increase compared to that same PI.

One may also attempt to go one step further to estimate the difference between a selected PI plus 2 ART drugs and placebo plus same 2 ART drugs. The FDA reviewer did this by averaging the difference between test PI arms and placebo arms in 4 other trials with PI's, using the amprenavir, nelfinavir, and indinavir NDA's. Finally, a second estimate of the difference between selected PI and placebo, both with a 2 drug background, was obtained by averaging 6 other trials with 3 drugs vs 2 drugs. The two additional trials did not involve PI's but rather were from the nevirapine NDA. Table 4.3 B summarizes this 3 step computation of imputed difference between LEX/r and placebo.

TABLE 4.3 B
COMPARISON OF LEX/r TO PLACEBO, USING TAD
USING TRIALS 30003, 888, AND OTHERS

Source	Arm1	Arm2	Difference	SEE
4.3 A	LEX/r	PI	.166	.160
**	PI	Plac	-.79	.051
	LEX/r	Plac	.166-.79 = -.624	**$.160^2+.051^2$ = .168
****	PI	Plac	-.76	.048
	LEX/r	Plac	.166-.76 = -.594	**$.168^2+.048^2$ = .175

** Averaging 4 trials with PI vs Placebo

**** Averaging 6 trials with 3rd Drug vs Placebo

The 4 trials involving PI vs Placebo in the presence of a 2 drug background had an average difference in TAD of -.79 (.79 greater mean reduction than placebo) and an inferred standard error of .051, computed as the square root of the sum of the squares of the four standard errors in the separate trials. This leads to an estimate of -.624 in TAD between LEX/r and placebo, with an adjusted 95% confidence interval of -1.00 to -.25. Recall, that since negative values indicate a superior TAD, this interval corresponds to an imputed mean average decrease of .25 to 1.0 log copies more than placebo. The full list of 6 trials involving PI or NNRTI vs Placebo in the presence of a 2 drug background had a slightly smaller average difference in TAD of -.76, with an imputed standard error of .048. This leads to an estimate of -.594 in TAD between LEX/r and placebo, with an adjusted 95% confidence interval of -.986 to -.202.

In table 4.3 C, the reviewer summarizes the imputed confidence intervals for the difference in TAD between LEX/r and various controls. This table also includes sensitivity analyses in which one attempts to reflect the additional uncertainty due to combining results from different enrolled populations in different trials by inflating the standard errors and deflating estimated differences by up to 20%.

TABLE 4.3 C

DIFFERENCES IN TAD, LEX/r AND CONTROLS

Control	Diff	Adjusted 95% Limits	Source	Population
LPV/r	.27	-.044, .584	Trial 30003	ART experienced
Selected PI	.166	-.193, .525	Imputed: 03, 888	Experienced
Placebo	-.624	-1.00, -.25	03,888, 4 others	Mixture
Placebo	-.594	-.986, -.202	03,888, 6 others	Mixture
	-.475	-.946, -.005	....	

....same set of trials with Diff deflated 20% and SEE inflated 20%

The second method used in section 4.2 was the survey of other NDA's comparing (ultimately approved) test drug plus 2 drug background to either a control regimen of 2 or 3 active drugs. The results from this survey are summarized graphically in the figure 4.3 below.

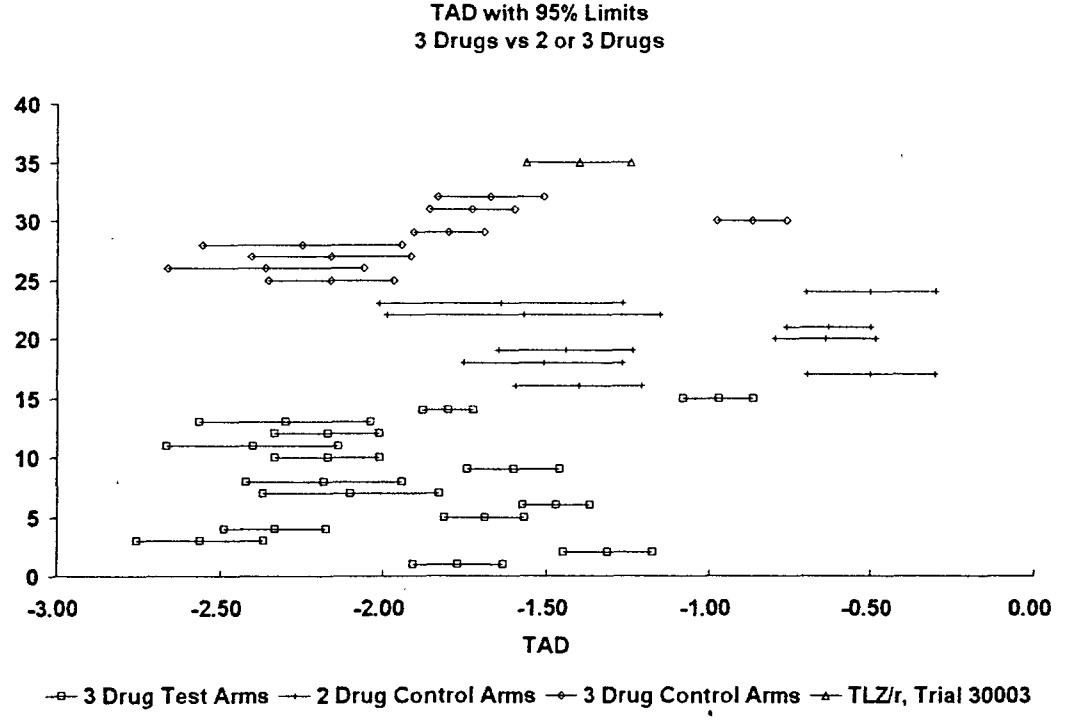

Figure 4.3 is similar to figure 4.2 but there are some differences, all relating to the fact that percent BLQ gets better, the larger it is, while TAD gets better as it gets more negative. Figure 4.3 plots the TAD (time averaged difference from baseline in log(HIV RNA level)) for test drug and control drug for 9 trials comparing a test drug to placebo and for 4 trials comparing a test drug to an active control. In all trials, both arms had a two drug background.

The 95% confidence intervals for TAD are given on the horizontal axis, the vertical axis is a stacking of the trials. As in figure 4.2, the top interval, marked by triangles is the 95% confidence interval for LEX/r in trial 30003. Below that, marked by diamonds are the intervals for 3 drug control arms. Below, those, marked by plus signs are the intervals for two drug control arms. At the bottom, marked by squares, are the intervals for 3 drug test arms. (All the test drugs were ultimately approved.)

In contrast to figure 4.2, the further to the left the interval is, the better that regimen performed. One can clearly see that the LEX/r arm in trial 30003 is in the same general range as the poorer performing half of the three drug regimens and as the better performing half of the two drug regimens. In contrast, to figure 4.2, the two drug regimens are not as clearly separated from the three drugs regimens by TAD as they were by percent < 400.

The imputed differences between LEX/r and placebo based on trials 888 and the average of four other PI trials or of six other trials with 3 drug test arms provide a strong suggestion of LEX/r activity as part of a 3 drug regimen in experienced population when measured by TAD. An overall conclusion from both methods of imputing the comparison of LEX/r to placebo is that one is at least close to convinced that LEX/r contributes to improvement in TAD when added to 2 NRTI's in an experienced population. The evidence is not quite as strong as that obtained using percent < 400.

4.4 Effect of Loss to Follow-up on Results

Loss to follow-up is reasonably regarded as inconsequential to conclusions drawn with respect to percent sustained BLQ. This is because there is substantial evidence that viral loads rebound quickly to detectable levels when therapy is discontinued. Thus, standard analyses that regard all subjects lost to follow-up as viral rebounds will give credible results.

Use of TAD as a response variable produces greater problems in the handling of loss to follow-up. There is reasonable evidence that viral loads rebound to approximately baseline levels when a previously effective therapy is discontinued. However, there is variability about the original baseline level. Thus, the most acceptable method of handling loss to follow-up when TAD is the response variable is to consider HIV RNA = baseline for visits subsequent to loss but the results are not as credible as with percent BLQ.

The FDA statistical reviewer has compared subjects in trial 30003 who completed 48 weeks of observation with those who were lost to follow-up before week 48. These results are summarized in table 4.4 A.

TABLE 4.4 A
COMPARISON OF COMPLETERS TO LTFU
MEANS OF LAST OBSERVED VALUE, TRIAL 30003

		Log HIV		CD4 Count	
Status	Arm	N	Mean	N	Mean
LTFU	LEX/r BID	23	4.34	25	357
	LPV/r	15	3.44	16	308
Complete	LEX/r BID	84	2.48	82	385
	LPV/r	88	2.49	87	369

One can see that the discontinued subjects had higher HIV RNA levels and lower CD4 counts at their last visit than did the completers in both arms. Surprisingly, if one expects discontinuing subjects to be equally unsuccessful on both arms, the difference between LEX/r and LPV/r is larger for discontinued

subjects than for completers on both HIV level and CD4 count.

For both log HIV level at last visit, the difference is more unfavorable for lexiva for discontinued subjects than for completers. (LEX/r HIV minus LPV/r HIV = 4.34 - 3.44 = .9 for discontinued, 2.48 - 2.49 = -.1 for completers). For CD4 count at last visit, the reverse relationship held: lexiva was better than LPV/r by a smaller amount for discontinued subjects than for completers. (LEX/r CD4 - LPV/r CD4 = 357-308 = 49 for LTFU, and 385-369 = 16 for completers. (Recall larger values are unfavorable for HIV and favorable for CD4 count.)

The overall conclusion is that problems with correctly imputing missing data to subjects discontinuing early makes it even more difficult to claim that LEX/r contributes any improvement to TAD in experienced subjects.

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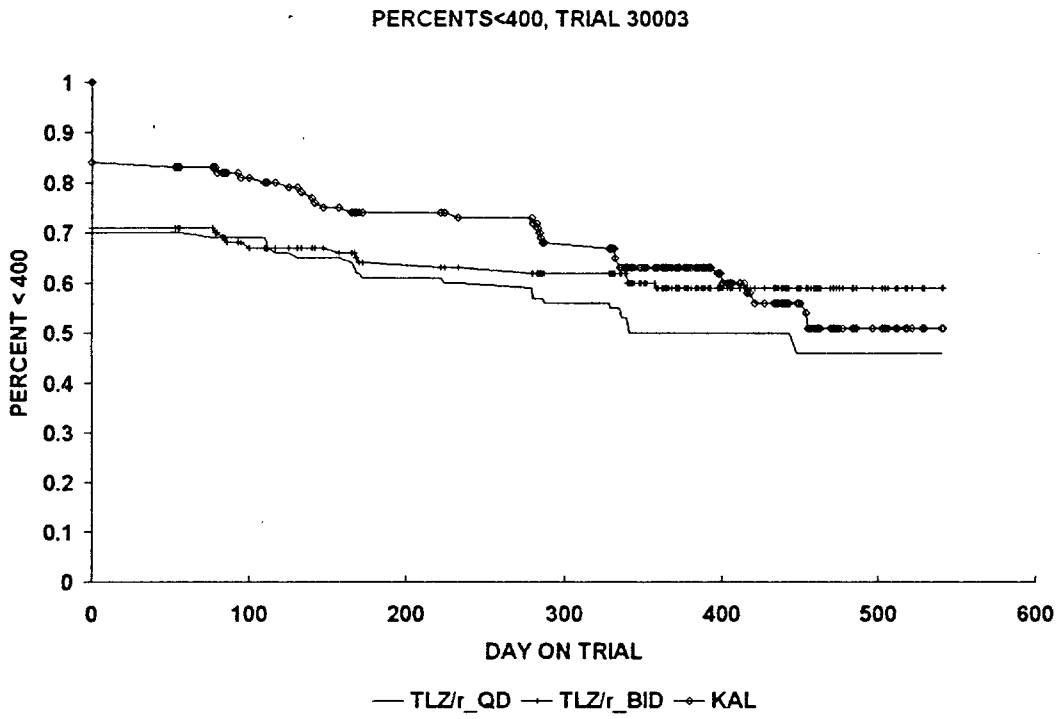
4.5 Time to Viral Rebound

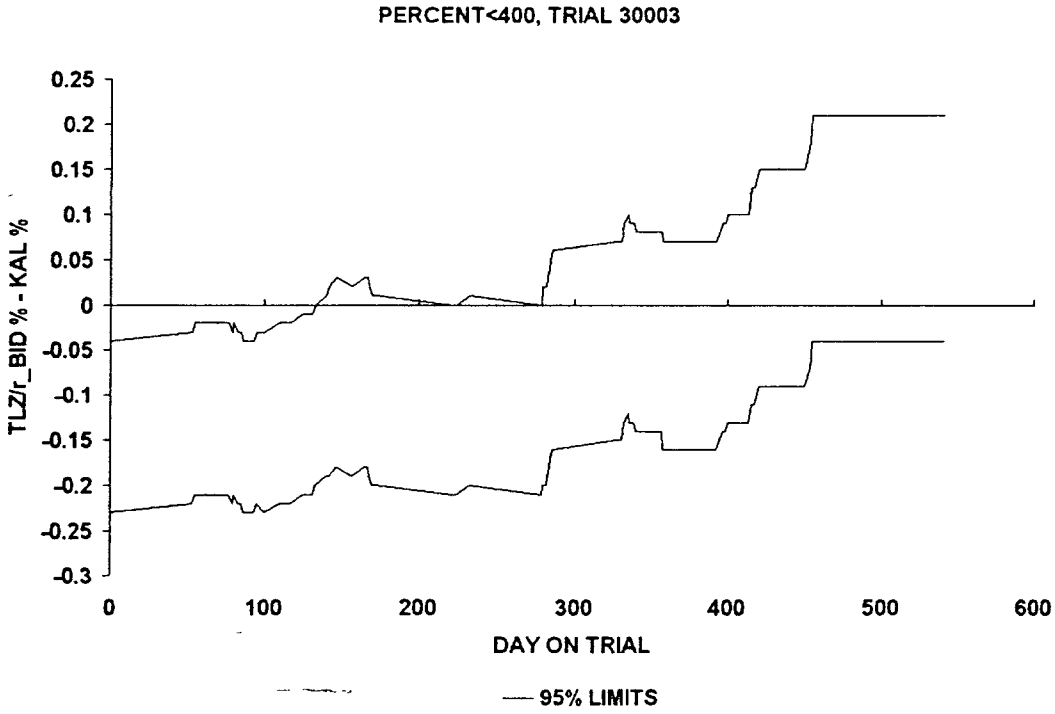
The analysis presented in section 4.2 above showed that in ART experienced subjects LEX/r led to sustained viral loads below 400 copies/mL in 18% fewer subjects than did Kaletra (LPV/r) when both were added to two other drugs. The FDA reviewer also conducted a Kaplan-Meier analysis of time to loss of viral suppression, using LOQ's of both 400 and 50 copies/mL. The results with LOQ = 400 are presented in figures 4.5 A and B. Figure 4.5 A includes both LEX/r arms from trial 30003: the bid dose for which an indication is sought and the qd dose. Figure 4.5 B shows the plot for the 95% confidence limits for lexiva survival minus Kaletra survival.

One can see from this graph that the early survival rate on bid LEX/r begins about 10% below that of Kaletra but the two arms have essentially the same survival by day 300, with bid lexiva appearing to be slightly (but not statistically significantly) after day 400. There is a statistically significant superiority of Kaletra over lexiva for about the first six months but after there is no significant difference between the arms. (The confidence levels in this plot are not adjusted for either multiple times or multiple arms.) In contrast, the qd dose of LEX/r is always inferior to that of Kaletra. The difference was in fact statistically significant at all times.

Results for percent below 50 copies/mL (not presented here) were generally similar, although bid LEX/r was inferior to Kaletra from day zero to beyond one year. The differences were never statistically significant.

Thus, if the meta-analysis arguments in section 4.2 above are adequate demonstration that bid LEX/r would have been superior to a placebo arm in experienced patients, then the Kaplan-Meier curves raise no additional concerns about the time course of LEX/r efficacy.


PERCENTS<400, TRIAL 30003
PERCENT < 400
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
100
200
300
400
500
600
DAY ON TRIAL
TLZ/r_QD
TLZ/r_BID
KAL


PERCENT<400, TRIAL 30003
TLZ/r_BID % - KAL %
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
-0.25
-0.3
0
100
200
300
400
500
600
DAY ON TRIAL
95% LIMITS

4.6 Results with CD4 Count

Results for CD4 count, using TAD (time averaged difference from baseline) are summarized for all three trials in table 4.6 A. Missing data are handled differently here. For HIV RNA levels, there is good evidence that rebound to close to baseline level occurs swiftly after discontinuing drug. There is not quite so good evidence that CD4 counts react more slowly to changes in drug regimen. Consequently, missing data in table 4.6 A were replaced by last observation carried forward (LOCF). Analyses were also conducted using missing data = baseline but are not reported here. Conclusions about differences among the treatments were not changed consequentially between the two methods of handling missing data.

TABLE 4.6 A
CHANGE FROM BASELINE IN
CD4 COUNT IN TRIALS 3000-1, 2, 3
ARM MEANS, DIFFERENCES, 95% LIMITS

	Mean		Mean	95% Limits	
Trial	LEX	Control	Diff	Lower	Upper
3001 (NFV control)	139.4	135.8	3.7	-26.7	34.0
3002 (NFV control)	136.9	149.7	-12.8	-28.9	3.2
3003					
(qd, LPV control)	53.7	64.1	-10.4	-35.7	14.8
(bid, LPV control)	49.6	64.1	-14.5	-38.2	9.2

The CD4 counts were also analyzed using the randomization stratification on baseline HIV RNA levels. There appeared to be no strata-treatment interactions. Results for the overall mean difference using Mantel-Haenszel pooling across the strata were not consequentially different from the results obtained by simple pooling in table 4.6 A. Overall, lexiva or boosted lexiva produced changes in CD4 count that were, with 95% confidence, with 30-40 cells of that produced by the active control regimens. The CD4 count data are generally supportive of the conclusions drawn from the HIV endpoints.

4.7 Results with ART Naive Patients

The applicant's analyses of ART naive patients, using the results from trials 30001 and 30002, appear to provide two adequate, well-controlled trials with evidence to support the use of LEX or LEX/r for this sub-population. The FDA statistical reviewer has conducted analyses on these trials using all three HIV RNA endpoints (TAD, percent <400, percent <50), and confirmed that both trials provide evidence of LEX efficacy. The results of the FDA re-analysis are given in table 4.7 A. This table gives the mean response to the LEX (trial 30001) or LEX/r arm (trial 30002) and the NFV control arm and the 95% confidence interval for the difference between LEX mean and NFV control mean. Means are computed from simple pooling the data across randomization strata but confidence intervals in this table are based on Mantel-Haenszel weighted pooling across the randomization strata rather than on simple pooling.

TABLE 4.7 A
VIRAL LOAD ENDPOINTS IN TRIALS 3000-1, -2

		Means		95%
Endpoint	Trial	LEX	NFV	Confidence Limits
%<400	30001	64%	49%	(1.7%, 27.4%)
	30002	60%	60%	(-8.2%, 7.0%)
%<50	30001	54%	40%	(1.1%, 26.7%)
	30002	51%	49%	(-6.3%, 9%)
TAD	30001	-2.17	-1.9	(-.57, .04)
	30002	-2.25	-2.32	(-.09, .23)
Applicant's Variant				
%<400	30001	66%	52%	(1.5%, 27.5%)
	30002	69%	69%	(-6.7%, 7.6%)
%<50	30001	55%	42%	(.1%, 26.4%)
	30002	57%	54%	(-4.6%, 10.7%)
TAD	30001	-2.18	-1.91	(-.59, .04)
	30002	-2.28	-2.35	(-.1, .23)

One can see from this table that LEX was, with 95% confidence, at least 1.7% better than NFV, an active control drug, in proportion of subjects with viral load sustained <400 c/ml in one trial and no more than 8% worse than NFV in the other

trial. LEX was, with 95% confidence, no more than 6% worse than NFV in proportion of subjects with viral load sustained <50 c/ml in one trial and at least 1.1% better in the other trial. Finally, LEX was, with 95% confidence, no more than .57 log copies worse than NFV in time averaged difference from baseline in HIV RNA in one trial and at least essentially tied in the other trial. Based on this table, the FDA statistical reviewer regards the applicant's claim of demonstrated efficacy of LEX or LEX/r when added to two other drugs in ART naive subjects to be confirmed. One could easily calculate the imputed differences between LEX and placebo for these data, as was done for trial 30003 in sections 4.2 and 4.3 above. One need only recall that nelfinavir was directly observed to be 60% better than placebo in trial 511 of the NFV NDA to be see that the formal computations would convincingly show LEX superior to placebo.

This table also includes the applicant's variant imputation of day starting new drug = day off assigned drug plus 4 days. One can see that this has no consequential effect on the estimated difference between lexiva and control.

4.8 Two [redacted] Questions

There are two issues that [redacted] for lexiva. The first concerns treatment experienced patients: Is boosted lexiva clinically equivalent to Kaletra with this population. The second concerns treatment naive patients: Is lexiva or boosted lexiva clinically superior to nelfinavir for patients in this population with higher baseline viral load?

This review has touched upon the first question several times in sections 4.1-4.6. The answer is that boosted lexiva has not been shown to be clinically equivalent to Kaletra and may even be inferior. This conclusion is based upon the following facts. First, the lower confidence bounds for the difference in percent BLQ, using LOQ = 400 and 50 respectively, were -18.4% and -20.2% (see table 4.2 A). These are generally considered to be so far below zero that they raise the possibility of clinical inferiority. Second, t-tests for the superiority of Kaletra to bid and qd boosted lexiva, respectively, on the endpoint of TAD

gave p-values of .043 and .053. (These were based on pooling on the randomization strata.) When testing for superiority of the single active control over either of two test doses, multiple comparison adjustments would not be required since the active control has only one chance to beat each test dose. Third, the Kaplan-Meier estimates of duration of viral suppression in figures 4.5 A and B show that the Kaletra arm was superior to the bid boosted lexiva arm for at least the first six months of therapy. All three of these points argue against a claim of clinical equivalence of boosted lexiva and Kaletra. (The recommendation to approve boosted lexiva for experienced patients is based on the conclusion that the drug would clearly have beaten a placebo comparator, had such a trial been ethical.)

The second question is prompted by the observation in table 4.8 A below that, for lexiva in trial 30001 and for boosted lexiva in trial 30002, percent <400 remains fairly constant at 74% to 62% as baseline HIV RNA level increases from <10K copies/ml to >500K copies/ml while, for nelfinavir in trial 30001, response decreases more sharply, from 66% to 31%, as baseline viral load increases from <100K to > 500K. (The <10K category is anomalous since it contains only 8 subjects.)

TABLE 4.8 A
PERCENT BLQ AS FUNCTION OF BASELINE HIV RNA
IN NAIVE PATIENTS

TRIAL_30001

	MEANS					
	BLQ_400		BLQ_50		N	
	LEX	NFV	LEX	NFV	LEX	NFV
1-10_K	67%	38%	67%	38%	15	8
10-100_K	63%	66%	51%	55%	78	38
100-250_K	71%	36%	62%	27%	21	11
250-500_K	62%	40%	48%	30%	29	10
>500_K	61%	31%	52%	19%	23	16

TRIAL_30002

	MEANS					
	BLQ_400		BLQ_50		N	
	LEX/r	NFV	LEX/r	NFV	LEX/r	NFV
1-10_K	74%	66%	74%	64%	30	33

10-100_K	60%	66%	54%	54%	167	161
100-250_K	60%	56%	56%	46%	32	52
250-500_K	50%	56%	30%	38%	42	34
>500_K	62%	44%	40%	34%	51	47

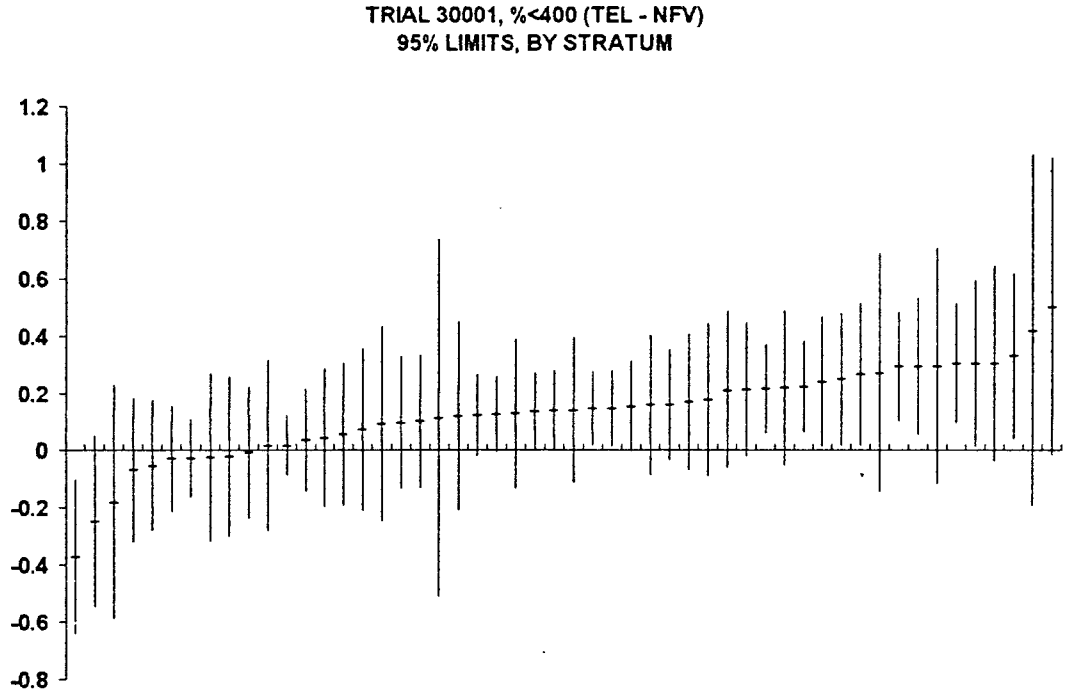
A more detailed examination of table 4.8 A leads one to consider lexiva superiority to nelfinavir at higher doses to be unproven. One can see that percent<400 for nelfinavir for trial 30002 also decreases but less sharply, from 66% to 44%. Furthermore, using an LOQ of 50 copies/ml, one sees that lexiva and boosted lexiva decline in efficacy, from 67-74% to 52-40% as baseline viral load increases. In trial 30001, unboosted lexiva was about the same as nelfinavir in the 10-100K category, which was the largest in terms of sample size, and appeared to have a fairly constant superiority over nelfinavir at the other levels of baseline viral load (from 67% vs 38% to 61% vs 31%). However, no such superiority is observable with boosted lexiva in trial 30002. One can only conclude that one of the two different nelfinavir patterns in the two trials is happenstance and that there is no way to tell, from these data alone, which it is. The one feature that is confirmed in both trials is that there is a dose-response pattern for both drugs with respect percent <50 copies/ml. For both lexiva (boosted or unboosted) and nelfinavir, percent BLQ declines with increasing baseline viral load, at least with the more stringent LOQ.

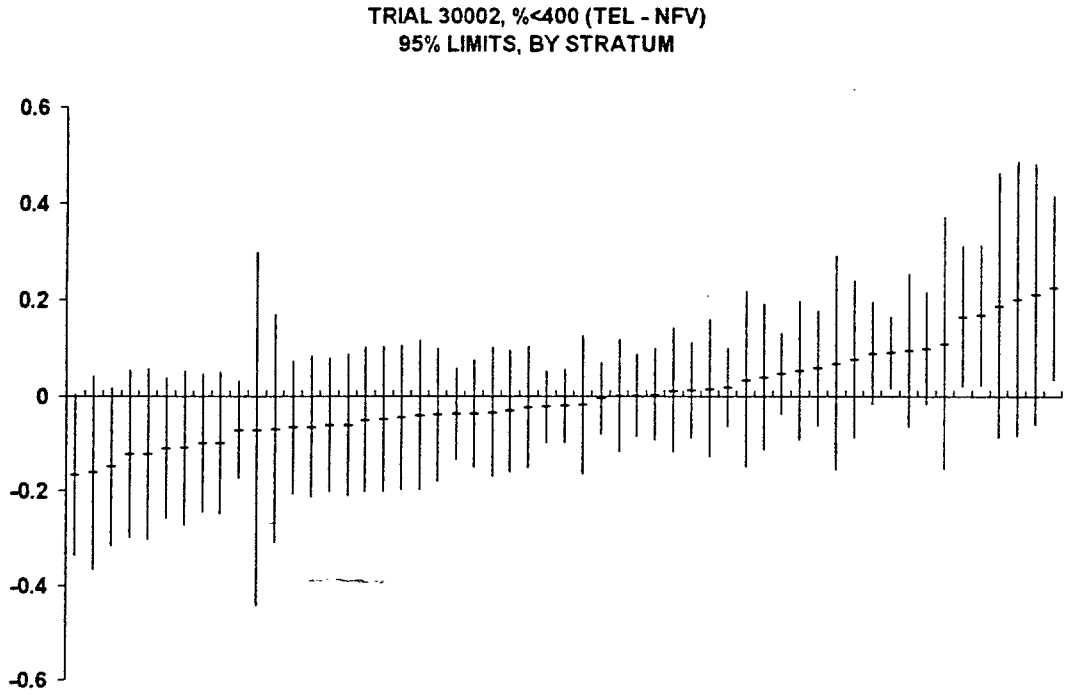
5. Results in Special Populations

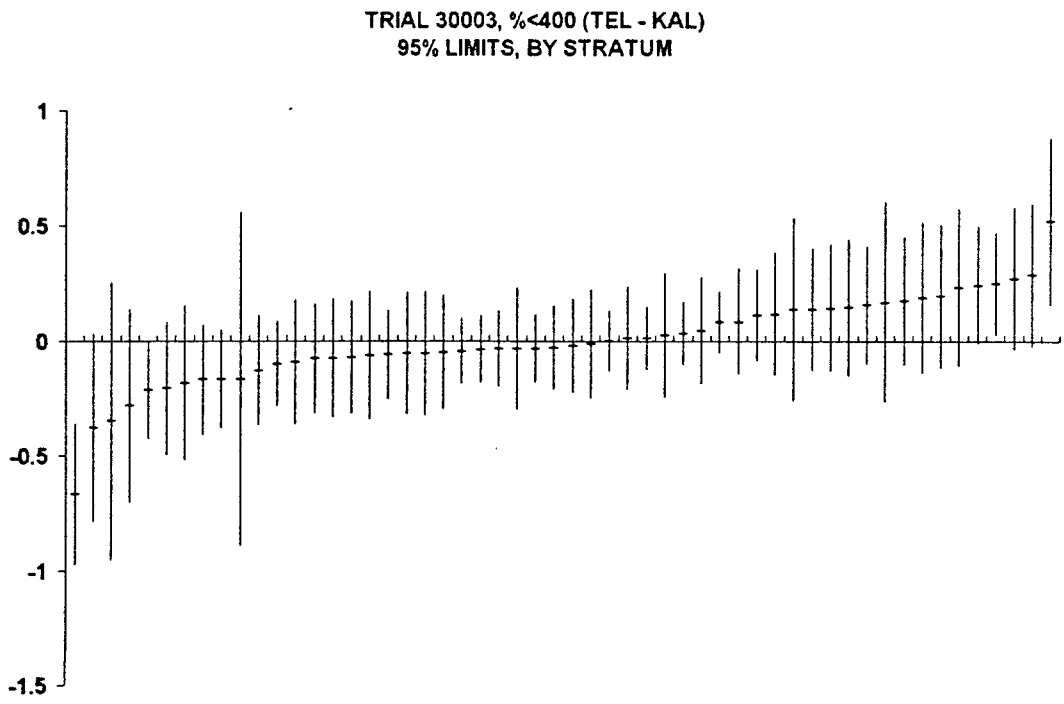
There was no evidence of interactions between treatment and any interesting covariates. Lexiva appeared to be roughly equally effective in both sexes, all races, at all levels studied for age, baseline HIV RNA, baseline CD4 count, previous AIDS diagnosis, source of HIV infection, geographic region, reason discontinued, concurrent hepatitis B or C, weight, exercise level, or alcohol consumption.

Figure 5 A shows a plot of estimated difference between LEX and NFV for trial 30001 in percent of subjects with viral load sustained below 400 copies/mL, together with 95% confidence intervals for the difference, for all the subgroups created by

subdivision according to any of the above covariates. (Very small subgroups have been deleted.) Figures 5 B and C show the corresponding plots for LEX/r versus NFV in trial 30002 and for LEX/r versus LPV/r in trial 30003.







The mean differences in these plots look just like what one would expect one took multiple observations from normal distribution with expected values of 14.5% (trial 30001), -0.6% (trial 30002), or -0.3% (trial 30003). There are two strata at the left ends of figures 5 A and C, respectively, with differences of LEX minus control that look a little low. The one in trial 30001 corresponds to the stratum for middle level of alcohol use; the one in trial 30003 corresponds to 'Yes' for other non-CDC HIV conditions, a stratum with a total of 12 subjects in both arms. Neither of these apparent anomalies is plausible as a real treatment-covariate interaction.

Thus, the plots support the contention that there were no identifiable sub-populations in which Lexiva or boosted Lexiva was less effective. Plots using TAD instead of %<400 looked similar and are not reproduced here.

Tables 5 A, B, and C give the differences in mean effect between LEX and NFV in trial 30001. Table 5 A shows results for TAD at week 48, table 5 B for %<400 at week 48, and table 5 C for

%<50 at week 48. (The negative numbers in table 5 A and the positive numbers in tables 5 B and C in the difference column both correspond to LEX superiority.) The tables also give 95% confidence limits for those differences, mean effects on LEX and on NFV, sample sizes on LEX and on NFV, and the p-values for the treatment differences for all subjects pooled together. Tables 5 D-F give the same results for the comparison of LEX/r to NFV in trial 30002; tables 5 G-I give the same results for the comparison of bid LEX/r to LPV/r in trial 30003. The primary did not support near equality for qd LEX/r to LPV/r;

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TABLE 5 A

WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE

TRIAL 30001

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX	NFV	N LEX	NFV	PVALUE
All	-0.27	-0.58	0.04	-2.17	-1.9	164	83	0.0843
STRATA_								
Pooled	-0.27	-0.57	0.04	-2.17	-1.90	164	83	0.0844
1-10_K	-0.51	-1.26	0.25	-1.65	-1.15	14	8	
10-100_K	0.11	-0.29	0.50	-1.96	-2.07	77	38	
>100_K	-0.61	-1.13	-0.08	-2.49	-1.89	73	37	
RSTRATA_								
Pooled	-0.27	-0.57	0.04	-2.17	-1.90	164	83	0.0858
1-10_K	-0.51	-1.25	0.24	-1.65	-1.15	15	8	
10-100_K	0.06	-0.34	0.46	-1.96	-2.02	76	39	
>100_K	-0.56	-1.09	-0.04	-2.50	-1.93	73	36	
SEX								
Pooled	-0.27	-0.59	0.04	-2.17	-1.90	164	83	
Female	-0.01	-0.55	0.52	-2.06	-2.05	51	26	
Male	-0.39	-0.77	-0.01	-2.22	-1.83	113	57	
RACE								
Pooled	-0.27	-0.58	0.04	-2.17	-1.90	164	83	
Black	0.01	-0.55	0.57	-1.86	-1.86	52	27	
Hispanic	-0.36	-0.83	0.10	-2.19	-1.83	70	38	
White	-0.51	-1.16	0.13	-2.52	-2.00	41	17	
AGE_Quartile								
Pooled	-0.28	-0.59	0.03	-2.17	-1.90	164	83	
<=30	-0.39	-1.09	0.30	-2.04	-1.65	43	17	
31-36	0.44	-0.18	1.07	-1.87	-2.31	32	17	
37-43	-0.30	-0.81	0.22	-2.33	-2.03	53	25	
>43	-0.73	-1.40	-0.06	-2.37	-1.65	36	24	
CONT								
Pooled	-0.27	-0.58	0.04	-2.17	-1.90	164	83	
N_America	-0.27	-0.60	0.05	-2.18	-1.91	151	75	
Other	-0.26	-1.35	0.83	-2.06	-1.80	13	8	

TABLE 5 A (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30001

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX	NFV	N LEX	NFV
HIV_Quartile_or_Levels							
Pooled	-0.30	-0.61	0.00	-2.17	-1.90	164	83
<15K	-0.32	-0.91	0.28	-1.52	-1.20	23	11
15-55K	0.08	-0.40	0.56	-1.90	-1.98	53	23
55-285K	-0.43	-1.00	0.14	-2.50	-2.08	42	25
>285K	-0.56	-1.25	0.14	-2.51	-1.96	46	24
<=10_K	-0.35	-1.07	0.37	-1.39	-1.04	15	7
10-100_K	-0.02	-0.40	0.36	-1.99	-1.97	78	36
>100_K	-0.56	-1.08	-0.03	-2.54	-1.98	71	40
1-10_K	-0.51	-1.26	0.25	-1.65	-1.15	14	8
10-100_K	0.11	-0.29	0.50	-1.96	-2.07	77	38
100-250_K	-0.05	-0.79	0.70	-2.42	-2.37	21	11
250-500_K	-0.38	-1.40	0.64	-2.38	-2.00	29	10
>500_K	-1.23	-2.13	-0.32	-2.71	-1.49	23	16
CD4_Quartile_or_Levels							
Pooled	-0.20	-0.51	0.11	-2.17	-1.90	164	83
<=72	-0.26	-0.96	0.45	-1.94	-1.69	35	24
73-196	-0.82	-1.60	-0.05	-2.71	-1.88	45	14
197-340	0.08	-0.41	0.58	-2.17	-2.25	46	22
>340	0.04	-0.52	0.59	-1.76	-1.79	38	23
<200	-0.57	-1.08	-0.07	-2.37	-1.80	80	39
>=200	0.00	-0.37	0.38	-1.98	-1.99	84	44
<50	-0.36	-1.19	0.47	-1.87	-1.51	27	17
>=50	-0.23	-0.56	0.10	-2.23	-2.00	137	66

TABLE 5 A (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX	NFV	LEX	NFV
Pooled	-0.02	-0.22	0.18	-2.17	-1.90	164	83
AE/Death	0.25	-0.91	1.41	-0.35	-0.60	9	5
Complete	-0.05	-0.28	0.18	-2.79	-2.74	114	45
LOE	-0.30	-0.90	0.31	-1.35	-1.05	12	17
LTFU	0.18	-0.29	0.65	-0.66	-0.84	29	16
CDC class. of HIV							
Pooled	-0.29	-0.59	0.02	-2.17	-1.90	164	83
Asymptomatic	-0.21	-0.58	0.15	-2.23	-2.02	101	54
Symptomatic	-0.44	-1.18	0.30	-1.76	-1.32	30	13
AIDS	-0.40	-1.22	0.42	-2.38	-1.97	33	16
Other non-CDC HIV conditions							
Pooled	-0.25	-0.56	0.06	-2.17	-1.90	164	83
No	-0.25	-0.57	0.06	-2.14	-1.89	156	82
HIV Risk Factor							
Pooled	-0.23	-0.53	0.07	-2.17	-1.90	164	83
Heterosexual	-0.08	-0.50	0.34	-2.18	-2.11	90	41
Homosexual	-0.56	-1.09	-0.03	-2.39	-1.83	55	31
IV_Drug_Use	0.02	-0.88	0.92	-0.93	-0.95	10	8
Other	0.20	-1.04	1.44	-2.11	-2.31	9	3
HBV Ag test							
Pooled	-0.27	-0.58	0.04	-2.17	-1.90	164	83
Negative	-0.25	-0.58	0.07	-2.16	-1.90	156	79
Positive	-0.65	-1.77	0.46	-2.47	-1.82	7	4
HCV Ab test							
Pooled	-0.25	-0.56	0.06	-2.17	-1.90	164	83
Negative	-0.28	-0.61	0.05	-2.25	-1.97	142	69
Reactive	-0.05	-0.92	0.81	-1.61	-1.56	21	14
Hepatitis Status							
Pooled	-0.25	-0.57	0.06	-2.17	-1.90	164	83
Hep_B_not_C	-0.82	-2.21	0.57	-2.47	-1.65	7	3
Hep_C_not_B	-0.11	-1.01	0.79	-1.61	-1.50	21	13
No_Hep	-0.25	-0.60	0.09	-2.23	-1.98	134	66

TABLE 5 A (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX	NFV	LEX	NFV
Pooled	-0.30	-0.60	0.00	-2.17	-1.90	164	83
0	-0.64	-1.01	-0.26	-2.41	-1.77	98	55
1-2	1.18	0.50	1.85	-1.57	-2.75	31	9
>2	-0.18	-0.86	0.50	-2.03	-1.85	35	19
WT_Quartile							
Pooled	-0.27	-0.58	0.04	-2.17	-1.90	164	83
<=61_kg	-0.12	-0.80	0.56	-1.92	-1.80	45	23
61-70_kg	-0.09	-0.73	0.55	-2.20	-2.11	41	16
71-80_kg	-0.53	-1.12	0.07	-2.34	-1.81	38	25
>80_kg	-0.32	-0.86	0.23	-2.28	-1.96	40	19
EXER_LEVEL							
Pooled	-0.30	-0.62	0.01	-2.17	-1.90	164	83
High	0.52	-0.72	1.76	-1.88	-2.40	20	5
Low	-0.69	-1.29	-0.10	-2.34	-1.65	40	31
Medium	0.04	-0.50	0.59	-2.08	-2.12	50	23
Sedentary	-0.42	-0.97	0.13	-2.33	-1.91	52	24

TABLE 5 B
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N		
	DIFF	LOW	UP	LEX	NFV	LEX	NFV	PVALUE
All	14.5%	1.5%	27.5%	64.0%	49.0%	166	83	0.0293
STRATA_								
1-10_K	29.2%	-12.0%	70.3%	67.0%	38.0%	15	8	
10-100_K	-3.0%	-21.5%	15.5%	63.0%	66.0%	78	38	
>100_K	29.2%	10.3%	48.2%	64.0%	35.0%	73	37	
RSTRATA_								
1-10_K	31.3%	-9.3%	71.8%	69.0%	38.0%	16	8	
10-100_K	-1.8%	-20.3%	16.8%	62.0%	64.0%	77	39	
>100_K	28.3%	9.1%	47.4%	64.0%	36.0%	73	36	
SEX	DIFF	LOW	UP	TEL	NFV	TEL	NFV	
Female	-0.8%	-23.8%	22.3%	61.0%	62.0%	51	26	
Male	21.4%	5.8%	36.9%	65.0%	44.0%	115	57	
RACE								
Black	9.5%	-13.6%	32.7%	58.0%	48.0%	52	27	
Hispanic	15.8%	-3.6%	35.3%	61.0%	45.0%	71	38	
White	17.4%	-9.3%	44.1%	76.0%	59.0%	42	17	
AGE_Quartile								
<=30	21.0%	-6.3%	48.4%	62.0%	41.0%	45	17	
31-36	-2.2%	-30.4%	26.0%	63.0%	65.0%	32	17	
37-43	10.0%	-13.2%	33.3%	66.0%	56.0%	53	25	
>43	26.4%	1.5%	51.3%	64.0%	38.0%	36	24	
CONT								
N_America	13.4%	-0.3%	27.1%	63.0%	49.0%	153	75	
Other	26.9%	-14.6%	68.5%	77.0%	50.0%	13	8	

TABLE 5 B (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30001

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX	NFV	N LEX	NFV
HIV_Quartile_or_Levels							
<15K	30.3%	-3.8%	64.4%	67.0%	36.0%	24	11
15-55K	-5.4%	-28.2%	17.4%	64.0%	70.0%	53	23
55-285K	24.7%	1.4%	48.0%	77.0%	52.0%	43	25
>285K	16.7%	-7.1%	40.4%	50.0%	33.0%	46	24
<=10_K	40.2%	-0.3%	80.6%	69.0%	29.0%	16	7
10-100_K	0.0%	-18.6%	18.6%	67.0%	67.0%	78	36
>100_K	22.2%	3.4%	41.0%	60.0%	38.0%	72	40
1-10_K	29.2%	-12.0%	70.3%	67.0%	38.0%	15	8
10-100_K	-3.0%	-21.5%	15.5%	63.0%	66.0%	78	38
100-250_K	35.1%	0.7%	69.4%	71.0%	36.0%	21	11
250-500_K	22.1%	-13.1%	57.2%	62.0%	40.0%	29	10
>500_K	29.6%	-0.6%	59.8%	61.0%	31.0%	23	16
CD4_Quartile_or_Levels							
<=72	13.9%	-11.6%	39.4%	51.0%	38.0%	35	24
73-196	32.7%	3.9%	61.5%	76.0%	43.0%	45	14
197-340	15.7%	-8.9%	40.2%	70.0%	55.0%	47	22
>340	-7.0%	-32.4%	18.3%	54.0%	61.0%	39	23
<200	24.0%	5.3%	42.6%	65.0%	41.0%	80	39
>=200	6.0%	-11.9%	23.8%	63.0%	57.0%	86	44
<50	24.6%	-3.0%	52.2%	48.0%	24.0%	27	17
>=50	10.8%	-3.5%	25.1%	67.0%	56.0%	139	66

TABLE 5 B (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX	NFV	LEX	NFV
AE/Death	0.0%	0.0%	0.0%	0.0%	0.0%	9	5
Complete	1.6%	-9.0%	12.2%	91.0%	89.0%	116	45
LOE	0.0%	0.0%	0.0%	0.0%	0.0%	12	17
LTFU	-2.8%	-16.4%	10.8%	3.0%	6.0%	29	16
CDC class. of HIV							
Asymptomatic	15.3%	-0.6%	31.2%	71.0%	56.0%	103	54
Symptomatic	30.3%	1.2%	59.3%	53.0%	23.0%	30	13
AIDS	1.5%	-28.3%	31.4%	52.0%	50.0%	33	16
Other non-CDC HIV conditions							
No	14.5%	1.3%	27.7%	63.0%	49.0%	158	82
Yes	-25.0%	-55.0%	5.0%	75.0%	100%	8	1
HIV Risk Factor							
Heterosexual	3.5%	-14.4%	21.4%	64.0%	61.0%	90	41
Homosexual	30.3%	9.5%	51.1%	75.0%	45.0%	57	31
IV_Drug_Use	-2.5%	-32.0%	27.0%	10.0%	13.0%	10	8
Other	11.1%	-51.3%	73.6%	44.0%	33.0%	9	3
HBV Ag test							
Negative	12.4%	-0.9%	25.8%	63.0%	51.0%	157	79
Positive	50.0%	-2.0%	102%	75.0%	25.0%	8	4
HCV Ab test							
Negative	13.8%	-0.3%	27.9%	66.0%	52.0%	144	69
Reactive	11.9%	-21.1%	44.9%	48.0%	36.0%	21	14
Hepatitis Status							
Hep_B_not_C	41.7%	-19.5%	103%	75.0%	33.0%	8	3
Hep_C_not_B	9.2%	-24.8%	43.2%	48.0%	38.0%	21	13
No_Hep	12.2%	-2.3%	26.6%	65.0%	53.0%	135	66

TABLE 5 B (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	TEL	NFV	TEL	NFV
0	22.2%	6.2%	38.3%	68.0%	45.0%	99	55
1-2	-37.3%	-64.3%	-10.2%	52.0%	89.0%	31	9
>2	21.8%	-5.4%	49.0%	64.0%	42.0%	36	19
WT_Quartile							
<=61_kg	5.5%	-19.6%	30.6%	53.0%	48.0%	45	23
61-70_kg	7.2%	-21.3%	35.6%	63.0%	56.0%	41	16
71-80_kg	29.2%	5.2%	53.3%	69.0%	40.0%	39	25
>80_kg	12.8%	-13.4%	39.0%	71.0%	58.0%	41	19
EXER_LEVEL							
High	-18.1%	-58.8%	22.7%	62.0%	80.0%	21	5
Low	23.8%	1.0%	46.6%	63.0%	39.0%	40	31
Medium	4.3%	-20.0%	28.6%	61.0%	57.0%	51	23
Sedentary	21.2%	-2.3%	44.6%	71.0%	50.0%	52	24

TABLE 5 C
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N		
	DIFF	LOW	UP	LEX	NFV	LEX	NFV	PVALUE
All	13.9%	0.9%	26.8%	54.0%	40.0%	166	83	0.0364
STRATA_								
1-10_K	29.2%	-12.0%	70.3%	67.0%	38.0%	15	8	
10-100_K	-4.0%	-23.3%	15.3%	51.0%	55.0%	78	38	
>100_K	29.1%	11.2%	47.0%	53.0%	24.0%	73	37	
RSTRATA_								
1-10_K	25.0%	-16.1%	66.1%	63.0%	38.0%	16	8	
10-100_K	-1.9%	-21.1%	17.3%	52.0%	54.0%	77	39	
>100_K	28.4%	10.2%	46.6%	53.0%	25.0%	73	36	
SEX								
Female	4.8%	-18.7%	28.4%	51.0%	46.0%	51	26	
Male	17.9%	2.5%	33.4%	55.0%	37.0%	115	57	
RACE								
Black	7.2%	-15.5%	29.9%	44.0%	37.0%	52	27	
Hispanic	17.9%	-1.1%	36.9%	52.0%	34.0%	71	38	
White	13.7%	-14.0%	41.4%	67.0%	53.0%	42	17	
AGE_Quartile								
<=30	23.9%	-2.2%	50.0%	53.0%	29.0%	45	17	
31-36	-9.2%	-38.5%	20.1%	44.0%	53.0%	32	17	
37-43	6.5%	-17.2%	30.1%	58.0%	52.0%	53	25	
>43	30.6%	6.8%	54.3%	56.0%	25.0%	36	24	
CONT								
N_America	13.6%	0.0%	27.2%	54.0%	40.0%	153	75	
Other	16.3%	-26.8%	59.5%	54.0%	38.0%	13	8	

TABLE 5 C (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30001

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX	NFV	N LEX	NFV
HIV_Quartile_or_Levels							
<15K	30.3%	-3.8%	64.4%	67.0%	36.0%	24	11
15-55K	5.0%	-19.4%	29.4%	53.0%	48.0%	53	23
55-285K	19.4%	-4.6%	43.5%	67.0%	48.0%	43	25
>285K	9.8%	-12.3%	31.9%	35.0%	25.0%	46	24
<=10_K	40.2%	-0.3%	80.6%	69.0%	29.0%	16	7
10-100_K	7.7%	-12.0%	27.4%	58.0%	50.0%	78	36
>100_K	13.3%	-5.2%	31.9%	46.0%	33.0%	72	40
1-10_K	29.2%	-12.0%	70.3%	67.0%	38.0%	15	8
10-100_K	-4.0%	-23.3%	15.3%	51.0%	55.0%	78	38
100-250_K	34.6%	1.1%	68.2%	62.0%	27.0%	21	11
250-500_K	18.3%	-15.5%	52.0%	48.0%	30.0%	29	10
>500_K	33.4%	5.5%	61.4%	52.0%	19.0%	23	16
CD4_Quartile_or_Levels							
<=72	17.9%	-6.0%	41.7%	43.0%	25.0%	35	24
73-196	19.8%	-9.2%	48.8%	56.0%	36.0%	45	14
197-340	14.1%	-11.0%	39.2%	60.0%	45.0%	47	22
>340	1.7%	-24.0%	27.4%	54.0%	52.0%	39	23
<200	21.8%	3.9%	39.7%	50.0%	28.0%	80	39
>=200	7.0%	-11.1%	25.1%	57.0%	50.0%	86	44
<50	26.8%	0.7%	52.9%	44.0%	18.0%	27	17
>=50	9.9%	-4.6%	24.5%	55.0%	45.0%	139	66

TABLE 5 C (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX	NFV	LEX	NFV
AE/Death	0.0%	0.0%	0.0%	0.0%	0.0%	9	5
Complete	5.6%	-9.7%	20.9%	77.0%	71.0%	116	45
LOE	0.0%	0.0%	0.0%	0.0%	0.0%	12	17
LTFU	-6.3%	-18.1%	5.6%	0.0%	6.0%	29	16
CDC class. of HIV							
Asymptomatic	15.7%	-0.5%	32.0%	60.0%	44.0%	103	54
Symptomatic	16.9%	-11.9%	45.8%	40.0%	23.0%	30	13
AIDS	8.0%	-21.2%	37.1%	45.0%	38.0%	33	16
Other non-CDC HIV conditions							
No	12.9%	-0.2%	26.1%	53.0%	40.0%	158	82
Yes	62.5%	29.0%	96.0%	63.0%	0.0%	8	1
HIV Risk Factor							
Heterosexual	4.6%	-13.9%	23.0%	53.0%	49.0%	90	41
Homosexual	26.2%	5.0%	47.4%	65.0%	39.0%	57	31
IV_Drug_Use	10.0%	-8.6%	28.6%	10.0%	0.0%	10	8
Other	0.0%	-61.6%	61.6%	33.0%	33.0%	9	3
HBV Ag test							
Negative	11.7%	-1.6%	25.1%	52.0%	41.0%	157	79
Positive	50.0%	-2.0%	102%	75.0%	25.0%	8	4
HCV Ab test							
Negative	11.4%	-2.9%	25.6%	55.0%	43.0%	144	69
Reactive	26.2%	-4.1%	56.5%	48.0%	21.0%	21	14
Hepatitis Status							
Hep_B_not_C	41.7%	-19.5%	103%	75.0%	33.0%	8	3
Hep_C_not_B	24.5%	-6.8%	55.9%	48.0%	23.0%	21	13
No_Hep	9.4%	-5.2%	24.0%	53.0%	44.0%	135	66

TABLE 5 C (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30001

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX	NFV	LEX	NFV
0	18.0%	2.0%	33.9%	53.0%	35.0%	99	55
1-2	-29.4%	-61.8%	3.0%	48.0%	78.0%	31	9
>2	24.3%	-2.6%	51.2%	61.0%	37.0%	36	19
WT_Quartile							
<=61_kg	18.5%	-5.4%	42.3%	49.0%	30.0%	45	23
61-70_kg	1.2%	-27.7%	30.1%	51.0%	50.0%	41	16
71-80_kg	15.3%	-9.2%	39.8%	51.0%	36.0%	39	25
>80_kg	16.0%	-10.8%	42.9%	63.0%	47.0%	41	19
EXER_LEVEL							
High	1.9%	-45.8%	49.6%	62.0%	60.0%	21	5
Low	21.7%	-0.1%	43.5%	48.0%	26.0%	40	31
Medium	-3.2%	-27.8%	21.4%	49.0%	52.0%	51	23
Sedentary	19.9%	-3.9%	43.6%	62.0%	42.0%	52	24

APPEARS THIS WAY
ON ORIGINAL

TABLE 5 D

WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE

TRIAL 30002

	MEAN	95% LIMITS		MEANS		N		
	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV	PVALUE
All	0.06	-0.1	0.24	-2.26	-2.32	318	318	0.4119
STRATA_								
Pooled	0.06	-0.10	0.22	-2.26	-2.32	318	318	0.4029
1-10_K	0.12	-0.26	0.52	-1.66	-1.80	29	31	
10-100_K	0.08	-0.12	0.28	-2.16	-2.24	164	159	
>100_K	0.04	-0.26	0.34	-2.50	-2.56	125	128	
RSTRATA_								
Pooled	0.06	-0.10	0.22	-2.26	-2.32	318	318	0.4042
1-10_K	0.18	-0.22	0.56	-1.64	-1.82	31	32	
10-100_K	0.12	-0.08	0.32	-2.16	-2.26	165	162	
>100_K	-0.02	-0.32	0.28	-2.54	-2.52	122	124	
SEX								
Pooled	0.06	-0.1	0.22	-2.26	-2.32	318	318	
Female	0.20	-0.1	0.48	-2.06	-2.24	95	76	
Male	0.00	-0.2	0.20	-2.34	-2.34	223	242	
RACE								
Pooled	0.06	-0.10	0.24	-2.26	-2.32	318	318	
Black	0.10	-0.16	0.38	-2.22	-2.32	120	102	
Hispanic	0.34	-0.26	0.92	-2.12	-2.46	23	24	
Other	0.16	-0.66	1.00	-2.14	-2.32	13	15	
White	0.00	-0.24	0.24	-2.30	-2.30	162	177	
AGE_Quartile								
Pooled	0.06	-0.10	0.24	-2.26	-2.32	318	318	
<=30	0.52	0.22	0.84	-1.82	-2.34	81	85	
31-36	-0.08	-0.38	0.22	-2.34	-2.26	92	87	
37-43	-0.26	-0.62	0.10	-2.48	-2.22	74	65	
>43	0.04	-0.30	0.38	-2.40	-2.44	71	81	
CONT								
Pooled	0.06	-0.10	0.22	-2.26	-2.32	318	318	
Europe	0.06	-0.20	0.32	-2.10	-2.18	136	135	
N_America	0.06	-0.22	0.32	-2.40	-2.44	131	137	
Other	0.10	-0.18	0.40	-2.24	-2.36	51	46	

TABLE 5 D (cont)

WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE

TRIAL 30002

	MEAN	95% LIMITS		MEANS		N	
	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV
HIV_Quartile_or_Levels							
Pooled	0.04	-0.12	0.20	-2.26	-2.32	318	318
<23K	0.12	-0.12	0.34	-1.70	-1.80	75	63
23-59K	0.22	-0.04	0.48	-2.00	-2.22	75	84
59-307K	0.10	-0.22	0.40	-2.40	-2.50	86	81
>307K	-0.22	-0.60	0.16	-2.82	-2.60	82	90
<=10_K	0.06	-0.24	0.36	-1.48	-1.54	31	32
10-100_K	0.14	-0.04	0.34	-2.02	-2.16	151	146
>100_K	-0.02	-0.30	0.26	-2.68	-2.66	136	140
1-10_K	0.12	-0.26	0.52	-1.66	-1.80	29	31
10-100_K	0.08	-0.12	0.28	-2.16	-2.24	164	159
100-250_K	0.06	-0.44	0.54	-2.46	-2.52	32	49
250-500_K	0.54	0.00	1.08	-2.10	-2.66	42	34
>500_K	-0.36	-0.86	0.14	-2.88	-2.52	51	45
CD4_Quartile_or_Levels							
Pooled	0.08	-0.08	0.24	-2.26	-2.32	318	318
<=72	-0.26	-0.62	0.10	-2.60	-2.34	85	83
73-196	0.26	-0.04	0.56	-2.28	-2.54	102	88
197-340	0.12	-0.16	0.40	-2.16	-2.28	71	90
>340	0.22	-0.10	0.52	-1.80	-2.00	60	57
<200	0.00	-0.24	0.24	-2.44	-2.44	184	173
>=200	0.18	-0.04	0.38	-1.98	-2.16	130	144
<50	-0.44	-0.86	0.00	-2.72	-2.30	62	68
>=50	0.18	0.00	0.36	-2.14	-2.32	252	249

TABLE 5 D (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30002

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV
Pooled	-0.08	-0.20	0.04	-2.26	-2.32	318	318
AE/Death	-0.08	-0.54	0.40	-0.76	-0.68	30	16
Complete	-0.20	-0.32	-0.06	-2.78	-2.58	228	255
LOE	1.18	0.40	1.98	-0.24	-1.44	3	8
LTFU	0.44	0.02	0.86	-1.04	-1.48	57	39
CDC class. of HIV							
Pooled	0.06	-0.10	0.22	-2.26	-2.32	318	318
Asymptomatic	0.24	0.04	0.44	-2.10	-2.34	178	167
Symptomatic	-0.02	-0.36	0.32	-2.26	-2.24	73	79
AIDS	-0.28	-0.68	0.12	-2.66	-2.38	67	71
Other non-CDC HIV conditions							
Pooled	0.08	-0.10	0.24	-2.26	-2.32	318	318
No	0.10	-0.06	0.26	-2.24	-2.34	302	298
Yes	-0.42	-1.16	0.32	-2.34	-1.92	16	20
HIV Risk Factor							
Pooled	0.06	-0.10	0.22	-2.26	-2.32	318	318
Heterosexual	0.04	-0.22	0.28	-2.20	-2.24	143	126
Homosexual	-0.04	-0.32	0.24	-2.46	-2.42	97	125
IV_Drug_Use	0.52	0.04	0.98	-1.72	-2.24	42	43
Other	-0.10	-0.68	0.48	-2.48	-2.38	36	24
HBV Ag test							
Pooled	0.06	-0.10	0.24	-2.26	-2.32	318	318
Negative	0.10	-0.08	0.26	-2.24	-2.34	291	292
Positive	-0.10	-0.66	0.44	-2.26	-2.16	25	23
HCV Ab test							
Pooled	0.08	-0.08	0.24	-2.26	-2.32	318	318
Negative	0.02	-0.16	0.20	-2.36	-2.36	261	256
Reactive	0.40	-0.04	0.82	-1.76	-2.16	55	59
Hepatitis Status							
Pooled	0.08	-0.10	0.24	-2.26	-2.32	318	318
Hep_B_not_C	-0.20	-0.76	0.36	-2.38	-2.18	22	22
Hep_C_not_B	0.38	-0.06	0.82	-1.78	-2.16	52	58
No_Hep	0.04	-0.14	0.22	-2.34	-2.38	239	234

TABLE 5 D (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30002

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV
Pooled	0.06	-0.10	0.24	-2.26	-2.32	318	318
0	0.12	-0.10	0.32	-2.24	-2.36	191	194
1-2	-0.16	-0.58	0.28	-2.36	-2.22	46	51
>2	0.08	-0.26	0.42	-2.22	-2.30	81	73
WT_Quartile							
Pooled	0.06	-0.10	0.24	-2.26	-2.32	318	318
<=61_kg	0.14	-0.20	0.46	-2.12	-2.26	78	83
61-70_kg	-0.04	-0.36	0.30	-2.24	-2.22	92	83
71-80_kg	0.26	-0.10	0.62	-2.10	-2.36	73	75
>80_kg	-0.08	-0.36	0.22	-2.52	-2.46	75	77
EXER_LEVEL							
Pooled	0.06	-0.10	0.22	-2.26	-2.32	318	318
High	-0.24	-0.64	0.16	-2.56	-2.32	35	41
Low	-0.06	-0.34	0.24	-2.28	-2.24	106	103
Medium	0.12	-0.20	0.44	-2.14	-2.28	96	83
Sedentary	0.26	-0.06	0.60	-2.20	-2.46	80	90

TABLE 5 E

WEEK 48 PERCENT < 400 COPIES/ML

TRIAL 30002

	MEAN	95% LIMITS		MEANS		N		
	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV	PVALUE
All	-0.6%	-8.2%	7.0%	60.0%	60.0%	322	327	0.8733
STRATA_								
1-10_K	6.6%	-15.8%	29.2%	74.0%	66.0%	30	33	
10-100_K	-7.2%	-17.6%	3.2%	60.0%	66.0%	167	161	
>100_K	5.8%	-6.4%	17.8%	58.0%	52.0%	125	133	
RSTRATA_								
1-10_K	1.2%	-21.4%	23.6%	68.0%	68.0%	32	34	
10-100_K	-8.0%	-18.2%	2.4%	58.0%	66.0%	168	166	
>100_K	8.6%	-3.6%	21.0%	60.0%	52.0%	122	127	
SEX								
Female	-11.2%	-26.0%	3.8%	42.0%	54.0%	96	78	
Male	4.6%	-4.0%	13.2%	68.0%	62.0%	226	249	
RACE								
Black	-3.2%	-16.2%	9.6%	50.0%	54.0%	122	109	
Hispanic	10.8%	-15.6%	37.2%	70.0%	60.0%	24	25	
Other	-7.2%	-44.2%	29.8%	46.0%	54.0%	13	15	
White	1.2%	-9.0%	11.2%	66.0%	66.0%	163	178	
AGE_Quartile								
<=30	-10.0%	-25.0%	5.0%	48.0%	58.0%	82	87	
31-36	-4.0%	-18.2%	10.0%	58.0%	62.0%	94	91	
37-43	9.4%	-6.6%	25.4%	66.0%	56.0%	75	68	
>43	5.2%	-9.4%	19.8%	72.0%	66.0%	71	81	
CONT								
Europe	-3.8%	-15.2%	7.6%	62.0%	66.0%	137	135	
N_America	8.8%	-2.0%	19.6%	74.0%	66.0%	134	143	
Other	-15.0%	-31.8%	1.8%	18.0%	32.0%	51	49	

TABLE 5 E (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30002

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX/r	NFV	N LX/r	NFV
HIV_Quartile_or_Levels							
<23K	-5.0%	-20.4%	10.4%	64.0%	68.0%	77	67
23-59K	-6.2%	-21.2%	8.8%	58.0%	64.0%	77	85
59-307K	-10.0%	-24.6%	4.6%	54.0%	64.0%	86	85
>307K	16.8%	2.0%	31.4%	64.0%	46.0%	82	90
<=10_K	13.6%	-8.8%	36.0%	72.0%	58.0%	32	36
10-100_K	-8.4%	-19.4%	2.4%	58.0%	66.0%	154	148
>100_K	4.2%	-7.4%	15.8%	58.0%	54.0%	136	143
1-10_K	6.6%	-15.8%	29.2%	74.0%	66.0%	30	33
10-100_K	-7.2%	-17.6%	3.2%	60.0%	66.0%	167	161
100-250_K	3.6%	-18.2%	25.4%	60.0%	56.0%	32	52
250-500_K	-5.8%	-28.4%	16.6%	50.0%	56.0%	42	34
>500_K	18.0%	-1.4%	37.6%	62.0%	44.0%	51	47
CD4_Quartile_or_Levels							
<=72	16.4%	1.8%	31.2%	66.0%	50.0%	85	85
73-196	-6.2%	-20.4%	8.0%	50.0%	56.0%	102	89
197-340	-2.0%	-16.6%	12.6%	64.0%	66.0%	74	93
>340	-11.0%	-27.4%	5.2%	64.0%	76.0%	61	60
<200	5.4%	-5.0%	15.6%	58.0%	52.0%	184	176
>=200	-6.6%	-17.6%	4.4%	64.0%	70.0%	134	150
<50	21.4%	4.8%	38.0%	68.0%	46.0%	62	69
>=50	-6.0%	-14.4%	2.4%	58.0%	64.0%	256	257

TABLE 5 E (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30002

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV
Hepatitis Status							
AE/Death	-2.6%	-15.4%	10.4%	4.0%	6.0%	30	17
Complete	9.0%	1.4%	16.6%	80.0%	70.0%	232	263
LOE	0.0%	0.0%	0.0%	0.0%	0.0%	3	8
LTFU	-16.8%	-33.8%	0.4%	14.0%	30.0%	57	39
CDC class. of HIV							
Asymptomatic	-3.8%	-13.6%	5.8%	66.0%	70.0%	182	172
Symptomatic	-4.2%	-20.0%	11.6%	46.0%	50.0%	73	81
AIDS	7.6%	-9.0%	24.0%	58.0%	50.0%	67	73
Other non-CDC HIV conditions							
No	-2.4%	-10.0%	5.2%	62.0%	64.0%	305	306
Yes	21.0%	-6.2%	48.2%	36.0%	14.0%	17	21
HIV Risk Factor							
Heterosexual	-0.2%	-12.0%	11.8%	52.0%	52.0%	145	129
Homosexual	9.8%	-2.0%	21.6%	76.0%	66.0%	98	131
IV_Drug_Use	-16.2%	-36.8%	4.2%	52.0%	68.0%	43	43
Other	-7.0%	-31.0%	17.0%	64.0%	70.0%	36	24
HBV Ag test							
Negative	-2.2%	-10.0%	5.6%	60.0%	62.0%	294	301
Positive	18.6%	-9.0%	46.2%	58.0%	40.0%	26	23
HCV Ab test							
Negative	1.8%	-6.6%	10.0%	62.0%	60.0%	263	264
Reactive	-12.4%	-30.0%	5.4%	52.0%	66.0%	57	60
Hepatitis Status							
Hep_B_not_C	20.0%	-8.6%	48.6%	60.0%	40.0%	23	22
Hep_C_not_B	-12.4%	-30.4%	5.6%	54.0%	66.0%	54	59
No_Hep	0.0%	-8.6%	8.8%	62.0%	62.0%	240	242

TABLE 5 E (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30002

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV
0	0.2%	-9.4%	10.0%	58.0%	58.0%	194	200
1-2	3.2%	-15.2%	21.8%	68.0%	64.0%	47	54
>2	-5.2%	-20.4%	10.2%	60.0%	64.0%	81	73
WT_Quartile							
<=61_kg	-4.6%	-20.0%	10.6%	44.0%	48.0%	78	85
61-70_kg	1.4%	-13.0%	16.0%	60.0%	58.0%	92	84
71-80_kg	3.8%	-11.6%	19.2%	64.0%	60.0%	75	78
>80_kg	-3.6%	-17.2%	10.2%	72.0%	76.0%	77	80
EXER_LEVEL							
High	22.4%	3.2%	41.6%	82.0%	60.0%	35	43
Low	1.0%	-12.0%	14.2%	62.0%	60.0%	108	105
Medium	-6.6%	-20.8%	7.4%	58.0%	64.0%	97	87
Sedentary	-6.6%	-21.4%	8.4%	50.0%	58.0%	81	91

TABLE 5 F
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30002

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX/r	NFV	N LX/r	NFV	PVALUE
All	1.4%	-6.4%	9.0%	50.0%	50.0%	322	327	0.7241
STRATA_								
1-10_K	9.6%	-13.2%	32.4%	74.0%	64.0%	30	33	
10-100_K	-0.2%	-11.0%	10.6%	54.0%	54.0%	167	161	
>100_K	1.0%	-11.0%	13.0%	40.0%	40.0%	125	133	
RSTRATA_								
1-10_K	4.0%	-18.6%	26.8%	68.0%	64.0%	32	34	
10-100_K	-1.2%	-12.0%	9.4%	52.0%	54.0%	168	166	
>100_K	4.0%	-8.2%	16.4%	44.0%	40.0%	122	127	
SEX								
Female	-4.0%	-18.8%	10.8%	40.0%	44.0%	96	78	
Male	4.4%	-4.6%	13.2%	56.0%	52.0%	226	249	
RACE								
Black	6.0%	-6.6%	18.6%	42.0%	36.0%	122	109	
Hispanic	2.6%	-24.8%	29.8%	62.0%	60.0%	24	25	
Other	6.2%	-30.6%	42.8%	46.0%	40.0%	13	15	
White	-1.0%	-11.6%	9.6%	56.0%	56.0%	163	178	
AGE_Quartile								
<=30	-2.2%	-17.2%	12.6%	42.0%	44.0%	82	87	
31-36	-9.2%	-23.6%	5.2%	44.0%	54.0%	94	91	
37-43	17.4%	1.4%	33.6%	58.0%	42.0%	75	68	
>43	3.8%	-11.8%	19.4%	60.0%	56.0%	71	81	
CONT								
Europe	-1.4%	-13.4%	10.4%	52.0%	52.0%	137	135	
N_America	8.2%	-3.2%	19.8%	64.0%	56.0%	134	143	
Other	-6.6%	-20.6%	7.4%	12.0%	18.0%	51	49	

TABLE 5 F (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30002

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX/r	NFV	N LX/r	NFV
HIV_Quartile_or_Levels							
<23K	-0.8%	-16.4%	14.8%	64.0%	66.0%	77	67
23-59K	9.0%	-6.4%	24.2%	58.0%	48.0%	77	85
59-307K	-12.2%	-27.0%	2.6%	40.0%	52.0%	86	85
>307K	7.0%	-7.4%	21.6%	42.0%	34.0%	82	90
<=10_K	16.4%	-6.2%	38.8%	72.0%	56.0%	32	36
10-100_K	0.4%	-10.8%	11.6%	56.0%	56.0%	154	148
>100_K	-1.6%	-13.0%	10.0%	40.0%	42.0%	136	143
1-10_K	9.6%	-13.2%	32.4%	74.0%	64.0%	30	33
10-100_K	-0.2%	-11.0%	10.6%	54.0%	54.0%	167	161
100-250_K	10.0%	-11.8%	32.0%	56.0%	46.0%	32	52
250-500_K	-7.2%	-28.8%	14.2%	30.0%	38.0%	42	34
>500_K	5.2%	-13.8%	24.2%	40.0%	34.0%	51	47
CD4_Quartile_or_Levels							
<=72	13.0%	-1.8%	27.6%	48.0%	36.0%	85	85
73-196	-5.8%	-19.8%	8.2%	40.0%	44.0%	102	89
197-340	3.2%	-11.8%	18.4%	58.0%	54.0%	74	93
>340	-2.8%	-19.6%	14.2%	64.0%	66.0%	61	60
<200	3.8%	-6.4%	13.8%	44.0%	40.0%	184	176
>=200	0.4%	-11.0%	11.8%	60.0%	60.0%	134	150
<50	16.6%	0.0%	33.4%	50.0%	34.0%	62	69
>=50	-2.6%	-11.2%	6.2%	50.0%	54.0%	256	257

TABLE 5 F (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30002

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV
AE/Death	-2.6%	-15.4%	10.4%	4.0%	6.0%	30	17
Complete	10.2%	1.8%	18.8%	68.0%	58.0%	232	263
LOE	0.0%	0.0%	0.0%	0.0%	0.0%	3	8
LTFU	-15.2%	-31.0%	0.8%	10.0%	26.0%	57	39
CDC class. of HIV							
Asymptomatic	1.8%	-8.6%	12.0%	60.0%	58.0%	182	172
Symptomatic	-6.6%	-21.8%	8.6%	32.0%	40.0%	73	81
AIDS	5.0%	-11.4%	21.2%	44.0%	38.0%	67	73
Other non-CDC HIV conditions							
No	0.4%	-7.4%	8.4%	52.0%	52.0%	305	306
Yes	9.2%	-15.8%	34.4%	24.0%	14.0%	17	21
HIV Risk Factor							
Heterosexual	7.0%	-4.6%	18.6%	44.0%	38.0%	145	129
Homosexual	4.2%	-8.6%	17.0%	62.0%	58.0%	98	131
IV_Drug_Use	-11.6%	-32.6%	9.4%	44.0%	56.0%	43	43
Other	-1.4%	-27.2%	24.4%	52.0%	54.0%	36	24
HBV Ag test							
Negative	-0.8%	-8.8%	7.2%	50.0%	50.0%	294	301
Positive	26.8%	-0.2%	53.8%	62.0%	34.0%	26	23
HCV Ab test							
Negative	3.2%	-5.4%	11.8%	52.0%	48.0%	263	264
Reactive	-7.6%	-25.8%	10.4%	48.0%	56.0%	57	60
Hepatitis Status							
Hep_B_not_C	28.8%	0.8%	56.8%	66.0%	36.0%	23	22
Hep_C_not_B	-7.8%	-26.2%	10.6%	48.0%	56.0%	54	59
No_Hep	0.8%	-8.2%	9.8%	50.0%	50.0%	240	242

TABLE 5 F (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30002

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX/r	NFV	LX/r	NFV
0	2.0%	-7.8%	11.8%	50.0%	48.0%	194	200
1-2	5.8%	-13.4%	25.2%	60.0%	54.0%	47	54
>2	-2.6%	-18.4%	13.2%	48.0%	50.0%	81	73
WT_Quartile							
<=61_kg	-4.2%	-19.0%	10.8%	36.0%	40.0%	78	85
61-70_kg	-0.8%	-15.6%	13.8%	46.0%	48.0%	92	84
71-80_kg	9.8%	-5.8%	25.6%	58.0%	48.0%	75	78
>80_kg	1.2%	-14.0%	16.2%	64.0%	62.0%	77	80
EXER_LEVEL							
High	19.2%	-2.4%	40.8%	66.0%	46.0%	35	43
Low	6.0%	-7.4%	19.4%	54.0%	48.0%	108	105
Medium	-12.6%	-26.8%	1.6%	50.0%	62.0%	97	87
Sedentary	1.2%	-13.4%	15.8%	40.0%	40.0%	81	91

TABLE 5 G

WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE

TRIAL 30003

	MEAN	95% LIMITS		MEANS		N		
	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL	PVALUE
All	0.27	0	0.54	-1.4	-1.67	104	103	0.0533
STRATA_								
Pooled	0.28	0.02	0.54	-1.40	-1.67	104	103	0.0347
1-10_K	-0.11	-0.48	0.26	-1.40	-1.29	41	43	
10-100_K	0.24	-0.16	0.64	-1.51	-1.75	45	46	
>100_K	1.43	0.67	2.20	-1.11	-2.55	18	14	
RSTRATA_								
Pooled	0.28	0.01	0.54	-1.40	-1.67	104	103	0.0394
1-10_K	-0.01	-0.39	0.37	-1.39	-1.38	40	41	
10-100_K	0.14	-0.27	0.54	-1.51	-1.65	46	47	
>100_K	1.37	0.63	2.11	-1.13	-2.50	18	15	
SEX								
Pooled	0.27	0.00	0.54	-1.40	-1.67	104	103	
Female	-0.04	-0.69	0.61	-1.54	-1.50	14	17	
Male	0.32	0.02	0.62	-1.38	-1.70	90	86	
RACE								
Pooled	0.27	0.00	0.55	-1.40	-1.67	104	103	
Black	-0.01	-0.61	0.60	-1.43	-1.42	22	33	
Hispanic	0.65	-0.14	1.45	-1.50	-2.16	9	11	
White	0.33	0.00	0.66	-1.38	-1.71	72	59	
AGE_Quartile								
Pooled	0.25	-0.02	0.53	-1.40	-1.67	104	103	
<=36	0.22	-0.38	0.83	-1.38	-1.60	28	25	
37-41	0.55	0.01	1.09	-1.15	-1.70	31	24	
42-46	-0.02	-0.53	0.49	-1.79	-1.77	23	26	
>46	0.24	-0.29	0.77	-1.36	-1.60	22	28	
CONT								
Pooled	0.27	-0.01	0.54	-1.40	-1.67	104	103	
Europe	0.34	-0.11	0.79	-1.47	-1.81	44	31	
N_America	0.28	-0.09	0.65	-1.26	-1.54	53	59	
Other	-0.07	-1.02	0.88	-1.94	-1.87	7	13	

TABLE 5 G (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N	
	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL
HIV_Quartile_or_Levels							
Pooled	0.26	0.00	0.52	-1.40	-1.67	104	103
<=2.1_K	-0.06	-0.48	0.37	-1.03	-0.97	14	14
2.1-11_K	0.04	-0.35	0.43	-1.40	-1.43	33	32
11-43_K	0.30	-0.20	0.79	-1.42	-1.71	33	32
>43_K	0.70	0.01	1.39	-1.59	-2.29	24	25
<=10_K	0.00	-0.32	0.31	-1.27	-1.27	46	43
10-100_K	0.26	-0.16	0.67	-1.43	-1.69	47	46
>100_K	1.02	0.04	2.01	-1.79	-2.81	11	14
1-10_K	-0.11	-0.48	0.26	-1.40	-1.29	41	43
10-100_K	0.24	-0.16	0.64	-1.51	-1.75	45	46
100-250_K	1.49	0.58	2.41	-1.19	-2.69	9	8
>250_K	1.33	-0.05	2.71	-1.03	-2.36	9	6
CD4_Quartile_or_Levels							
Pooled	0.22	-0.06	0.49	-1.40	-1.67	104	103
<=179	0.41	-0.15	0.97	-1.58	-2.00	28	32
180-285	0.37	-0.14	0.88	-1.39	-1.76	20	32
286-441	-0.32	-0.84	0.21	-1.51	-1.19	32	23
>441	0.45	-0.10	1.00	-1.04	-1.50	24	16
<200	0.44	-0.05	0.94	-1.56	-2.00	32	38
>=200	0.14	-0.17	0.46	-1.33	-1.47	72	65
<50	1.53	0.26	2.80	-0.93	-2.46	7	8
>=50	0.17	-0.11	0.44	-1.43	-1.60	97	95

TABLE 5 G (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL
Pooled	0.19	-0.06	0.43	-1.40	-1.67	104	103
AE/Death	0.10	-0.16	0.35	-0.09	-0.19	2	6
Complete	0.20	-0.07	0.46	-1.61	-1.81	89	94
LTFU	0.00	-0.13	0.13	-0.07	-0.07	9	3
CDC class. of HIV							
Pooled	0.26	-0.01	0.53	-1.40	-1.67	104	103
Asymptomatic	0.43	-0.02	0.89	-1.23	-1.66	43	37
Symptomatic	0.06	-0.37	0.49	-1.72	-1.78	28	31
AIDS	0.22	-0.28	0.72	-1.34	-1.56	33	35
Other non-CDC HIV conditions							
Pooled	0.27	0.00	0.55	-1.40	-1.67	104	103
No	0.25	-0.04	0.53	-1.40	-1.65	95	100
Yes	0.88	0.23	1.52	-1.36	-2.24	9	3
HIV Risk Factor							
Pooled	0.25	-0.03	0.53	-1.40	-1.67	104	103
Heterosexual	0.13	-0.35	0.61	-1.58	-1.71	28	40
Homosexual	0.22	-0.19	0.63	-1.38	-1.60	56	43
IV_Drug_Use	-0.01	-1.01	0.99	-1.49	-1.48	11	10
Other	1.12	0.44	1.80	-0.82	-1.94	9	10
HBV Ag test							
Pooled	0.27	0.00	0.54	-1.40	-1.67	104	103
Negative	0.24	-0.04	0.52	-1.43	-1.67	100	98
Positive	1.00	0.00	2.00	-0.65	-1.66	4	5
HCV Ab test							
Pooled	0.26	-0.01	0.53	-1.40	-1.67	104	103
Negative	0.19	-0.12	0.49	-1.39	-1.58	88	85
Reactive	0.65	0.09	1.22	-1.43	-2.08	16	18
Hepatitis Status							
Pooled	0.26	0.00	0.53	-1.40	-1.67	104	103
Hep_B_not_C	0.61	-0.51	1.72	-0.88	-1.48	3	4
Hep_C_not_B	0.54	-0.03	1.10	-1.53	-2.07	15	17
No_Hep	0.17	-0.14	0.48	-1.41	-1.58	85	81

TABLE 5 G (cont)
WEEK 48 TIME AVERAGED DIFFERENCE FROM BASELINE
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL
Pooled	0.27	0.00	0.54	-1.40	-1.67	104	103
<=0	0.32	-0.06	0.69	-1.43	-1.75	53	54
1	0.57	-0.11	1.24	-1.02	-1.59	10	9
2-4	-0.19	-0.90	0.53	-1.54	-1.35	17	19
>4	0.38	-0.22	0.99	-1.37	-1.75	24	21
WT_Quartile							
Pooled	0.28	0.02	0.55	-1.40	-1.67	104	103
<=65_kg	0.45	-0.14	1.05	-1.47	-1.93	28	20
66-73_kg	0.66	0.13	1.19	-1.06	-1.72	25	27
74-82_kg	-0.24	-0.76	0.28	-1.64	-1.40	26	30
>82_kg	0.32	-0.18	0.81	-1.39	-1.70	25	26
EXER_LEVEL							
Pooled	0.23	-0.05	0.51	-1.40	-1.67	104	103
High	-0.36	-1.06	0.35	-1.83	-1.47	14	15
Low	0.36	-0.12	0.84	-1.30	-1.67	29	34
Medium	0.59	0.10	1.07	-1.29	-1.88	24	37
Sedentary	-0.04	-0.69	0.62	-1.41	-1.37	36	17

TABLE 5 H
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N		
	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL	PVALUE
All	-3.2%	-16.5%	10.0%	58.0%	61.0%	107	103	0.6342
STRATA_								
1-10_K	6.4%	-12.9%	25.7%	74.0%	67.0%	42	43	
10-100_K	-4.3%	-24.6%	15.9%	54.0%	59.0%	46	46	
>100_K	-18.4%	-51.9%	15.1%	32.0%	50.0%	19	14	
RSTRATA_								
1-10_K	4.9%	-14.3%	24.0%	76.0%	71.0%	41	41	
10-100_K	-1.2%	-21.2%	18.9%	54.0%	55.0%	48	47	
>100_K	-25.6%	-58.2%	7.1%	28.0%	53.0%	18	15	
SEX								
Female	30.3%	-3.0%	63.5%	71.0%	41.0%	14	17	
Male	-9.2%	-23.5%	5.1%	56.0%	65.0%	93	86	
RACE								
Black	13.6%	-13.0%	40.3%	59.0%	45.0%	22	33	
Hispanic	-28.3%	-70.1%	13.5%	44.0%	73.0%	9	11	
White	-9.1%	-25.5%	7.2%	59.0%	68.0%	75	59	
AGE_Quartile								
<=36	-2.0%	-29.0%	25.0%	50.0%	52.0%	28	25	
37-41	-17.0%	-42.8%	8.7%	45.0%	63.0%	33	24	
42-46	5.2%	-18.8%	29.2%	78.0%	73.0%	23	26	
>46	8.1%	-18.7%	34.8%	65.0%	57.0%	23	28	
CONT								
Europe	-5.4%	-27.7%	16.8%	59.0%	65.0%	44	31	
N_America	-4.8%	-23.0%	13.4%	55.0%	59.0%	55	59	
Other	13.5%	-26.5%	53.5%	75.0%	62.0%	8	13	

TABLE 5 H (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30003

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX/r	KAL	N LX/r	KAL
HIV_Quartile_or_Levels							
<=2.1_K	14.3%	-15.6%	44.2%	86.0%	71.0%	14	14
2.1-11_K	1.8%	-20.4%	24.0%	71.0%	69.0%	34	32
11-43_K	-20.2%	-43.8%	3.5%	45.0%	66.0%	33	32
>43_K	2.3%	-24.7%	29.3%	42.0%	40.0%	26	25
<=10_K	4.7%	-13.8%	23.2%	74.0%	70.0%	47	43
10-100_K	-10.7%	-30.8%	9.4%	46.0%	57.0%	48	46
>100_K	-8.3%	-46.6%	29.9%	42.0%	50.0%	12	14
1-10_K	6.4%	-12.9%	25.7%	74.0%	67.0%	42	43
10-100_K	-4.3%	-24.6%	15.9%	54.0%	59.0%	46	46
100-250_K	-16.7%	-63.0%	29.7%	33.0%	50.0%	9	8
>250_K	-20.0%	-69.1%	29.1%	30.0%	50.0%	10	6
CD4_Quartile_or_Levels							
<=179	-5.2%	-30.2%	19.9%	45.0%	50.0%	29	32
180-285	-8.8%	-35.6%	18.1%	60.0%	69.0%	20	32
286-441	14.1%	-11.3%	39.5%	71.0%	57.0%	34	23
>441	-20.8%	-49.9%	8.3%	54.0%	75.0%	24	16
<200	-9.8%	-33.0%	13.4%	45.0%	55.0%	33	38
>=200	-1.1%	-17.1%	14.9%	64.0%	65.0%	74	65
<50	-33.9%	-81.3%	13.5%	29.0%	63.0%	7	8
>=50	-1.1%	-14.8%	12.7%	60.0%	61.0%	100	95

TABLE 5 H (cont)

WEEK 48 PERCENT < 400 COPIES/ML

TRIAL 30003

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL
AE/Death	0.0%	0.0%	0.0%	0.0%	0.0%	2	6
Complete	0.4%	-13.1%	13.9%	67.0%	67.0%	92	94
LTFU	0.0%	0.0%	0.0%	0.0%	0.0%	9	3
CDC class. of HIV							
Asymptomatic	-14.4%	-35.9%	7.1%	48.0%	62.0%	44	37
Symptomatic	11.8%	-9.3%	32.9%	83.0%	71.0%	29	31
AIDS	-1.4%	-25.0%	22.2%	50.0%	51.0%	34	35
Other non-CDC HIV conditions							
No	0.2%	-13.4%	13.8%	60.0%	60.0%	98	100
Yes	-66.7%	-97.5%	-35.9%	33.0%	100%	9	3
HIV Risk Factor							
Heterosexual	-0.7%	-23.8%	22.4%	64.0%	65.0%	28	40
Homosexual	-6.2%	-25.6%	13.1%	54.0%	60.0%	59	43
IV_Drug_Use	41.8%	3.9%	79.8%	82.0%	40.0%	11	10
Other	-36.7%	-78.6%	5.2%	33.0%	70.0%	9	10
HBV Ag test							
Negative	-2.0%	-15.5%	11.5%	59.0%	61.0%	103	98
Positive	-35.0%	-95.4%	25.4%	25.0%	60.0%	4	5
HCV Ab test							
Negative	-6.2%	-20.8%	8.3%	55.0%	61.0%	91	85
Reactive	13.9%	-17.1%	44.8%	75.0%	61.0%	16	18
Hepatitis Status							
Hep_B_not_C	-16.7%	-89.1%	55.8%	33.0%	50.0%	3	4
Hep_C_not_B	21.2%	-9.8%	52.1%	80.0%	59.0%	15	17
No_Hep	-6.0%	-20.9%	8.8%	56.0%	62.0%	88	81

TABLE 5 H (cont)
WEEK 48 PERCENT < 400 COPIES/ML
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL
<=0	-9.3%	-27.6%	9.1%	56.0%	65.0%	54	54
1	5.6%	-39.3%	50.4%	50.0%	44.0%	10	9
2-4	18.0%	-13.2%	49.2%	71.0%	53.0%	17	19
>4	-9.0%	-36.7%	18.7%	58.0%	67.0%	26	21
WT_Quartile							
<=65_kg	-9.3%	-36.3%	17.7%	61.0%	70.0%	28	20
66-73_kg	-9.3%	-36.0%	17.4%	50.0%	59.0%	26	27
74-82_kg	8.9%	-17.0%	34.8%	56.0%	47.0%	27	30
>82_kg	-7.7%	-32.7%	17.3%	65.0%	73.0%	26	26
EXER_LEVEL							
High	18.6%	-14.2%	51.4%	79.0%	60.0%	14	15
Low	-6.6%	-31.0%	17.8%	55.0%	62.0%	29	34
Medium	-11.0%	-34.7%	12.7%	59.0%	70.0%	27	37
Sedentary	11.6%	-16.9%	40.1%	53.0%	41.0%	36	17

TABLE 5 I
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N		
	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL	PVALUE
All	-4.7%	-18.2%	8.8%	46.0%	50.0%	107	103	0.496
STRATA_								
1-10_K	-3.4%	-24.4%	17.7%	55.0%	58.0%	42	43	
10-100_K	0.0%	-20.4%	20.4%	46.0%	46.0%	46	46	
>100_K	-16.5%	-49.2%	16.1%	26.0%	43.0%	19	14	
RSTRATA_								
1-10_K	-2.4%	-23.7%	18.8%	59.0%	61.0%	41	41	
10-100_K	1.2%	-18.7%	21.1%	44.0%	43.0%	48	47	
>100_K	-24.4%	-56.2%	7.3%	22.0%	47.0%	18	15	
SEX								
Female	21.8%	-12.6%	56.3%	57.0%	35.0%	14	17	
Male	-9.4%	-24.0%	5.2%	44.0%	53.0%	93	86	
RACE								
Black	4.5%	-21.8%	30.8%	41.0%	36.0%	22	33	
Hispanic	-32.3%	-72.4%	7.7%	22.0%	55.0%	9	11	
White	-8.3%	-25.2%	8.6%	49.0%	58.0%	75	59	
AGE_Quartile								
<=36	2.4%	-24.4%	29.3%	46.0%	44.0%	28	25	
37-41	-22.7%	-47.8%	2.4%	27.0%	50.0%	33	24	
42-46	16.2%	-9.9%	42.3%	74.0%	58.0%	23	26	
>46	-6.5%	-34.0%	20.9%	43.0%	50.0%	23	28	
CONT								
Europe	1.6%	-21.4%	24.6%	50.0%	48.0%	44	31	
N_America	-10.8%	-29.0%	7.3%	40.0%	51.0%	55	59	
Other	8.7%	-34.5%	51.8%	63.0%	54.0%	8	13	

TABLE 5 I (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30003

	MEAN DIFF	95% LIMITS LOW	UP	MEANS LEX/r	KAL	N LX/r	KAL
HIV_Quartile_or_Levels							
<=2.1_K	-14.3%	-49.4%	20.8%	57.0%	71.0%	14	14
2.1-11_K	-6.4%	-30.3%	17.5%	53.0%	59.0%	34	32
11-43_K	-13.7%	-37.7%	10.3%	39.0%	53.0%	33	32
>43_K	14.5%	-10.6%	39.6%	38.0%	24.0%	26	25
<=10_K	-7.5%	-27.7%	12.8%	55.0%	63.0%	47	43
10-100_K	-8.2%	-28.0%	11.7%	38.0%	46.0%	48	46
>100_K	13.1%	-23.5%	49.7%	42.0%	29.0%	12	14
1-10_K	-3.4%	-24.4%	17.7%	55.0%	58.0%	42	43
10-100_K	0.0%	-20.4%	20.4%	46.0%	46.0%	46	46
100-250_K	-27.8%	-71.8%	16.2%	22.0%	50.0%	9	8
>250_K	-3.3%	-50.6%	43.9%	30.0%	33.0%	10	6
CD4_Quartile_or_Levels							
<=179	-12.4%	-36.9%	12.1%	34.0%	47.0%	29	32
180-285	-10.0%	-37.6%	17.6%	40.0%	50.0%	20	32
286-441	13.9%	-12.2%	40.1%	62.0%	48.0%	34	23
>441	-20.8%	-51.7%	10.0%	42.0%	63.0%	24	16
<200	-8.4%	-31.2%	14.4%	36.0%	45.0%	33	38
>=200	-3.8%	-20.5%	12.8%	50.0%	54.0%	74	65
<50	-35.7%	-79.0%	7.6%	14.0%	50.0%	7	8
>=50	-2.5%	-16.6%	11.5%	48.0%	51.0%	100	95

TABLE 5 I (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N	
REASON	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL
AE/Death	0.0%	0.0%	0.0%	0.0%	0.0%	2	6
Complete	-2.1%	-16.4%	12.3%	53.0%	55.0%	92	94
LTFU	0.0%	0.0%	0.0%	0.0%	0.0%	9	3
CDC class. of HIV							
Asymptomatic	-17.7%	-39.1%	3.8%	36.0%	54.0%	44	37
Symptomatic	14.1%	-10.2%	38.4%	69.0%	55.0%	29	31
AIDS	-4.6%	-27.8%	18.5%	38.0%	43.0%	34	35
Other non-CDC HIV conditions							
No	-3.1%	-17.0%	10.9%	47.0%	50.0%	98	100
Yes	-33.3%	-94.9%	28.3%	33.0%	67.0%	9	3
HIV Risk Factor							
Heterosexual	-2.5%	-26.6%	21.6%	50.0%	53.0%	28	40
Homosexual	-6.5%	-26.0%	13.1%	42.0%	49.0%	59	43
IV_Drug_Use	32.7%	-7.5%	72.9%	73.0%	40.0%	11	10
Other	-37.8%	-78.5%	3.0%	22.0%	60.0%	9	10
HBV Ag test							
Negative	-2.4%	-16.2%	11.4%	48.0%	50.0%	103	98
Positive	-60.0%	-103%	-17.1%	0.0%	60.0%	4	5
HCV Ab test							
Negative	-5.4%	-20.1%	9.3%	43.0%	48.0%	91	85
Reactive	1.4%	-31.3%	34.1%	63.0%	61.0%	16	18
Hepatitis Status							
Hep_B_not_C	-50.0%	-99.0%	-1.0%	0.0%	50.0%	3	4
Hep_C_not_B	7.8%	-25.6%	41.3%	67.0%	59.0%	15	17
No_Hep	-3.8%	-18.9%	11.2%	44.0%	48.0%	88	81

TABLE 5 I (cont)
WEEK 48 PERCENT < 50 COPIES/ML
TRIAL 30003

	MEAN	95% LIMITS		MEANS		N	
ALK_Quartile	DIFF	LOW	UP	LEX/r	KAL	LX/r	KAL
<=0	-7.4%	-26.2%	11.4%	46.0%	54.0%	54	54
1	6.7%	-36.6%	49.9%	40.0%	33.0%	10	9
2-4	-0.3%	-33.0%	32.4%	47.0%	47.0%	17	19
>4	-6.2%	-34.9%	22.5%	46.0%	52.0%	26	21
WT_Quartile							
<=65_kg	-5.0%	-33.6%	23.6%	50.0%	55.0%	28	20
66-73_kg	-6.0%	-32.5%	20.5%	38.0%	44.0%	26	27
74-82_kg	4.1%	-21.2%	29.4%	41.0%	37.0%	27	30
>82_kg	-15.4%	-41.5%	10.7%	54.0%	69.0%	26	26
EXER_LEVEL							
High	18.1%	-16.5%	52.7%	71.0%	53.0%	14	15
Low	-8.1%	-32.8%	16.6%	45.0%	53.0%	29	34
Medium	-17.0%	-41.3%	7.3%	37.0%	54.0%	27	37
Sedentary	9.2%	-18.8%	37.1%	44.0%	35.0%	36	17

6. Statistical Reviewer's Conclusions

The applicant has demonstrated in one clinical trial with ART naive patients that lexiva at 1400 mg bid, when added to a background regimen of two NRTI's, produces a statistically and clinically significant reduction in viral load, including a significant increase in the proportion of patients whose viral load is undetectable by the Amplicor or the Ultrasensitive assay. This clinical benefit is sustained to at least 48 weeks. A second clinical trial in this same population demonstrated a similar statistically and clinically significant reduction in viral load for lexiva at 1400 mg qd, boosted by ritonavir at 200 mg qd. Both trials showed the lexiva effects by comparison to a nelfinavir control.

The trials were conducted across several continents within a diverse adult population. There was no convincing evidence that the observed clinical benefit is reduced in any of the racial, gender, or age categories examined.

The applicant has also conducted one clinical trial with patients who have already failed at least regimen containing a PI comparing lexiva at 700 mg bid boosted with ritonavir at 100 mg bid to Kaletra (lopinavir at 400 mg bid plus ritonavir at 100 mg bid), when each regimen was added to a background regimen of two NRTI's. The estimated reduction in viral load in the bid boosted lexiva arm and the Kaletra arm were nearly equal, particularly as measured by proportion of patients with undetectable viral load at week 48. Although the confidence limits were too wide to permit direct conclusion of statistical equivalence between bid boosted lexiva and Kaletra, meta-analysis supports the inference that boosted bid lexiva would have been statistically significantly superior to placebo with respect to these endpoints.

A second arm in this trial used lexiva at 1400 mg qd boosted by ritonavir at 200 mg qd. This arm performed at a statistically and clinically significantly inferior level to both the bid boosted lexiva and the Kaletra control. One should conclude that ART experienced patients should be treated with the bid boosted

lexiva regimen rather than the qd regimen.

Again, there was no convincing evidence in this experienced population that boosted lexiva effects differed consequentially among racial, gender, or age categories.

Thomas Hammerstrom, Ph.D.
/S/

Mathematical Statistician

Concur: Dr. Soon
cc:
Archival NDA #21-548
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HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Mr. Fleischer
HFD-530/Mr. Sillivan
HFD-725/Dr. Hammerstrom
HFD-700/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Ms. Broadwater

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/s/

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10/20/03 05:03:00 PM
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Greg Soon
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