CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-567
APPLICANT:	Bristol-Myers-Squibb
NAME OF DRUG:	Reyataz® (Atazanavir)
INDICATION:	Treatment of HIV Infection
TYPE OF REVIEW:	Clinical
DOCUMENTS REVIEWED:	Volumes 1, 6, 7.1-7.8
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0. Executive Summary

The applicant has demonstrated in three clinical trials with ART (anti-retroviral therapy) naive patients that atazanavir, when added to a background regimen of two NRTI's, (nucleoside reverse transcriptase inhibitor) produces a statistically and clinically significant reduction in HIV viral load, including a significant increase in the proportion of patients whose HIV viral load is undetectable by the Amplicor or the Ultrasensitive assay. This clinical benefit is sustained to at least 48 weeks.

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 tested atazanavir for 24 weeks in one trial with patients who have already failed at least regimen containing a PI (protease inhibitor). In that trial, atazanavir was statistically and clinically significantly inferior to Kaletra when each was added to a background regimen of two NRTI's. Meta-analysis supports the inference that atazanavir would have been statistically significantly superior to placebo with respect to proportion of subjects whose HIV viral load was undetectable had it been ethical to include such an arm in the trial.

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

1. Background

The applicant submitted two randomized, controlled phase III clinical trials with atazanavir for this application: trial 34 and trial 43. In addition, two randomized, controlled phase II clinical trials had sufficient information to be relevant to the efficacy determination: trial 007 and trial 008.

2. Trials 34, 43, 7, and 8

2.1 Objectives in Trials

The primary objective of study 34 was to compare the efficacy of atazanavir (ATV) at a dose of 400 mg qd to that of efavirenz (EFV) at 600 mg qd 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 zidovudine (ZDV) at 300 mg bid.

The primary objective of study 43 was to compare the efficacy of atazanavir (ATV) at a dose of 400 mg qd to that of lopinavir at 400 mg bid plus ritonavir at 100 mg bid (LPV/r) in treatment experienced patients. The comparator drugs in both arms were added to a background regimen of two other drugs.

In trial 34, the primary efficacy endpoint was percent of subjects achieving sustained viral load below 400 copies/mL through 48 weeks. The study population in trial 34 was 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 2000 copies/mL and CD4 count >= 100 cells/mm^3.

In trial 43, the primary efficacy endpoint was change from baseline in log HIV·RNA level. The study population in trial 43 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 and CD4 count >= 50 cells/mm^3.

The primary objective in trials 7 and 8 was to select the most effective dose among 200, 400, 500, and 600 mg qd atazanavir as compared to nelfinavir in treatment naive patients. In both

trials, all subjects received a background regimen of two NRTI's.

In trials 7 and 8, the primary efficacy endpoint was change from baseline in log HIV RNA level. The study population in both trials was HIV-1 infected patients who were ART naive. They were also required to have confirmed viral load of at least 2000 copies/mL and CD4 count >= 100 cells/mm^3.

2.2 Summary of Study Design

Trial 34 was a double blind, randomized, two-arm, parallel, active controlled, multi-center trial, conducted at 91 centers in South America (13 centers), Europe (37 centers), Asia (7 centers), North America (30 centers), and Africa (4 centers). Subjects were randomly assigned in a 1:1 ratio to 400 mg qd atazanavir + background or 600 mg EFV qd + background. Randomization was stratified by baseline HIV RNA level (< or > 30K copies/mL).

Trial 43 was an open-label, randomized, two-arm, parallel, active controlled, multi-center trial, conducted at 68 centers in North America (39 centers), South America (14 centers), Europe (14 centers), and Australia (1 center). Subjects were randomly assigned in a 1:1 ratio to 400 mg qd atazanavir + background or 400/100mg lopinavir/ritonavir bid + background. The randomization was stratified by site. The possible choices of background in trial 43 are given in table 2.2 A.

TABLE 2.2 A
BACKGROUND REGIMENS FOR TRIAL 43

ZDV 300 mg bid plus 3TC 150 mg bid
ZDV 300 mg bid plus ddI 400 mg qd
ABC 300 mg bid plus ddI 400 mg qd
ABC 300 mg bid plus 3TC 150 mg bid
ABC 300 mg bid plus d4t 40 mg bid
d4t 40 mg bid plus 3TC 150 mg bid
d4t 40 mg bid plus ddI 400 mg qd

Trials 7 and 8 were partially blind, randomized, multi-arm, parallel, active controlled, multicenter trials. In trial 7, subjects were randomly assigned in a 1:1:1:1 ratio to 200, 400, or 500 mg qd atazanavir + ddI/d4t or 750 mg nelfinavir (NFV) tid

+ ddI/d4t. In trial 8, subjects were randomly assigned in a 2:2:1 ratio to 400 or 600 mg qd atazanavir + 3TC/d4t or 1250 mg NFV bid + 3TC/d4t. In both trials, subjects knew whether they were on ATV or NFV but were blinded as to the dose of ATV if they received the former. In both trials, randomization was stratified by baseline HIV RNA level (< or > 30K copies/mL). Both were multi-center trial, conducted at centers in South America (2 centers in trial 7 and 6 in trial 8), Europe (16 centers in trial 7 and 22 in trial 8), Asia (2 centers in trial 8), North America (16 centers in trial 7 and 21 in trial 8) and Africa (2 centers in trial 7 and 3 in trial 8).

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2.3 Patient Accounting and Baseline Characteristics

810 patients were randomized in trial 34. Of these, 5 patients never started treatment. Of the 805 eligible patients who started treatment, 144 discontinued treatment before week 48 and a further 31 discontinued treatment after week 48. Table 2.3 A summarizes the primary reasons for discontinuation from study 34 and from treatment.

TABLE 2.3 A
PATIENT STATUS, TRIAL 34

	ATV		EFV	
Randomized	405		405	
In Treated ITT	404		401	
Continuing		326		304
Withdrew by Week 48		65		79
AE/Death		26		36
LTFU		30		34
LOE		9		9
Withdrew after Week 48		13		18
AE/Death		2		3
LTFU		7		9
LOE		4		6

In trial 34, the study population was 65% male with a mean age of 34 years. They were 36% Latino, 33% white, 16% Asian/Pacific Islander, and 14% black. (This classification ignores the fact that Latino is a language group, not an ethnic group.) 5% were current or former IV drug users. The mean CD4 count at baseline was 320 cells/mm^3; the mean HIV RNA level was 4.8 logs. 5% of patients had prior AIDS defining events.

The subjects were enrolled at 91 centers on North and South America, Europe, Asia, and Africa. The exact distribution of patients by continent is given in table 2.3 B.

TABLE 2.3 B
PATIENTS BY CONTINENT, TRIAL 34

Continent	Pats	Continent	Pats
S America	275	Europe	222
N America	109	Asia	125
Africa	74		

300 patients were randomized in trial 43. Of these, 10 patients never started treatment. Of the 290 eligible patients who started treatment, 31 discontinued treatment before the end of the study, 20 before week 24. Table 2.3 C summarizes the primary reasons for discontinuation from study 43 and from treatment.

TABLE 2.3 C
PATIENT STATUS, TRIAL 43

	ATV		LPV/r	
Randomized	150		150	
In Treated ITT	144		146	
Continuing		124		135
Withdrew by Week 24		10		10
AE/Death		2		4
LTFU		4		6
LOE		4		0
Withdrew after Week 24		10		1
AE/Death		1		0
LTFU		2		1
LOE		7		0

The subjects were enrolled at 68 centers on North and South America, Europe, and Australia. The exact distribution of patients and sites by country is given in table 2.3 D.

TABLE 2.3 D
PATIENTS BY CONTINENT, TRIAL 43

Continent	Pats	Continent	Pats
S America	227	Europe	51
N America	207		

In trial 43, the study population was 79% male with a mean age of 38 years. They were 52% Latino, 41% white and 9% black.

5% were current or former IV drug users. The mean CD4 count at baseline was 320 cells/mm^3; the mean HIV RNA level was 4.1 logs. 26% of patients had prior AIDS defining events.

Phenotypic sensitivity for other AIDS drugs was defined as virus with IC_{50} < 2.5* IC_{50} of the control strain. The baseline proportions with phenotypic sensitivity to other ARV's in trial 43 are given in table 2.3 E. Prior ARV experience is also given in this table. Percentages of different ART's in the background regimen are given in table 2.3 F.

TABLE 2.3 E

BASELINE PHENOTYPIC SENSITIVITY AND PRIOR USE, TRIAL 43

Drug	% Sensitive	% Prior Use	Drug	% Sensitive	% Prior Use
NRTI's			PI's		
3TC	38%	84%	ATV	76%	0%
ABC	56%	3%	LPV	85%	0%
D4T	94%	52%	AMP	91%	<1%
DDI	96%	36%	NFV	46%	52%
DDC	na	15%	RTV	72%	19%
ZDV	74%	77%	SQV	79%	15%
			IND	na	43%
NNRTI's					
EFV	85%	5%			
DLV	na	1%			
NVP	83%	9%			

TABLE 2.3 F

COMPOSITION OF THE NRTI BACKGROUND, TRIAL 43

	ATV	LPV/r
DDI	69%	64%
D4T	58%	53%
3TC	23%	23%
ZDV	21%	25%
ABC	29%	34%

420 patients were randomized in trial 7 and 467 patients were randomized in trial 8. Of these, 214 patients in trial 7 and 195 patients in trial 8 were randomized to atazanavir arms at doses other than 400 mg qd and are thus not directly relevant to efficacy at that dose. Of the remaining 206 patients in trial 7

and 272 patients in trial 8, 8 never started treatment. Of the 470 eligible patients who started treatment, 74 discontinued treatment before week 48 and a further 68 discontinued treatment after week 48. Tables 2.3 G and H summarize the primary reasons for discontinuation from studies 7 and 8.

TABLE 2.3 G
PATIENT STATUS, TRIAL 7

	ATV 400	NFV
Randomized	103	103
In Treated ITT	101	100
Withdrew by Week 48	16	26
AE/Death	3	5
LTFU	12	8
LOE	1	3
Withdrew after Week 48	20	27
AE/Death	4	6
LTFU	13	12
LOE	3	9
Completed	65	57

TABLE 2.3 H
PATIENT STATUS, TRIAL 8

	ATV 400	NFV
Randomized	181	91
In Treated ITT	178	91
Withdrew by Week 48	22	10
AE/Death	8	3
LTFU	11	5
LOE	3	2
Withdrew after Week 48	9	12
AE/Death	2	1
LTFU	7	7
LOE	0	4
Completed	147	69

In trial 7, the study population was 64% male with a mean age of 35 years. They were 56% white, 32% black, and 6% Latino. 14% were current or former IV drug users. In trial 8, the study population was 63% male with a mean age of 35 years. They were 55% white, 25% black, 14% Asian/Pacific Islander, and 3% Latino. 7% were current or former IV drug users. The mean CD4 count at

baseline was 348 cells/mm^3 in trial 7 and 295 cells/mm^3 in trial 8; the mean HIV RNA level was 4.7 logs in both trials. 5% of patients in trial 7 and 11% in trial 8 had prior AIDS defining events.

The subjects were enrolled at 90 centers on North and South America, Europe, Asia, and Africa. The exact distribution of patients by continent is given in table 2.3 I.

TABLE 2.3 I
PATIENTS BY CONTINENT, TRIALS 7 AND 8

Continent	Trial 7	Trial 8	Continent	Trial 7	Trial 8
S America	59	130	Europe	151	174
N America	78	89	Asia	0	66
Africa	132	119			

2.4 Summary of Methods of Assessment

2.4.1 Schedule of Measurements

Patients had HIV RNA and CD4 counts was measured at weeks 0, every 4 weeks to week 16, and every 8 weeks to week 72. Plasma samples were assessed by the Roche Amplicor assay at baseline and by Roche Ultrasensitive assay during treatment. HIV RNA levels > 75 K copies/mL were remeasured by the Roche Amplicor assay.

2.4.2 Criteria for Switching Regimen

Subjects in trial 43 were allowed to substitute one background NRTI for another if toxicity to the original NRTI was observed. 10 out of 146 LPV/r subjects and 6 out of 144 ATV subjects switched some of their NRTI drugs.

Subjects were also allowed to dose reduce ATV if they experienced hyperbilirubinemia (confirmed > 5*ULN or unconfirmed > 5*ULN with clinical jaundice).

2.4.3 Assessment of Treatment Effects

In trial 34, 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 43, the protocol specified primary endpoint at week 24 was time averaged change from baseline in log HIV RNA level. The applicant used last observation carried forward (LOCF) 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 <baseline-1 log copies/mL. Loss to follow-up counted as failure.

In trials 7 and 8, the protocol specified primary endpoint at week 48 was time averaged change from baseline in log HIV RNA level. The applicant used last observation carried forward (LOCF) to replace missing data. Two secondary viral endpoints were percent successful with success defined as <50 copies/mL or <400 copies/mL. Loss to follow-up counted as failure.

2.5 Summary of Statistical Analysis

Confidence intervals for the difference between ATV and LPV/r were computed using stratification by NRTI background (5 strata: zdv+3tc, zdv+ddi, d4t+3tc, d4t+ddi, abc+any) and using Cochran-Mantel-Haenszel weighting. The standard error in the confidence intervals was computed omitting subjects who did not complete the first 24 weeks in order to prevent the additional data from the LOCF imputation from narrowing the confidence limits.

ATV was to be judged effective if the two-sided 95% lower bound for the difference between ATV and LPV/r was no worse than .5 log copies/mL. (The applicant mistakenly used 97.5% limits to adjust for the fact that a safety endpoint based hypercholesteremia was also used. Since the drug would not be approvable unless it was effective with respect to viral load, regardless of its effect of cholesterol levels, no multiple comparison adjustment is necessary.) The safety endpoint is discussed below in section 4.7.

2.6 Summary of Applicant's Results

The results for trials 34, 7, and 8 are given in table 2.6 A and B. Table 2.6 A gives the numbers and percentages of subjects with viral load sustained below 400 copies/mL on the ATV 400 mg and control arms on all three trials. It also gives the 95% confidence intervals for the differences between percent successful on ATV and control. Table 2.6 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 ATV may not work as well as the control arm.

TABLE 2.6 A
PERCENT < 400 COPIES, TRIALS 34, 7, 8

	Trial 34		Trial 7		Trial 8	
Arm	ATV	EFV	ATV	NFV bid	ATV	NFV tid
N	281/404	258/401	48/78	50/82	123/181	54/91
%	= 70%	= 64%	= 62%	= 61%	= 68%	= 59%
Interval	-1.2%, 11.7%		-14.5%, 15.5%		-3.5%, 20.3%	

TABLE 2.6 B
PERCENT < 50 COPIES, TRIALS 34, 7, 8

	Trial 34		Trial 7		Trial 8	
Arm	ATV	EFV	ATV	NFV bid	ATV	NFV tid
N	131/404	150/401	26/78	23/82	60/181	35/91
%	= 32%	= 37%	= 33%	= 28%	= 33%	= 38%
Interval	-11.4%, 1.5%		-9.0%, 19.4%		-17.5%, 6.3%	

The results for these three trials using change from baseline in log HIV RNA, out to week 48, are given in table 2.6 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 difference from baseline (TAD). Thus, the point estimates in table 2.6 C and the confidence intervals refer to slightly different measures of the change in viral load. For example, one will note that the confidence interval for trial 8 is centered on an estimated difference of -.14 in TAD rather than the value of -.20 reported for differences in week 48 means.

In this table, the TAD is computed with LOCF for subjects lost to follow up before week 48. (In table 2.6 C and D but not in A and B, the confidence intervals for trials 7 and 8 include a multiple comparison adjustment for the presence of two or three doses of ATV in those two trials.) (One should also note that the applicant does not compute a TAD for each subject. Rather they compute difference between arms at each visit, assuming all subjects were measured on exactly the same day after start of drug. The difference between arms in TAD is then computed as a suitable weighted average of the differences at each visit.)

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

TABLE 2.6 C
CHANGE FROM BASELINE TO WEEK 48 IN LOG HIV
TRIALS 34, 7, 8

	Trial 34		Trial 7		Trial 8	
Arm	ATV	EFV	ATV	NFV bid	ATV	NFV tid
N	337	321	64	65	153	80
Mean	-2.67	-2.74	-2.42	-2.33	-2.51	-2.31
Interval	-.01, .15		-.16, .32		-.32, .04	

Table 2.6 D gives the mean change from baseline in CD4 counts at week 48. The entries are laid out as in table 2.6 C but now positive values in the confidence limits are evidence of ATV superiority.

TABLE 2.6 D
CHANGE FROM BASELINE TO WEEK 48 IN CD4 COUNT
TRIALS 34, 7, 8

	Trial 34		Trial 7		Trial 8	
Arm	ATV	EFV	ATV	NFV bid	ATV	NFV tid
N	329	314	63	65	153	78
Mean	176	160	221	185	234	211
Interval	9.7, 36.5		-14.5, 44.3		-46.4, 6.0	

The reported results in trial 43 are given in tables 2.6 E and F. Table 2.6 E gives the mean change from baseline for all

3. Summary of Applicant's Conclusions

The applicant concluded that the antiviral efficacy of 400 mg qd atazanavir in treatment naive subjects was similar to that of efavirenz and to that of nelfinavir when added to a background regimen of two NRTI's.

The applicant also concluded that 400 mg qd atazanavir had demonstrable antiviral efficacy in treatment experienced subjects. This conclusion was not substantiated by the applicant's reported analysis of their primary endpoint. In the absence of controlled clinical trial results supporting their claim, the applicant compared the findings on the ATV arm in trial 43 to published efficacy results of treatment experienced subjects treated with two NRTI's alone.

A reasonable conclusion from the applicant's presentation is that 400 mg qd ATV has been shown to be effective in treatment naive subjects but has not been shown to be effective in treatment experienced subjects.

4. Statistical Reviewer's Comments and Analyses

4.1 Problems with the Applicant's Analysis

The applicant's analyses with time averaged differences (TAD) 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 ATV 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.

4.2 Results with Percent BLQ

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 43 to estimate whether ATV would have shown superiority to placebo in experienced patients. The first method is to combine the treatment estimates in trial 43 with those from trials in the Kaletra NDA to get an estimate of the difference between ATV 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 ATV plus 2 antiretrovirals.

The first of these two methods proceeds as follows. In trial 43, the data provide an estimate of the difference in efficacy of ATV 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 ATV and placebo.

Trial 888 is the more comparable of the two LPV/r trials to trial 43. Trial 43 used patients who were PI failures with baseline log HIV RNA = 4.1 copies/mL and baseline CD4 count = 320; 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 43 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 43 shows that ATV 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 ATV to placebo.

In order to estimate the difference in efficacy of ATV and placebo, one must combine the results from all trials 43 and 888. An outline of the computation required is given in table 4.2 A.

TABLE 4.2 A
COMPARISON OF ATV TO OTHER PI, USING %BLQ
USING TRIALS 43 AND 888

Observed Data						
Source	Arm1	Arm2	Mean1	Mean2	Difference	SEE
ATV NDA						
Trial 43	ATV	LPV/r	70/150=47%	98/150=65%		
LPV/r NDA						
Trial 888	LPV/r	PI	84/148=57%	46/140=33%		
Imputed						
	Arm1	Arm2	Difference		SEE	
	ATV	PI				

The estimates from trials 43 and 888 from the ATV and the LPV/r NDA's were added to get an estimated difference between ATV and control. The result of this combination gives an estimated difference of 5% more subjects sustained <400 copies at 24 weeks than with a selected PI control. However, the tentative 95% confidence interval is of -10.8% to 20.8%. In other words, ATV might credibly produce anything from a 21% improvement over the other PI control to an 11% loss relative to the other PI control. Parenthetically, one should note that 5 patients on ATV and 6 on LPV/r in trial 43 were counted as viral failures at week 24 even though their last visit was at week 16. None of them had achieved confirmed viral suppression by that date. Also 15 patients on ATV and 11 on LPV/r were counted as viral successes at week 24 even though their last visit was at week 16. All were BLQ and none had yet rebounded.

One may attempt to go one step further in this combination 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 5 other trials with PI's, using the amprenavir, nelfinavir, and indinavir NDA's. As a further sensitivity analysis, a second estimate of the difference between selected PI and placebo, both with a 2 drug background, was obtained by averaging 11 other trials with 3 drugs vs 2 drugs. The six additional trials did not involve PI's but rather were from the nevirapine, delavirdine, and abacavir NDA's. Table 4.2 B summarizes this 3 step computation of imputed difference between ATV and placebo.

TABLE 4.2 B
COMPARISON OF ATV TO PLACEBO, USING %BLQ
USING TRIALS 43, 888, AND OTHERS

Source	Arm1	Arm2	Difference	SEE
4.2 A	ATV	PI		
†	PI	Plac		
	ATV	Plac		
††	PI	Plac		
	ATV	Plac		

† Averaging 5 trials with PI vs Placebo
†† Averaging 12 trials with 3rd Drug vs Placebo

The 5 trials involving PI vs Placebo in the presence of a 2 drug background had an average difference in percent <400 of 40% and an inferred standard error of 2.8%, computed as the square root of the sum of the squares of the five standard errors in the separate trials. This leads to an estimate of in %BLQ between ATV and placebo, with a 95% confidence interval of 28% to 62%. The full list of 12 trials involving PI, NRTI, or NNRTI vs Placebo in the presence of a 2 drug background had a smaller average difference in percent <400 of 31%, with an imputed standard error of 1.9%. This leads to an estimate of in %BLQ between ATV and placebo, with a 95% confidence interval of 19.8% to 52.2%.

The other usable trial in the LPR/r NDA was trial 863. Trial 863 compared LPV/r to NFV (nelfinavir), each added to a background of two NRTI's. This is approximately the same background used in trial 43. However, the enrolled patients in trial 863 were ART naive. From this trial, one can get an estimate of the difference in efficacy of LPV/r and NFV, together with a standard error of that estimate. As a second step, the

data from the NDA for NFV provide an estimate of the difference in efficacy of NFV and placebo, together with a standard error of that estimate. In the NFV NDA, two trials compared NFV directly placebo. Trial 511 compared NFV to placebo when added to a background of two NRTI's, the same background used in trials 43 and 863. Trial 506 compared NFV to placebo when added to one NRTI. This background is less relevant to trial 43. Estimates using trial 506 are deferred to the appendix. In order to estimate the parameter of interest, the difference in efficacy of ATV and placebo, one must combine the results from all trials 43, 863, and 511 in three different NDA's. An outline of the computation required is given in table 4.2 C.

TABLE 4.2 C
COMPARISON OF ATV TO PLACEBO, USING
USING TRIALS 43, 863, 511

Observed Data Source	Arm1	Arm2	Mean1	Mean2	Difference	SEE
ATV NDA						
Trial 43	ATV	LPV/r	70/150=47%	98/150=65%		
LPV/r NDA						
Trial 863	LPV/r	NFV	259/326=79%	233/327=71%		
NFV NDA						
Trial 511	NFV	Plac	66/99=67%	7/101=7%		
Imputed						
	Arm1	Arm2	Difference		SEE	
	ATV	NFV				
	NFV	Plac				
	ATV	Plac				

The estimates from trials 43 and 863 from the ATV and the LPV/r NDA's were added to get an estimated difference between ATV and NFV and that result was added to the estimated difference between NFV and placebo from trial 511 to get a final estimated difference between ATV and placebo. The final result gives an estimated difference of 49% more subjects with HIV RNA sustained below copies compared to placebo with a tentative 95% confidence interval of 32% to 66%. In other words, ATV might credibly produce anything from a 32% to 66% improvement compared to placebo. Table 4.2 D gives a summary of the estimated differences with confidence intervals for ATV and various controls.

TABLE 4.2 D

DIFFERENCES IN PERCENT ATV AND CONTROLS

Control	Diff	95% Limits	Source	Population
LPV/r	-19%	-30%, -7.9%	Trial 43	ART experienced
PI	5%	-10.8%, 20.8%	Imputed: 43, 888	Experienced
	5%	-11.7%, 23.7%	†	
	4.5%	-12.3%, 23.1%	††	
Placebo	45%	28%, 62%	43,888, 5 others	Mixture
Placebo	36%	20%, 52%	43,888, 11 others	Mixture
Placebo	49%	32%, 66%	43, 863, 511	Mixture

† same trial with SEE inflated 10%

†† same trial with Diff deflated 10% and SEE inflated 10%

One can see that ATV is observed to be statistically and clinically significantly inferior to LPV/r with data from a randomized clinical trial with ART experienced patients. ATV is estimated to be superior to an investigator selected PI but, with 95% confidence, could be as much as 10.8% worse, based on comparing results in two different trials, both with ART experienced patients. It is worth noting that it has often been assumed that a third active drug adds at least 10% to the proportion of subjects sustained BLQ when added to a 2 drug background regimen. By this loose criterion, ATV just misses being close enough to the selected PI in trial 888 to be effective. Finally, ATV is estimated to be statistically and clinically significantly than placebo, based on comparing results in chains of three trials, each sharing one arm with the previous link. Unfortunately, these chains of trials were not restricted to ART experienced patients.

The quality of the estimates in table 4.2 A-D are not as good as that from comparing two arms within a single randomized trial. Background regimens are not the same across trials, disease progress is not the same, treatment history is not the same. The differences between trial 43 and 888 were discussed above. Table 4.2 E documents some of these differences for all the trials compared.

TABLE 4.2 E
COMPARISONS OF POPULATIONS IN THREE NDA'S

NDA, Trial	Background Regimen	Baseline Log HIV	CD4	Experience
ATV, 43	2 NRTI's	4.1	320	PI failures
LPV/r, 863	d4T + 3TC	4.9	251	ART naive
LPV/r, 888	NVP + 2 NRTI's	4.1	322	PI, NRTI experienced, NNRTI naive
NFV, 511	AZT + 3TC	4.9	289	Limited
NFV, 506	d4T	4.9	279	Limited

It is conventional to perform sensitivity analyses on the estimates and confidence intervals in table 4.2 D to compensate for the discrepancies in the populations enrolled in the different trials. The estimated effects of inflating the standard error by 10% and of deflating the difference in response by 10% to reflect increased uncertainty from different populations were also given in table 4.2 D, for the comparison to the selected PI's in trial 888. When either one or both of these sensitivity adjustments is made, it appears within the range of credibility that ATV is as much as 11% or 12% worse than the selected PI. (No comparable sensitivity analysis was done for the comparison to placebo using trials 843 and either 511 or the average of five or twelve other trials. The margin of superiority was so large that it would be clearly be preserved under any such adjustments.)

The FDA statistical reviewer would summarize these analyses by concluding that there is highly suggestive evidence that ATV makes a positive contribution to the two NRTI background when assessed by proportion with sustained viral suppression.

The second method for determining what, if anything, ATV 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.

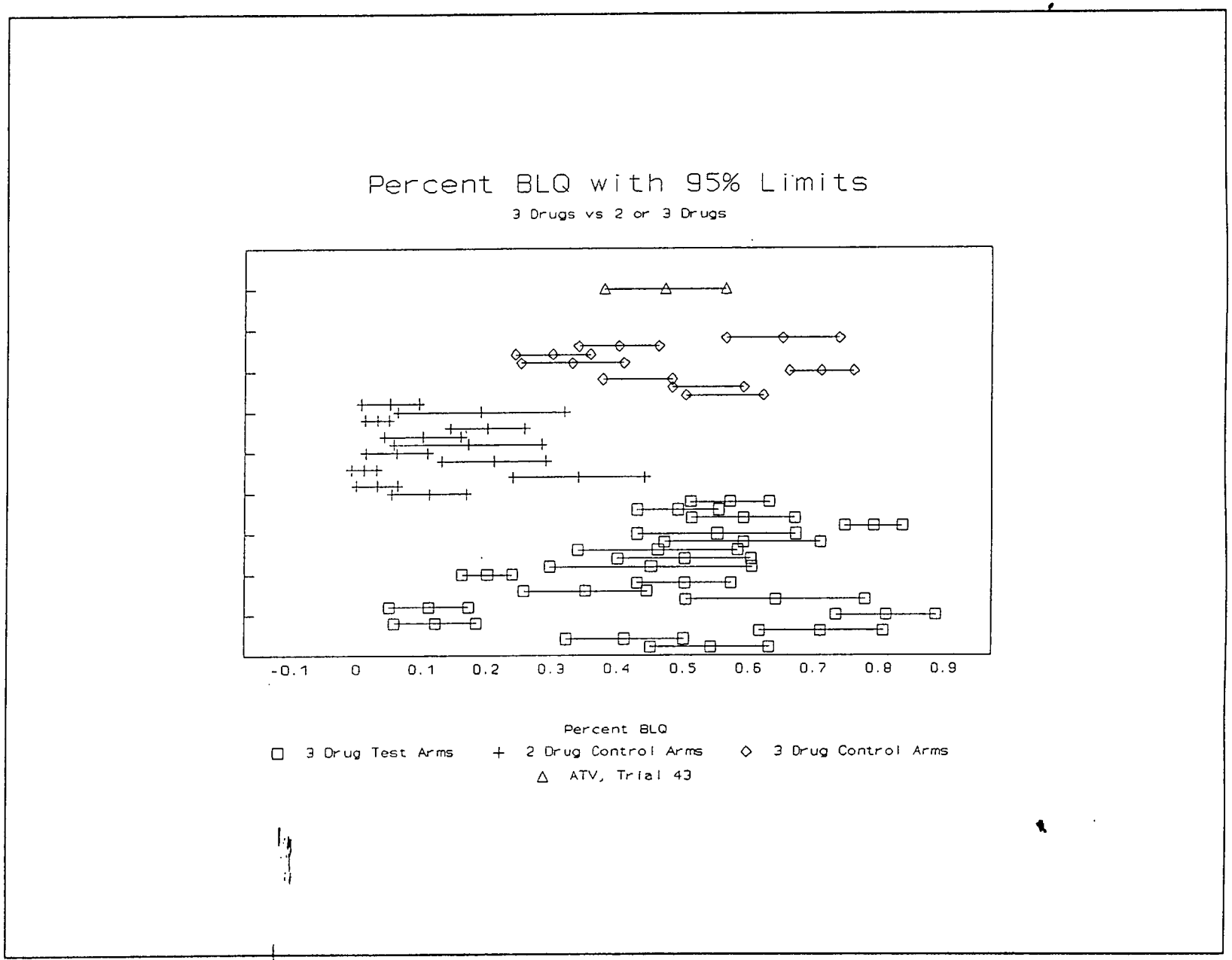
Percent BLQ with 95% Limits
3 Drugs vs 2 or 3 Drugs
-0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Percent BLQ
3 Drug Test Arms
2 Drug Control Arms
3 Drug Control Arms
ATV, Trial 43

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 7 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 ATV in trial 43. 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 ATV arm in trial 43 is comparable to many of the three drug arms and is clearly to the right of all but one of the two drug arms. That rightmost interval among the two drug arms corresponds to a trial in which the percent BLQ was measured at week 16, not week 24. It is reasonable to expect that performance on an 2 drug regimen would decline in the course of an additional 8 weeks.

An overall conclusion from this survey of other trials is that ATV 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 ATV is effective in the experienced population of trial 43, 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 ATV to an imputed placebo, using TAD (time averaged difference) instead of percent sustained BLQ as the response variable.

Tables 4.3 A, B, and C contain the computations for method 1, comparing ATV 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.

TABLE 4.3 A
COMPARISON OF ATV TO PLACEBO, USING TAD
USING TRIALS 43, 888

Observed Data

Source	Arm1	Arm2	Mean1	Mean2	Difference	SEE
ATV NDA						
Trial 43	ATV	LPV/r	-1.39	-1.65	.26	.093
LPV/r NDA						
Trial 888	LPV/r	PI	-.972	-.867	-.104	.078

Imputed

Arm1	Arm2	Difference	SEE
ATV	PI	.26-.104 = .156	$\sqrt{.093^2+.078^2}$ = .121

† PI selected by geno/phenotypic analysis

The final result gives an estimated difference of .156 (a .156 log copies lesser average reduction with ATV than with a selected PI) with a tentative 95% confidence interval of -.081 to .393. In other words, ATV might credibly produce anything from a .081 log copy reduction compared to an optimized PI to a .393 log copy increase compared to that same PI.

One may also repeat the attempt made with percent BLQ in section 4.2 to go one step further to estimate the difference between a selected PI plus 2 ART drugs and placebo plus same 2 ART drugs. As before, 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 ATV and placebo.

TABLE 4.3 B
COMPARISON OF ATV TO PLACEBO, USING TAD
USING TRIALS 43, 888, AND OTHERS

Source	Arm1	Arm2	Difference	SEE
4.3 A	ATV	PI	.156	.121
†	PI	Plac	-.79	.051
	ATV	Plac	.156-.79 = -.634	$\sqrt{.121^2+.051^2}$ = .131
††	PI	Plac	-.76	.048
	ATV	Plac	.156-.76 = -.604	$\sqrt{.121^2+.048^2}$ = .130

† 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 .131, 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 -.634 in TAD between ATV and placebo, with a 95% confidence interval of -.891 to -.377. Recall, that since negative values indicate a superior TAD, this interval corresponds to an imputed mean average decrease of .377 to .891 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 .130. This leads to an estimate of -.604 in TAD between ATV and placebo, with a 95% confidence interval of -.859 to -.349.

Table 4.3 C contains the computations from trial 863, which compared LPV/r to NFV (nelfinavir), each added to a background of two NRTI's. (Recall, trial 863 enrolled patients who were ART naive.) As was the case in table 4.2 B, one also needs data from trial 511 in NFV NDA to finally get a difference from placebo.

TABLE 4.3 C
COMPARISON OF ATV TO PLACEBO, USING TAD
USING TRIALS 43, 863, 511

Observed Data

Source	Arm1	Arm2	Mean1	Mean2	Difference	SEE
ATV NDA						
Trial 43	ATV	LPV/r	-1.39	-1.65	.26	.093
LPV/r NDA						
Trial 863	LPV/r	NFV	-1.798	-1.801	.003	.057
NFV NDA						
Trial 511	NFV	Placebo	-1.77	-1.40	-.37	.083

Imputed

Arm1	Arm2	Difference	SEE
ATV	NFV	.26+.003 = .263	$\sqrt{.093^2+.057^2} = .109$
NFV	Plac	-.37	.083
ATV	Plac	.263-.37 = -.107	$\sqrt{.109^2+.083^2} = .137$

The final result gives an estimated difference of -.107 (a .107 log copies greater average reduction with ATV than with placebo) with a tentative 95% confidence interval of -.376 to .162. In other words, ATV might credibly produce anything from a .376 log copy reduction compared to placebo to a .162 log copy increase compared to placebo.

The problems with the quality of these estimates as compared to that from a single randomized trial have already been discussed in section 4.2 above. See table 4.2 E for some of the differences among the samples in the different trials. In table 4.3 D, the reviewer summarizes the imputed confidence intervals for the difference in TAD between ATV 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 10%.

TABLE 4.3 D

DIFFERENCES IN TAD, ATV AND CONTROLS

Control	Diff	95% Limits	Source	Population
LPV/r	.26	.078, .44	Trial 43	ART experienced
Selected PI	.156	-.081, .393	Imputed: 43, 888	Experienced
Placebo	-.634	-.891, -.377	43,888, 4 others	Mixture
Placebo	-.604	-.859, -.349	43,888, 6 others	Mixture
	-.544	-.824, -.263	††	
Placebo	-.107	-.376, .162	43, 863, 511	Mixture

†† same set of trials with Diff deflated 10% and SEE inflated 10%

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.

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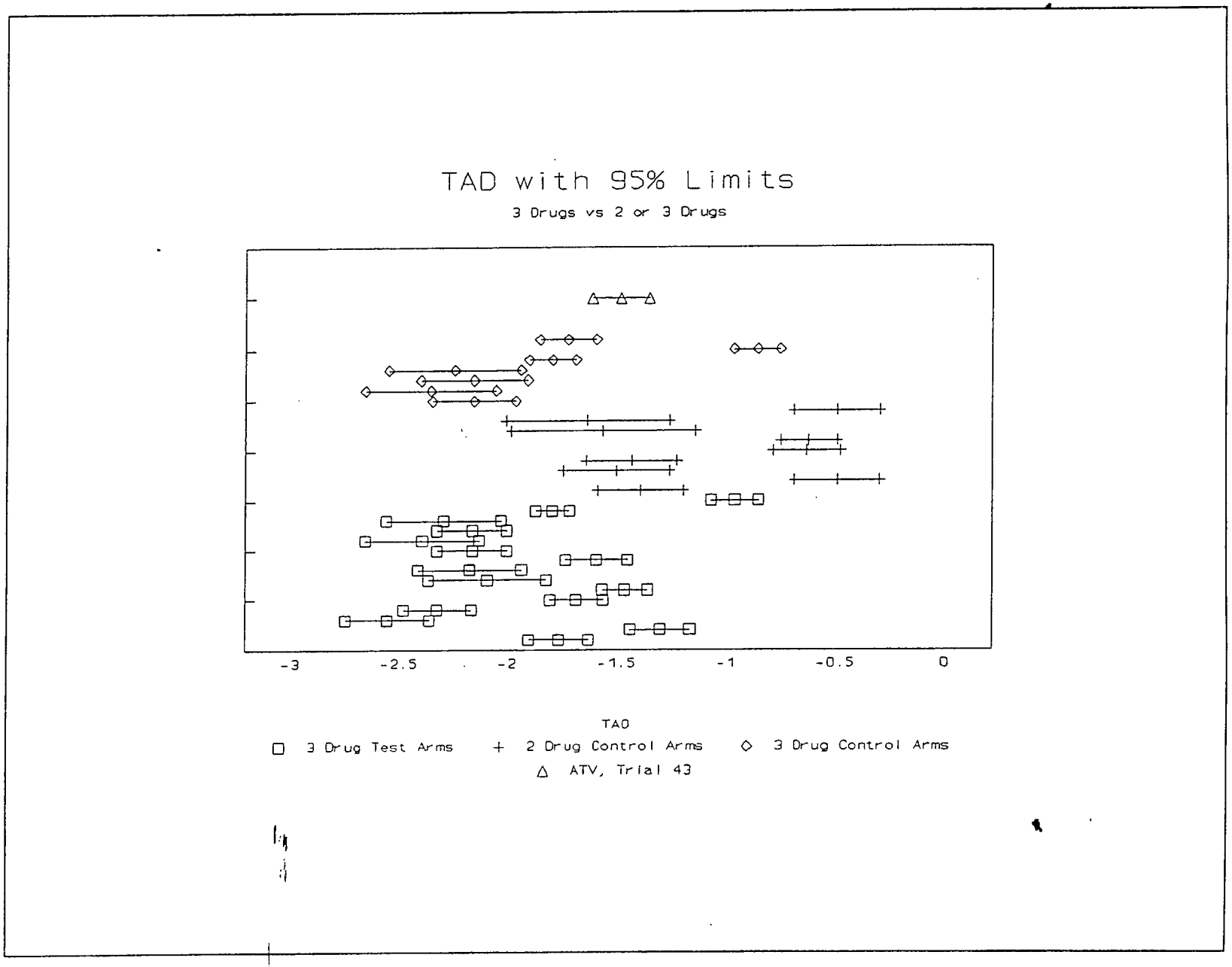
TAD with 95% Limits
3 Drugs vs 2 or 3 Drugs
-3
-2.5
-2
-1.5
-1
-0.5
0
TAD
3 Drug Test Arms
2 Drug Control Arms
3 Drug Control Arms
ATV, Trial 43

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 ATV in trial 43. 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 ATV arm in trial 43 is generally further to the right of (inferior to) most of the three drug arms and completely overlaps five of the two drug arms.

The imputed difference between ATV and placebo based on trials 888 and the average of four other PI trials provide a suggestion of ATV activity as part of a 3 drug regimen in experienced population when measured by TAD. However, an overall conclusion from both methods of imputing the comparison of ATV to placebo is that one is well short of no convincing evidence that ATV contributes anything to improvement in TAD when added to 2 NRTI's in an experienced population.

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 43 who completed 24 weeks of observation with those who were lost to follow-up before week 24. These results are summarized in table 4.4 A.

TABLE 4.4 A
COMPARISON OF COMPLETERS TO LTFU
TRIAL 43

			Mean, Last Value	
Arm	Status	N	Log HIV	CD4 Count
ATV	LTFU	38	2.93	324
	Complete	112	2.55	421
LPV/r	LTFU	33	2.64	433
	Complete	117	2.03	445

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. Also, as might be expected if discontinuing subjects are those with less successful results, the difference between ATV and LPV/r is smaller for discontinued subjects than for completers (2.93 - 2.64 = .302 for discontinued, 2.55 - 2.03 = .512 for completers). Surprisingly,

the corresponding relation does not hold for CD4 count: discontinued subjects do not look more similar than completers. The difference in CD4 count between ATV and LPV/r was 324-433 = 109 for LTFU, only 421-445 = -24 for completers.

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

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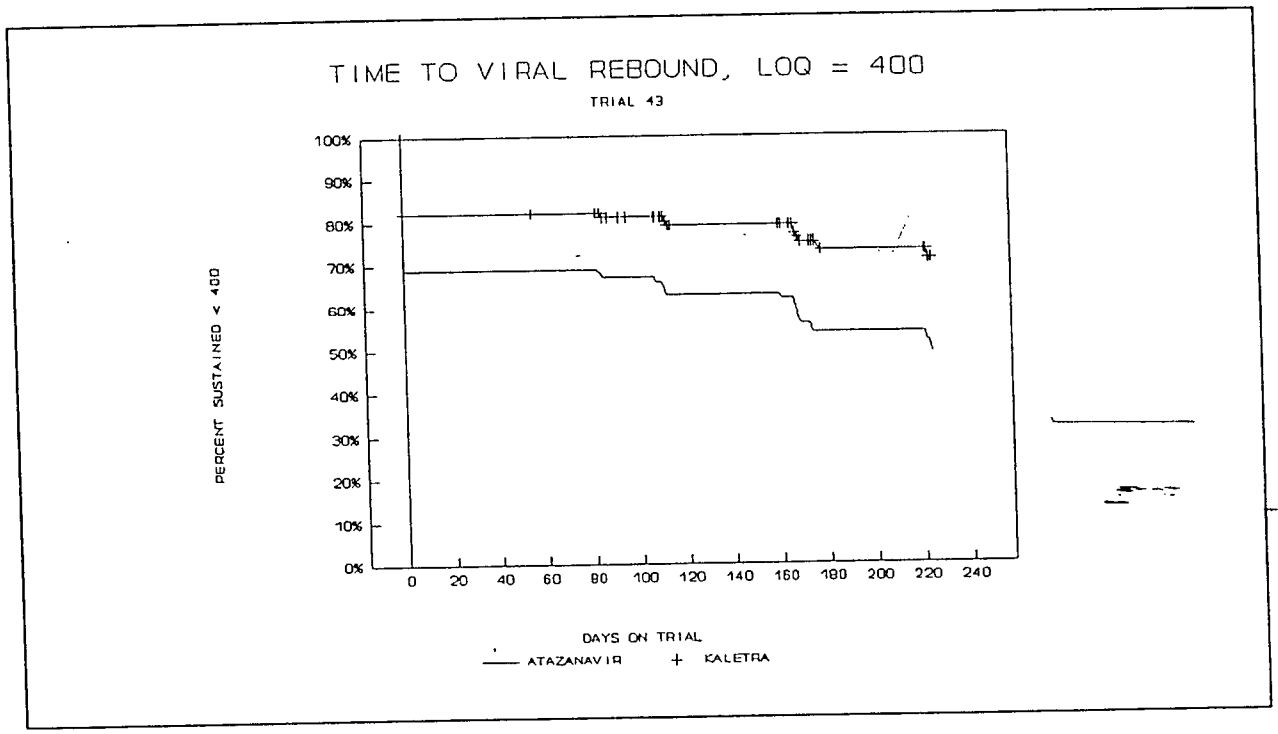
4.5 Time to Viral Rebound

The analysis presented in section 4.2 above showed that in ART experienced subjects ATV 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 figure 4.5. One can see from this graph that the approximate 20% inferiority of ATV to Kaletra is maintained nearly constantly over the time course of the trial. Thus, if the meta-analysis arguments in section 4.2 above are adequate demonstration that ATV would have been superior to a placebo arm, then the Kaplan-Meier curves raise no additional concerns about the time course of ATV efficacy. Results with an LOQ = ___ copies/mL look quite similar to those in figure 4.5 (with both curves shifted downward). Those results are therefore not presented here.



4.6 Results in ART Naive Patients

The applicant's analyses of ART naive patients, using the results from trials 34, 7, and 8, appear to provide two or more adequate, well-controlled trials with evidence to support the use of ATV 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 all three trials provide evidence of ATV efficacy. The results of the FDA re-analysis are given in table 4.5 A. This table gives the mean response to the ATV arm and the control arm (either EFV in trial 34 or NFV in trials 7 and 8), and the 95% confidence interval for the difference between ATV mean and 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 4.5 A
VIRAL LOAD ENDPOINTS IN TRIALS 34, 7, AND 8

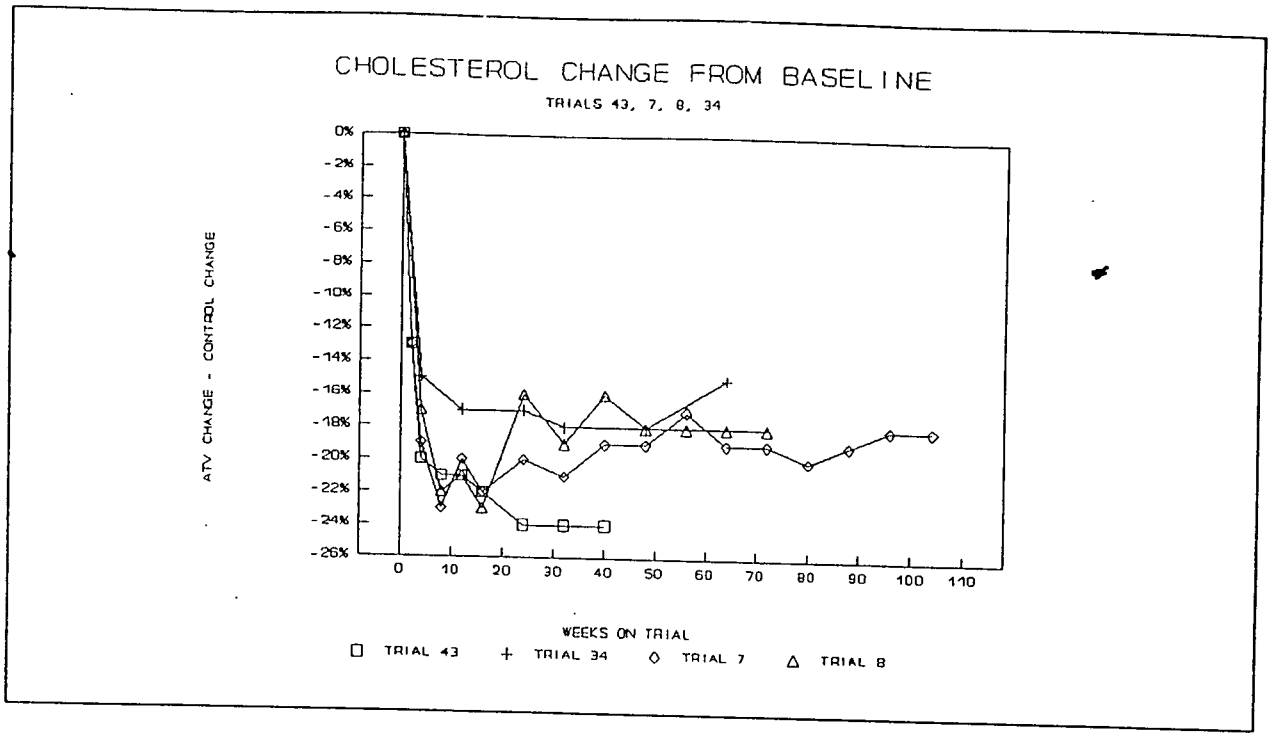
		Means		95%
Endpoint	Trial	ATV	Control	Confidence Limits
%<400	34	69%	64%	(-2.1%, 11.1%)
	7	60%	61%	(-14.7%, 12%)
	8	67%	59%	(-4.5%, 19.9%)
%<50	34	30%	35%	(-11.6%, 1.0%)
	7	34%	36%	(-14.5%, 11.2%)
	8	33%	38%	(-17.8%, 6.2%)
TAD	34	-2.05	-1.94	(-.23, .01)
	7	-1.83	-1.91	(-.14, .28)
	8	-1.88	-1.87	(-.24, .10)

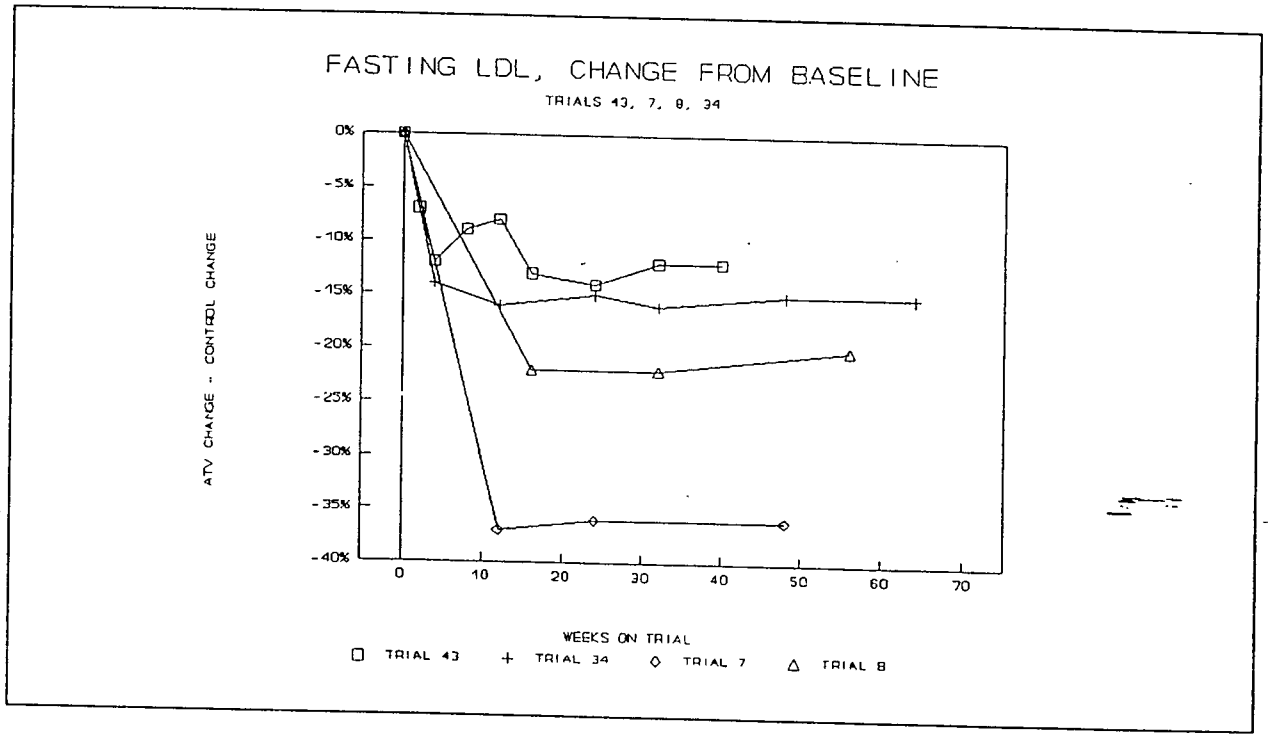
One can see from this table that ATV was, with 95% confidence, no more than 5% worse than an active control drug in proportion of subjects with viral load sustained <400 c/ml in two out of three trials. It was estimated to be as good as control in the third trial but with a lower bound of 14.7% worse. ATV was, with 95% confidence, no more than 15% worse than an active control drug in proportion of subjects with viral load sustained <50 c/ml in two out of three trials. It was estimated to be only 5% worse in the third trial but with a lower bound of 17.8% worse. Finally, ATV was, with 95% confidence, no more than .24

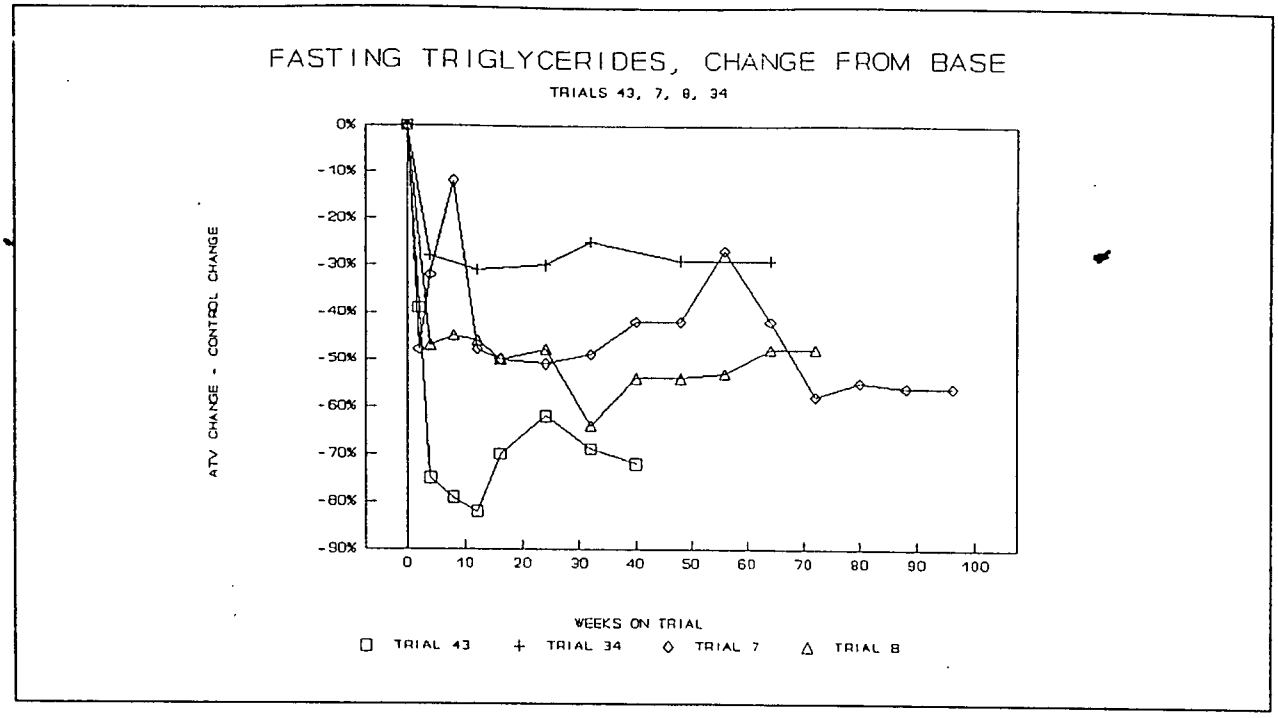
log copies worse than an active control drug in time averaged difference from baseline in HIV RNA in all three trials. Based on this table, the FDA statistical reviewer regards the applicant's claim of demonstrated efficacy of ATV when added to two other drugs in ART naive subjects to be confirmed. One could easily calculate the imputed differences between ATV and placebo for these data, as was done for trial 43 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 with patients with limited experience while it is credibly observed in trials 7 and 8 to be no more than 13.4% or 4.8% better than atazanavir. Also, in trial ACTG 364, efavirenz was superior to placebo in percent <400 copies/mL by 31% (72% to 41%) when both were added to a background of nelfinavir plus two NRTI's while in trial 34 it was at worst no more than 1.5% better than atazanavir.

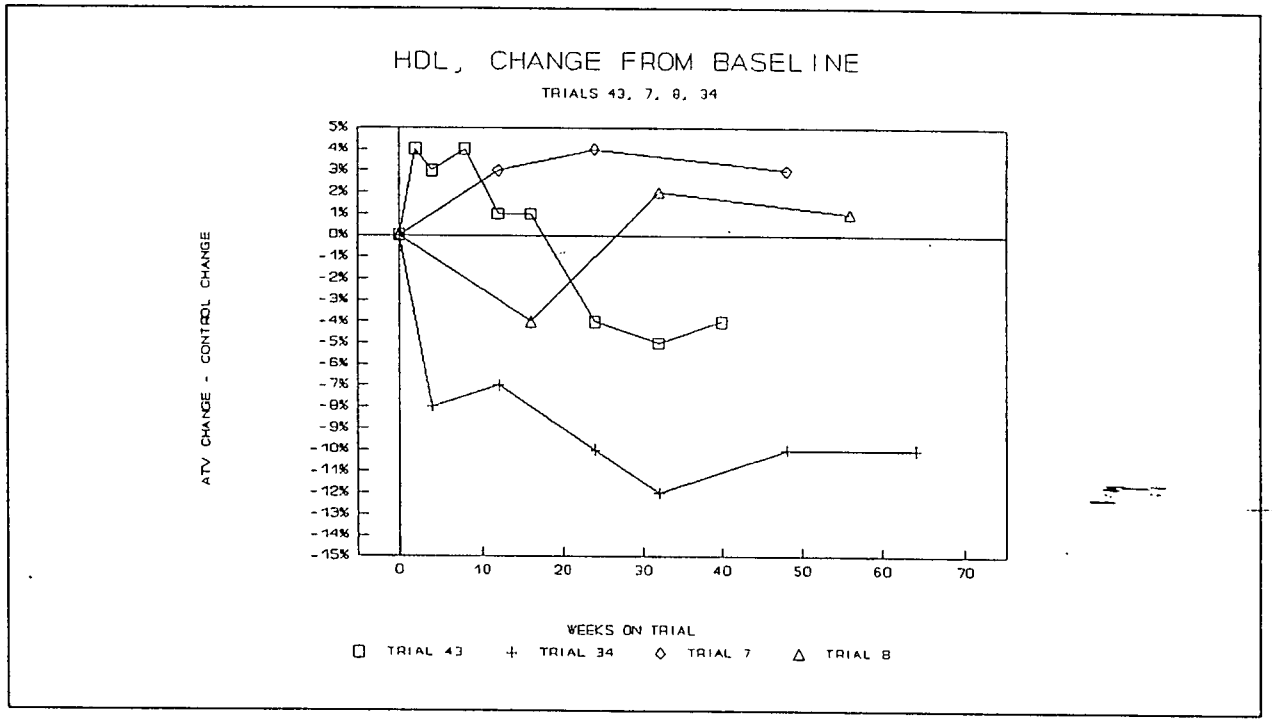
4.7 Results with Lipid Levels

The applicant has also included an analysis to show that ATV is superior to other PI's with respect to increases in cholesterol, low density lipoprotein (LDL), and triglycerides. The FDA statistical reviewer has confirmed these results in general. Figures 4.7 A-D show the weekly time plots of percentage change in four lipid parameters in four trials comparing ATV to three different controls (EFV in trial 34, LPV/r in trial 43, and NFV in trials 7 and 8). Each figure shows the difference between ATV and the control for each of the four trials at each week. Figure 4.7 A shows results for total cholesterol, figure 4.7 B shows results for fasting LDL, figure 4.7 C shows results for fasting triglycerides, figure 4.7 D shows results for high density lipoprotein (HDL). One can see that there is a noticeable difference between ATV and control in all four trials for all parameters except HDL. The FDA reviewer has performed Student t-tests at each week to compare ATV and control levels. Every week after baseline for all three of total cholesterol, fasting LDL, and fasting triglycerides, differences are highly statistically significant. The observed patterns shown in the figures represent real phenomena, not random variation.


CHOLESTEROL CHANGE FROM BASELINE
TRIALS 43, 7, 8, 34
ATV CHANGE - CONTROL CHANGE
0%
-2%
-4%
-6%
-8%
-10%
-12%
-14%
-16%
-18%
-20%
-22%
-24%
-26%
0
10
20
30
40
50
60
70
80
90
100
110
WEEKS ON TRIAL
TRIAL 43
TRIAL 34
TRIAL 7
TRIAL 8


FASTING LDL, CHANGE FROM BASELINE
TRIALS 43, 7, 8, 34
ATV CHANGE - CONTROL CHANGE
0%
-5%
-10%
-15%
-20%
-25%
-30%
-35%
-40%
0
10
20
30
40
50
60
70
WEEKS ON TRIAL
TRIAL 43
TRIAL 34
TRIAL 7
TRIAL 8


FASTING TRIGLYCERIDES, CHANGE FROM BASE
TRIALS 43, 7, 8, 34
ATV CHANGE - CONTROL CHANGE
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
-80%
-90%
0
10
20
30
40
50
60
70
80
90
100
WEEKS ON TRIAL
TRIAL 43
TRIAL 34
TRIAL 7
TRIAL 8


HDL, CHANGE FROM BASELINE
TRIALS 43, 7, 8, 34
ATV CHANGE - CONTROL CHANGE
5%
4%
3%
2%
1%
0%
-1%
-2%
-3%
-4%
-5%
-6%
-7%
-8%
-9%
-10%
-11%
-12%
-13%
-14%
-15%
0
10
20
30
40
50
60
70
WEEKS ON TRIAL
TRIAL 43
TRIAL 34
TRIAL 7
TRIAL 8

5. Results in Special Populations

There was no evidence of interactions between treatment and any interesting covariates. Atazanavir appeared to be roughly equally effective for all choices of background NRTI's (the stratifying variable at randomization), and in both sexes, all races, at all levels studied for age, baseline HIV RNA, baseline CD4 count, previous AIDS diagnosis, geographic region, reason discontinued, concurrent hepatitis B or C, height, weight, body mass index (BMI), or blood pressure (SBP and DBP).

Figure 5 A shows a plot of estimated difference between ATV and LPV/r for trial 43 in mean change from baseline in HIV RNA levels (TAD), 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.) Figure 5 B shows the corresponding plot for percent of subjects with viral load sustained below 400 copies/mL.

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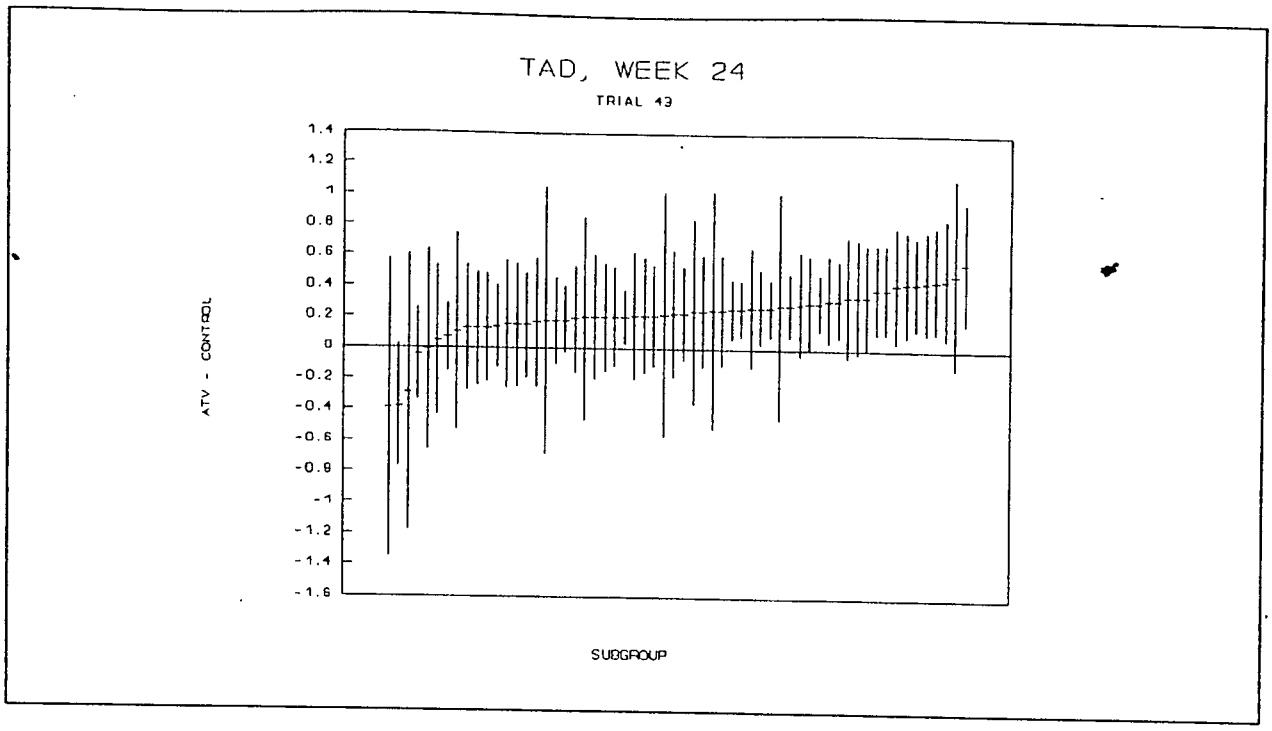
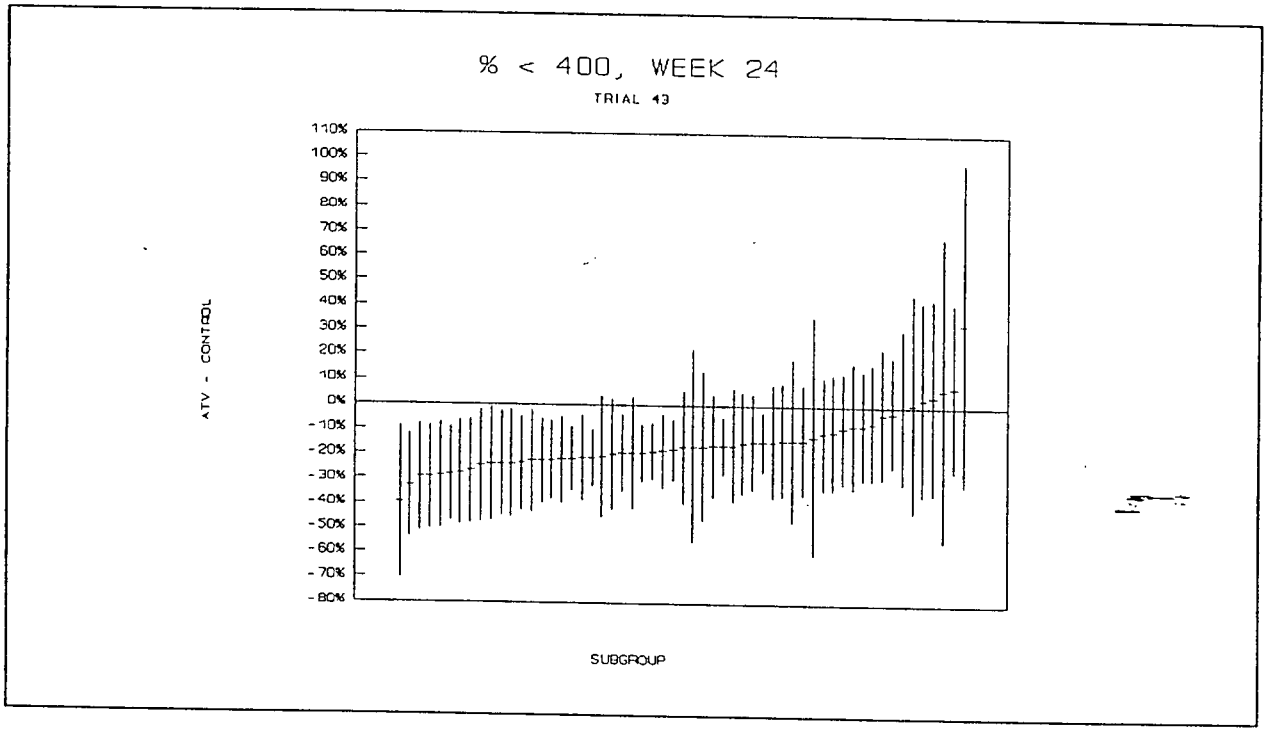

TAD, WEEK 24
TRIAL 43
ATV - CONTROL
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
SUBGROUP


% < 400, WEEK 24
TRIAL 43
ATV - CONTROL
110%
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
-80%
SUBGROUP

The mean differences in these plots look just like what one would expect one took multiple observations from a normal distribution with expected values of .26 (for TAD) or -19% (for percent < 400). Thus, the plot supports the contention that there were no identifiable sub-populations in which Atazanavir was less effective. Tables 5 A, 5 B, and 5 C give the differences in mean effect between ATV and LPV/r. (The positive numbers in table 5 A and the negative numbers in tables 5 B and C in the difference column both correspond to LPV/r superiority.) The tables also give 95% confidence limits for those differences, mean effects on ATV and on LPV/r, sample sizes on ATV and on LPV/r, and the p-values for the treatment differences for all subjects pooled together.

(One may observe that blood pressure, SBP and DBP, were concentrated mostly at a few points. Consequently, dividing those variables by their first, second, and third quartiles produced four subgroups rather unequal in size.)

TABLE 5 A

WEEK 24 CHANGE FROM BASELINE IN HIV RNA

TRIAL 43

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	ATV	LPV/r	ATV	LPV	P-value
All	.26	.08	.44	-1.39	-1.65	150	150	.0056
NRTI's								
ABC+NRTI	.39	.10	.68	-1.28	-1.67	42	50	
ZDV+3TC	.20	-.46	.85	-1.26	-1.46	10	17	
d4T+3TC	.24	-.36	.84	-1.55	-1.79	19	15	
ddI+ZDV	.17	-.25	.58	-1.59	-1.76	19	16	
ddI+d4T	.23	-.08	.53	-1.53	-1.75	54	48	
SEX_								
Female	.15	-.25	.55	-1.41	-1.56	35	27	
Male	.28	.08	.49	-1.39	-1.67	115	123	
RACE_GRP								
Black	.28	-.45	1.01	-.98	-1.26	9	11	
Other	.32	.08	.57	-1.53	-1.85	77	78	
White	.18	-.10	.46	-1.28	-1.46	64	61	
AGE_Quartile								
1st Q	.43	.09	.77	-1.30	-1.74	47	47	
2nd Q	-.38	-.77	.02	-1.75	-1.38	37	23	
3rd Q	.56	.17	.96	-1.21	-1.78	36	38	
4th Q	.29	-.04	.63	-1.29	-1.59	30	42	
REGION								
Europe	-.01	-.66	.64	-1.11	-1.10	13	12	
N_America	.30	.00	.60	-1.32	-1.62	60	61	
S_America	.27	.03	.51	-1.49	-1.76	77	77	
HIV_Quartile								
1st Q	.46	.07	.85	-1.81	-2.27	33	42	
2nd Q	.43	.13	.73	-1.57	-2.00	44	31	
3rd Q	-.04	-.33	.26	-1.41	-1.37	32	43	
4th Q	.07	-.15	.28	-.84	-.91	41	34	
CD4_Quartile								
1st Q	.20	-.20	.60	-1.56	-1.76	36	36	
2nd Q	.44	.10	.77	-1.30	-1.74	41	48	
3rd Q	.20	-.15	.55	-1.36	-1.56	43	34	
4th Q	.13	-.27	.54	-1.36	-1.50	30	32	
REASON								
AE/Death	.18	-.68	1.05	-.57	-.75	3	4	
Complete	.20	.03	.37	-1.59	-1.79	124	135	
LTFU	.25	-.11	.60	-.04	-.28	12	11	

TABLE 5 A (continued)
WEEK 24 CHANGE FROM BASELINE IN HIV RNA
TRIAL 43

Covariate	Diff	95% Limit Lower	Upper	Mean Change ATV	LPV/r	N ATV	LPV
PRIOR_AIDS							
No	.18	-.03	.40	-1.40	-1.59	114	108
Yes	.45	.11	.80	-1.35	-1.81	36	42
IV_DRUG_USE							
No	.30	.12	.48	-1.42	-1.72	139	139
Yes	-.39	-1.35	.57	-1.41	-1.01	8	8
HEP_B_S_AG							
Unknown	.22	-.57	1.01	-.53	-.75	10	8
Negative	.27	.08	.45	-1.44	-1.70	134	139
Positive	-.29	-1.18	.60	-1.80	-1.51	6	3
HEP_C_AB							
Unknown	.25	-.52	1.02	-.25	-.50	7	6
Negative	.26	.06	.45	-1.49	-1.74	121	130
Positive	.05	-.43	.53	-1.22	-1.27	22	14
BMI_Quartile							
1st Q	.23	-.18	.64	-1.28	-1.51	43	38
2nd Q	.21	-.16	.59	-1.53	-1.74	35	38
3rd Q	.34	.00	.68	-1.28	-1.63	38	35
4th Q	.20	-.12	.52	-1.51	-1.71	34	39
HT_Quartile							
1st Q	.27	-.12	.65	-1.40	-1.67	39	47
2nd Q	.13	-.22	.48	-1.48	-1.61	46	29
3rd Q	.34	-.03	.71	-1.36	-1.70	34	32
4th Q	.34	-.05	.73	-1.28	-1.62	31	42

TABLE 5 A (continued)
WEEK 24 CHANGE FROM BASELINE IN HIV RNA
TRIAL 43

Covariate	Diff	95% Limit Lower	Upper	Mean Change ATV	LPV/r	N ATV	LPV
WT_Quartile							
1st Q	.21	-.20	.62	-1.36	-1.57	45	34
2nd Q	.42	.05	.79	-1.28	-1.70	34	44
3rd Q	.19	-.16	.53	-1.49	-1.68	38	34
4th Q	.21	-.12	.54	-1.43	-1.64	33	38
DBP_Quartile							
1st Q	.32	.05	.60	-1.41	-1.73	68	75
2nd Q	.10	-.53	.74	-1.68	-1.78	12	12
3rd Q	.24	-.12	.60	-1.34	-1.58	37	35
4th Q	.15	-.26	.56	-1.30	-1.46	33	28
SBP_Quartile							
1st Q	.39	.10	.68	-1.37	-1.75	60	65
2nd Q	.15	-.19	.48	-1.40	-1.55	46	43
3rd Q	.49	-.12	1.11	-1.29	-1.78	10	3
4th Q	.13	-.24	.49	-1.45	-1.58	34	39

TABLE 5 B

WEEK 24 PERCENT WITH HIV RNA < 400

TRIAL 43

		95% Limit		Mean %		N		
Covariate	Diff	Lower	Upper	ATV	LPV/r	ATV	LPV	P-value
All	-18.7%	-29.7%	-07.6%	47%	65%	150	150	.0009
NRTI's								
ABC+NRTI	-28.0%	-47.0%	-09.0%	50%	78%	42	50	
ZDV+3TC	02.9%	-36.1%	42.0%	50%	47%	10	17	
d4T+3TC	-14.0%	-46.8%	18.7%	53%	67%	19	15	
ddI+ZDV	-00.3%	-31.2%	30.5%	68%	69%	19	16	
ddI+d4T	-23.6%	-42.5%	-04.7%	39%	63%	54	48	
SEX_								
Female	-21.0%	-45.2%	03.3%	46%	67%	35	27	
Male	-18.1%	-30.5%	-05.7%	47%	65%	115	123	
RACE_GRP								
Black	01.0%	-42.8%	44.8%	56%	55%	9	11	
Other	-18.5%	-33.5%	-03.6%	53%	72%	77	78	
White	-21.5%	-38.6%	-04.4%	38%	59%	64	61	
AGE_Quartile								
1st Q	-14.9%	-34.2%	04.4%	55%	70%	47	47	
2nd Q	-03.5%	-29.5%	22.5%	49%	52%	37	23	
3rd Q	-29.5%	-51.3%	-07.8%	39%	68%	36	38	
4th Q	-24.3%	-47.0%	-01.5%	40%	64%	30	42	
REGION								
Europe	03.8%	-35.3%	43.0%	54%	50%	13	12	
N_America	-22.2%	-39.5%	-05.0%	45%	67%	60	61	
S_America	-19.5%	-34.8%	-04.1%	47%	66%	77	77	
HIV_Quartile								
1st Q	-32.9%	-53.8%	-12.0%	24%	57%	33	42	
2nd Q	-28.7%	-50.0%	-07.4%	45%	74%	44	31	
3rd Q	-02.6%	-24.6%	19.4%	63%	65%	32	43	
4th Q	-14.0%	-35.9%	07.9%	54%	68%	41	34	
CD4_Quartile								
1st Q	-19.4%	-41.9%	03.0%	33%	53%	36	36	
2nd Q	-16.5%	-37.1%	04.0%	44%	60%	41	48	
3rd Q	-29.3%	-50.3%	-08.4%	44%	74%	43	34	
4th Q	-08.1%	-29.9%	13.6%	70%	78%	30	32	
REASON								
AE/Death	00.0%	00.0%	00.0%	00%	00%	3	4	
Complete	-16.1%	-27.7%	-04.6%	56%	73%	124	135	
LTFU	00.0%	00.0%	00.0%	00%	00%	12	11	

TABLE 5 B (Continued)
WEEK 24 PERCENT WITH HIV RNA < 400
TRIAL 43

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % LPV/r	N ATV	N LPV
PRIOR_AIDS							
No	-21.9%	-34.7%	-09.2%	45%	67%	114	108
Yes	-09.1%	-31.1%	12.8%	53%	62%	36	42
IV_DRUG_USE							
No	-19.4%	-30.8%	-08.0%	47%	67%	139	139
Yes	-12.5%	-60.7%	35.7%	50%	63%	8	8
HEP_B_S_AG							
Negative	-21.3%	-32.7%	-09.9%	48%	69%	134	139
Positive	33.3%	-32.0%	98.7%	67%	33%	6	3
Unknown	07.5%	-26.3%	41.3%	20%	13%	10	8
HEP_C_AB							
Negative	-14.9%	-26.9%	-02.8%	52%	67%	121	130
Positive	-39.6%	-70.3%	-09.0%	32%	71%	22	14
Unknown	-16.7%	-46.5%	13.2%	00%	17%	7	6
BMI_Quartile							
1st Q	-23.9%	-45.0%	-02.8%	42%	66%	43	38
2nd Q	-27.5%	-48.5%	-06.5%	51%	79%	35	38
3rd Q	-06.7%	-29.6%	16.2%	45%	51%	38	35
4th Q	-14.1%	-36.7%	08.5%	50%	64%	34	39
HT_Quartile							
1st Q	-22.8%	-43.5%	-02.1%	41%	64%	39	47
2nd Q	-10.8%	-33.8%	12.2%	48%	59%	46	29
3rd Q	-16.0%	-38.8%	06.8%	56%	72%	34	32
4th Q	-24.7%	-47.2%	-02.3%	42%	67%	31	42

TABLE 5 B (Continued)
WEEK 24 PERCENT WITH HIV RNA < 400
TRIAL 43

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % LPV/r	N ATV	N LPV
WT_Quartile							
1st Q	-26.9%	-47.7%	-06.1%	47%	74%	45	34
2nd Q	-23.8%	-45.5%	-02.1%	35%	59%	34	44
3rd Q	-14.7%	-37.3%	07.9%	50%	65%	38	34
4th Q	-11.2%	-34.0%	11.5%	55%	66%	33	38
DBP_Quartile							
1st Q	-22.3%	-38.1%	-06.5%	47%	69%	68	75
2nd Q	-16.7%	-55.5%	22.2%	50%	67%	12	12
3rd Q	-19.8%	-42.2%	02.7%	46%	66%	37	35
4th Q	-08.1%	-33.2%	17.0%	45%	54%	33	28
SBP_Quartile							
1st Q	-22.7%	-39.7%	-05.7%	45%	68%	60	65
2nd Q	-15.1%	-35.4%	05.2%	50%	65%	46	43
3rd Q	06.7%	-54.7%	68.0%	40%	33%	10	3
4th Q	-17.0%	-39.6%	05.5%	47%	64%	34	39

TABLE 5 C

WEEK 24 PERCENT WITH HIV RNA < 50

TRIAL 43

		95% Limit		Mean %		N		
Covariate	Diff	Lower	Upper	ATV	LPV/r	ATV	LPV	P-value
All	-14.7%	-25.4%	-03.9%	29%	43%	150	150	.0074
NRTIN_								
ABC+NRTI	-15.0%	-34.7%	04.6%	31%	46%	42	50	
ZDV+3TC	26.5%	-10.5%	63.4%	50%	24%	10	17	
d4T+3TC	-08.4%	-40.8%	24.0%	32%	40%	19	15	
ddI+ZDV	-07.9%	-41.0%	25.2%	42%	50%	19	16	
ddI+d4T	-29.6%	-47.4%	-11.9%	20%	50%	54	48	
SEX_								
Female	-24.1%	-48.4%	00.1%	31%	56%	35	27	
Male	-12.8%	-24.8%	-00.9%	28%	41%	115	123	
RACE_GRP								
Black	17.2%	-24.6%	59.0%	44%	27%	9	11	
Other	-18.8%	-34.1%	-03.6%	32%	51%	77	78	
White	-14.2%	-29.9%	01.6%	22%	36%	64	61	
AGE_Quartile								
1st Q	-21.3%	-40.5%	-02.1%	28%	49%	47	47	
2nd Q	03.1%	-21.9%	28.0%	38%	35%	37	23	
3rd Q	-19.7%	-41.0%	01.5%	25%	45%	36	38	
4th Q	-17.1%	-38.3%	04.1%	23%	40%	30	42	
REGION								
Europe	-10.9%	-48.4%	26.6%	31%	42%	13	12	
N_America	-12.6%	-29.7%	04.5%	32%	44%	60	61	
S_America	-16.9%	-31.7%	-02.1%	26%	43%	77	77	
HIV_Quartile								
1st Q	-14.1%	-31.4%	03.3%	12%	26%	33	42	
2nd Q	-21.1%	-43.1%	00.9%	27%	48%	44	31	
3rd Q	01.2%	-21.7%	24.0%	50%	49%	32	43	
4th Q	-26.1%	-47.7%	-04.5%	27%	53%	41	34	
CD4_Quartile								
1st Q	-13.9%	-34.6%	06.9%	22%	36%	36	36	
2nd Q	-13.1%	-32.1%	05.9%	24%	38%	41	48	
3rd Q	-25.0%	-46.5%	-03.6%	28%	53%	43	34	
4th Q	-06.7%	-31.5%	18.1%	43%	50%	30	32	
REASON								
Complete	-13.5%	-25.4%	-01.6%	35%	48%	124	135	
AE/Death	00.0%	00.0%	00.0%	00%	00%	3	4	
LTFU	00.0%	00.0%	00.0%	00%	00%	12	11	

TABLE 5 C (continued)
WEEK 24 PERCENT WITH HIV RNA < 50
TRIAL 43

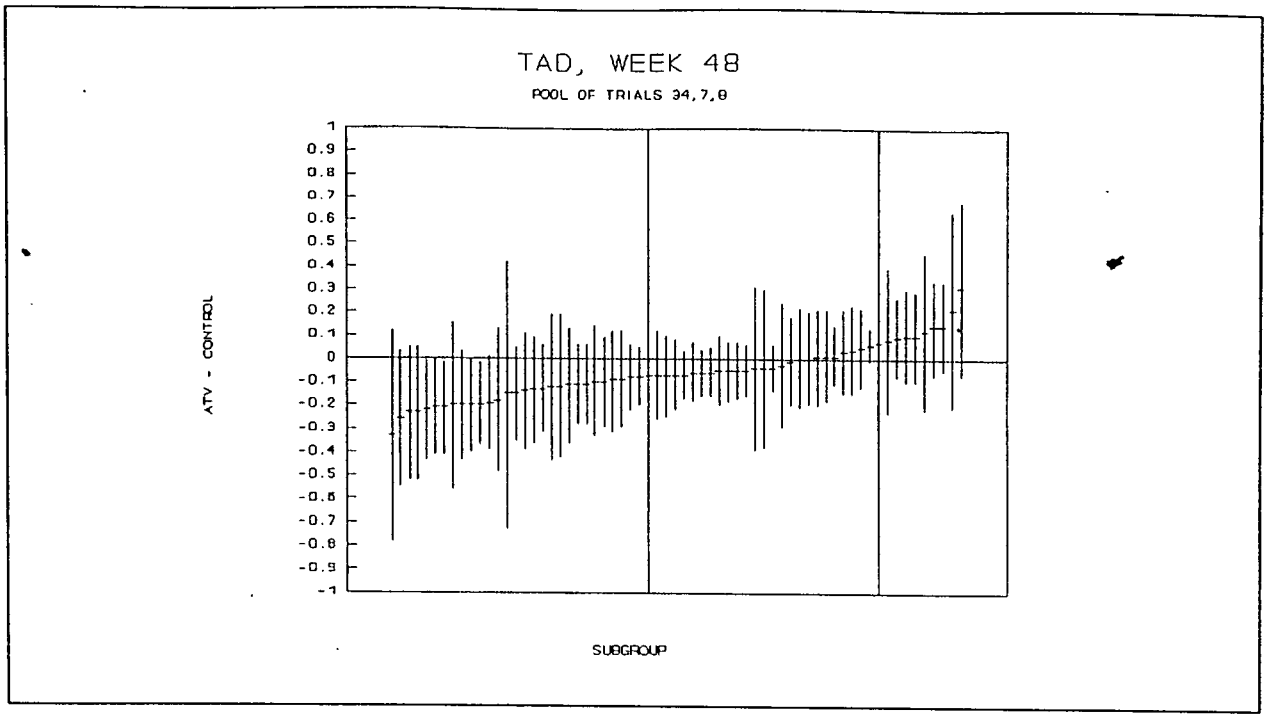
Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % LPV/r	N ATV	N LPV
PRIOR_AIDS							
No	-14.6%	-27.2%	-02.0%	30%	44%	114	108
Yes	-15.5%	-36.0%	05.0%	25%	40%	36	42
IV_DRUG_USE							
No	-15.1%	-26.3%	-03.9%	29%	45%	139	139
Yes	-12.5%	-57.5%	32.5%	25%	38%	8	8
HEP_B_S_AG							
Negative	-14.0%	-25.4%	-02.6%	31%	45%	134	139
Positive	-16.7%	-77.8%	44.4%	17%	33%	6	3
Unknown	-12.5%	-35.4%	10.4%	00%	13%	10	8
HEP_C_AB							
Negative	-11.6%	-23.5%	00.3%	32%	44%	121	130
Positive	-31.8%	-62.6%	-01.1%	18%	50%	22	14
Unknown	-16.7%	-46.5%	13.2%	00%	17%	7	6
BMI_Quartile							
1st Q	-22.1%	-42.9%	-01.3%	28%	50%	43	38
2nd Q	-10.7%	-32.7%	11.3%	31%	42%	35	38
3rd Q	-13.5%	-34.4%	07.5%	24%	37%	38	35
4th Q	-11.2%	-33.4%	10.9%	32%	44%	34	39
HT_Quartile							
1st Q	-23.7%	-43.2%	-04.3%	23%	47%	39	47
2nd Q	-11.3%	-34.2%	11.6%	37%	48%	46	29
3rd Q	-17.5%	-40.6%	05.6%	29%	47%	34	32
4th Q	-10.8%	-31.2%	09.7%	23%	33%	31	42

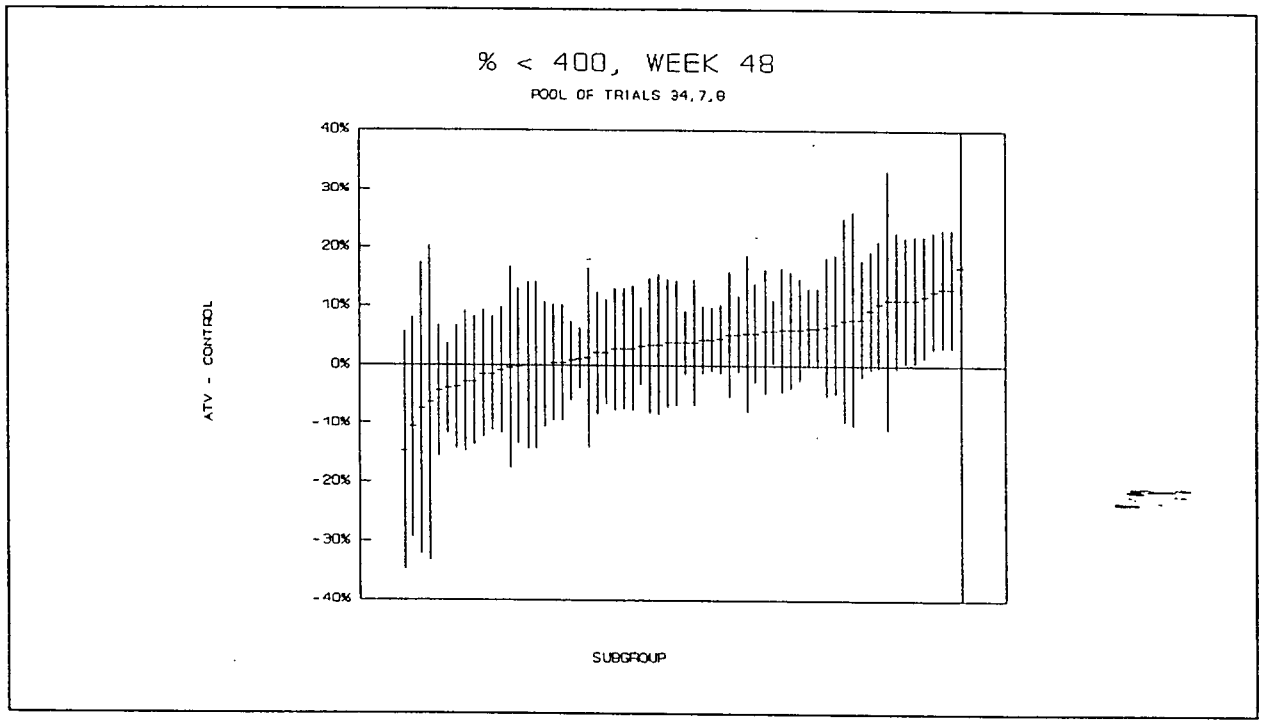
TABLE 5 C (continued)
WEEK 24 PERCENT WITH HIV RNA < 50
TRIAL 43

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % LPV/r	N ATV	N LPV
WT_Quartile							
1st Q	-35.1%	-55.9%	-14.3%	27%	62%	45	34
2nd Q	-10.6%	-30.5%	09.4%	24%	34%	34	44
3rd Q	-01.1%	-23.1%	21.0%	34%	35%	38	34
4th Q	-14.4%	-36.7%	07.8%	30%	45%	33	38
DBP_Quartile							
1st Q	-19.9%	-35.6%	-04.3%	29%	49%	68	75
2nd Q	-16.7%	-55.5%	22.2%	33%	50%	12	12
3rd Q	-10.1%	-31.6%	11.4%	27%	37%	37	35
4th Q	-04.9%	-27.9%	18.2%	27%	32%	33	28
SBP_Quartile							
1st Q	-20.9%	-37.6%	-04.2%	28%	49%	60	65
2nd Q	-09.1%	-28.9%	10.7%	30%	40%	46	43
3rd Q	10.0%	-08.6%	28.6%	10%	00%	10	3
4th Q	-08.7%	-30.7%	13.4%	32%	41%	34	39

Figure 5 C shows a plot of estimated difference between ATV and control (either EFV or NFV) for trials 34, 7, and 8 pooled together in mean change from baseline in HIV RNA levels (TAD), 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.) Figure 5 D shows the corresponding plot for percent of subjects with viral load sustained below 400 copies/mL.

APPEARS THIS WAY
ON ORIGINAL


TAD, WEEK 48
POOL OF TRIALS 34,7,8
ATV - CONTROL
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1
SUBGROUP


% < 400, WEEK 48
POOL OF TRIALS 34,7,8
ATV - CONTROL
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
SUBGROUP

The mean differences in these plots look just like what one would expect one took multiple observations from a normal distribution with expected values of -.06 (for TAD) or 4.4% (for percent < 400). Thus, the plot supports the contention that there were no identifiable sub-populations in which Atazanavir was less effective. Tables 5 D, 5 E, and 5 F give the differences in mean effect between ATV and control. (The negative numbers in table 5 D and the positive numbers in tables 5 E and F in the difference column both correspond to ATV superiority.) The tables also give 95% confidence limits for those differences, mean effects on ATV and on control, sample sizes on ATV and on control, and the p-values for the treatment differences for all subjects pooled together.

APPEARS THIS WAY
ON ORIGINAL

TABLE 5 D

WEEK 48 CHANGE FROM BASELINE IN HIV RNA

TRIALS 34, 7, 8 POOLED

		95% Limit		Mean Change		N		
Covariate	Diff	Lower	Upper	ATV	Cont	ATV	Con	P-value
All	-.06	-.16	.04	-2.15	-2.09	686	597	.2366
STRATA_								
<30000	-.08	-.22	.06	-1.82	-1.74	213	184	
>=30000	-.05	-.18	.07	-2.29	-2.24	473	413	
SEX_								
Female	-.07	-.25	.10	-2.15	-2.07	257	206	
Male	-.05	-.17	.07	-2.14	-2.09	429	391	
RACE_GRP								
Asian/Pac	-.12	-.42	.19	-2.59	-2.48	58	71	
Black	-.20	-.43	.03	-2.25	-2.05	142	122	
Hispanic	.01	-.20	.21	-2.15	-2.16	153	142	
Other	.08	-.23	.39	-2.19	-2.28	39	24	
White	-.07	-.22	.08	-2.00	-1.92	294	238	
AGE_Quartile								
1st Q	-.20	-.40	.00	-2.27	-2.07	151	154	
2nd Q	.14	-.05	.33	-2.10	-2.24	204	159	
3rd Q	.00	-.19	.20	-2.14	-2.14	166	133	
4th Q	-.21	-.41	.00	-2.10	-1.89	165	151	
REGION								
Africa	-.14	-.39	.11	-2.41	-2.27	107	91	
Asia	-.03	-.29	.24	-2.51	-2.48	81	82	
Europe	-.11	-.28	.06	-1.90	-1.79	199	178	
N_America	-.23	-.52	.05	-2.05	-1.82	101	82	
S_America	.09	-.08	.26	-2.15	-2.24	198	164	
HIV_Quartile								
1st Q	-.13	-.36	.09	-2.60	-2.46	172	149	
2nd Q	-.13	-.31	.06	-2.34	-2.22	170	150	
3rd Q	.05	-.12	.22	-1.99	-2.04	169	153	
4th Q	-.05	-.20	.10	-1.66	-1.61	175	145	
CD4_Quartile								
1st Q	-.10	-.29	.09	-2.05	-1.95	165	142	
2nd Q	.03	-.15	.21	-2.07	-2.10	180	161	
3rd Q	-.07	-.26	.12	-2.17	-2.09	191	178	
4th Q	-.10	-.33	.14	-2.31	-2.22	150	116	

TABLE 5 D (continued)
WEEK 48 CHANGE FROM BASELINE IN HIV RNA
TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	Upper	Mean Change ATV	Cont	N ATV	Con
REASON							
Complete	.06	-.01	.13	-2.41	-2.47	550	449
AE/Death	-.20	-.56	.15	-.94	-.73	44	51
LOE	.31	-.07	.68	-.99	-1.30	16	25
LTFU	-.26	-.55	.03	-1.20	-.94	76	72
PRIOR_AIDS							
No	-.04	-.14	.06	-2.14	-2.10	645	558
Yes	-.33	-.78	.12	-2.29	-1.96	40	37
IV_DRUG_USE							
No	-.07	-.17	.03	-2.18	-2.11	636	553
Yes	.12	-.22	.46	-1.77	-1.89	48	41
HEP_B_S_AG							
Negative	-.06	-.16	.05	-2.17	-2.12	601	510
Positive	-.15	-.73	.42	-2.15	-2.00	22	29
Unknown	-.04	-.38	.30	-1.90	-1.86	63	58
HEP_C_AB							
Negative	-.05	-.16	.06	-2.20	-2.15	559	483
Positive	-.12	-.43	.19	-1.96	-1.84	73	58
Unknown	-.04	-.39	.31	-1.87	-1.83	54	56
BMI_Quartile							
1st Q	.04	-.15	.23	-2.12	-2.16	158	142
2nd Q	-.21	-.41	-.02	-2.25	-2.03	156	154
3rd Q	.14	-.07	.34	-2.06	-2.20	171	140
4th Q	-.19	-.39	.01	-2.16	-1.97	201	161
HT_Quartile							
1st Q	-.01	-.20	.18	-2.07	-2.07	159	148
2nd Q	-.15	-.35	.05	-2.19	-2.05	169	147
3rd Q	.01	-.18	.21	-2.18	-2.20	170	139
4th Q	-.09	-.29	.12	-2.13	-2.05	188	163

TABLE 5 D (continued)
WEEK 48 CHANGE FROM BASELINE IN HIV RNA
TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	Upper	Mean Change ATV	Cont	N ATV	Con
WT_Quartile							
1st Q	-.20	-.37	-.02	-2.23	-2.03	165	148
2nd Q	.10	-.10	.30	-2.04	-2.14	148	144
3rd Q	.10	-.10	.29	-2.04	-2.14	188	145
4th Q	-.22	-.43	-.01	-2.26	-2.04	185	160
DBP_Quartile							
1st Q	-.09	-.31	.12	-2.26	-2.17	128	124
2nd Q	.21	-.21	.64	-2.23	-2.44	23	26
3rd Q	-.18	-.48	.13	-2.27	-2.09	79	79
4th Q	-.06	-.18	.07	-2.09	-2.03	456	368
SBP_Quartile							
1st Q	.00	-.21	.22	-2.23	-2.24	121	119
2nd Q	-.11	-.36	.13	-2.30	-2.19	99	98
3rd Q	-.07	-1.88	1.73	-2.11	-2.04	6	4
4th Q	-.08	-.20	.05	-2.09	-2.01	460	376

TABLE 5 E

WEEK 48 PERCENT WITH HIV RNA < 400

TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % Cont	N ATV	N Con	P-value
All	04.4%	-00.9%	09.7%	65%	61%	689	599	.1043
STRATA_								
<30000	02.2%	-06.7%	11.2%	72%	70%	214	185	
>=30000	05.3%	-01.1%	11.8%	62%	57%	475	414	
SEX_								
Female	06.1%	-02.6%	14.8%	68%	62%	258	206	
Male	03.3%	-03.4%	09.9%	64%	60%	431	393	
RACE_GRP								
Asian/Pac	11.1%	-00.6%	22.8%	91%	80%	58	71	
Black	06.5%	-05.3%	18.3%	64%	57%	144	122	
Hispanic	03.9%	-06.9%	14.7%	68%	64%	153	142	
Other	-10.6%	-29.3%	08.1%	77%	88%	39	24	
White	05.5%	-03.0%	13.9%	58%	53%	295	240	
AGE_Quartile								
1st Q	10.4%	-00.4%	21.2%	68%	57%	151	154	
2nd Q	-01.5%	-11.2%	08.2%	66%	68%	206	160	
3rd Q	-02.8%	-13.7%	08.2%	63%	65%	166	133	
4th Q	11.1%	00.4%	21.9%	65%	54%	166	152	
REGION								
Africa	-00.2%	-13.4%	13.0%	66%	66%	108	91	
Asia	06.0%	-04.7%	16.6%	89%	83%	81	82	
Europe	13.1%	03.1%	23.1%	58%	45%	199	179	
N_America	00.0%	-14.2%	14.1%	60%	60%	103	83	
S_America	00.4%	-09.4%	10.3%	66%	65%	198	164	
HIV_Quartile								
1st Q	11.2%	00.4%	22.1%	58%	46%	172	149	
2nd Q	02.9%	-07.8%	13.5%	64%	61%	170	150	
3rd Q	02.7%	-07.6%	13.0%	68%	65%	169	153	
4th Q	00.5%	-09.4%	10.3%	72%	71%	178	147	
CD4_Quartile								
1st Q	02.1%	-08.3%	12.5%	70%	68%	165	142	
2nd Q	02.8%	-07.4%	13.0%	66%	63%	180	161	
3rd Q	06.0%	-03.9%	16.0%	64%	58%	191	178	
4th Q	07.0%	-04.8%	18.8%	62%	55%	153	118	

TABLE 5 E (continued)
WEEK 48 PERCENT WITH HIV RNA < 400
TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % Cont	N ATV	N Con
REASON							
Complete	01.1%	-04.0%	06.3%	79%	78%	550	449
AE/Death	03.5%	-08.4%	15.5%	11%	08%	44	51
LOE	-04.0%	-11.7%	03.7%	00%	04%	16	25
LTFU	-00.9%	-11.6%	09.8%	13%	14%	79	74
PRIOR_AIDS							
No	03.8%	-01.6%	09.2%	66%	62%	648	560
Yes	11.1%	-10.9%	33.2%	63%	51%	40	37
IV_DRUG_USE							
No	05.8%	00.3%	11.2%	67%	61%	638	553
Yes	-14.6%	-34.9%	05.7%	46%	60%	48	43
HEP_B_S_AG							
Negative	04.4%	-01.3%	10.1%	67%	62%	601	510
Positive	-06.4%	-33.3%	20.4%	59%	66%	22	29
Unknown	07.7%	-09.7%	25.1%	56%	48%	66	60
HEP_C_AB							
Negative	04.5%	-01.3%	10.3%	68%	63%	559	483
Positive	-00.4%	-17.5%	16.8%	55%	55%	73	58
Unknown	07.9%	-10.3%	26.1%	56%	48%	57	58
BMI_Quartile							
1st Q	03.8%	-06.9%	14.4%	69%	65%	159	142
2nd Q	05.8%	-04.8%	16.4%	68%	62%	157	154
3rd Q	-01.5%	-12.3%	09.4%	60%	62%	171	141
4th Q	09.3%	-00.8%	19.4%	65%	56%	202	162
HT_Quartile							
1st Q	03.8%	-07.2%	14.7%	62%	58%	160	148
2nd Q	00.0%	-10.6%	10.6%	64%	64%	170	148
3rd Q	05.2%	-05.5%	15.9%	67%	62%	170	139
4th Q	07.9%	-02.1%	17.9%	68%	60%	189	164

TABLE 5 E (continued)
WEEK 48 PERCENT WITH HIV RNA < 400
TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % Cont	N ATV	N Con
WT_Quartile							
1st Q	11.7%	01.3%	22.1%	72%	60%	167	148
2nd Q	-04.4%	-15.6%	06.8%	58%	63%	148	144
3rd Q	-03.7%	-14.2%	06.7%	61%	64%	188	146
4th Q	12.7%	02.7%	22.8%	70%	57%	186	161
DBP_Quartile							
1st Q	03.4%	-08.1%	14.9%	70%	66%	128	124
2nd Q	-07.4%	-32.2%	17.5%	70%	77%	23	26
3rd Q	01.3%	-14.0%	16.5%	61%	59%	79	79
4th Q	06.3%	-00.3%	13.0%	65%	58%	459	370
SBP_Quartile							
1st Q	-02.8%	-14.6%	09.1%	66%	69%	121	119
2nd Q	05.4%	-07.9%	18.7%	68%	62%	99	98
3rd Q	16.7%	-45.2%	78.5%	67%	50%	6	4
4th Q	06.4%	-00.2%	13.0%	65%	58%	463	378

TABLE 5 F

WEEK 48 PERCENT WITH HIV RNA < 50

TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	Upper	Mean % ATV	Cont	N ATV	Con	P-value
All	-04.3%	-09.5%	00.8%	31%	35%	689	599	.0997
STRATA_								
<30000	-02.9%	-12.6%	06.9%	43%	45%	214	185	
>=30000	-05.0%	-11.0%	00.9%	26%	31%	475	414	
SEX_								
Female	-01.0%	-10.0%	08.0%	40%	41%	258	206	
Male	-06.8%	-13.0%	-00.6%	26%	32%	431	393	
RACE_GRP								
Asian/Pac	00.3%	-15.5%	16.1%	71%	70%	58	71	
Black	-01.3%	-13.1%	10.5%	39%	40%	144	122	
Hispanic	-08.7%	-18.6%	01.2%	21%	30%	153	142	
Other	-15.4%	-39.9%	09.1%	51%	67%	39	24	
White	-00.9%	-08.0%	06.2%	22%	23%	295	240	
AGE_Quartile								
1st Q	-00.7%	-11.2%	09.9%	32%	33%	151	154	
2nd Q	-04.2%	-14.0%	05.6%	32%	36%	206	160	
3rd Q	-12.0%	-22.7%	-01.3%	27%	39%	166	133	
4th Q	-01.0%	-11.4%	09.3%	33%	34%	166	152	
REGION								
Africa	-00.9%	-14.8%	13.0%	52%	53%	108	91	
Asia	-01.6%	-15.1%	12.0%	73%	74%	81	82	
Europe	-00.1%	-07.4%	07.3%	16%	16%	199	179	
N_America	-04.4%	-17.0%	08.2%	23%	28%	103	83	
S_America	-09.5%	-18.7%	-00.3%	22%	32%	198	164	
HIV_Quartile								
1st Q	00.8%	-08.6%	10.3%	25%	24%	172	149	
2nd Q	-04.2%	-14.1%	05.7%	26%	31%	170	150	
3rd Q	-04.6%	-14.9%	05.7%	31%	36%	169	153	
4th Q	-10.0%	-20.8%	00.8%	41%	51%	178	147	
CD4_Quartile								
1st Q	-04.3%	-15.1%	06.6%	35%	39%	165	142	
2nd Q	-06.4%	-16.5%	03.8%	33%	39%	180	161	
3rd Q	-01.6%	-11.0%	07.8%	30%	31%	191	178	
4th Q	-05.2%	-16.1%	05.7%	26%	31%	153	118	

TABLE 5 F (continued)
WEEK 48 PERCENT WITH HIV RNA < 50
TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % Cont	N ATV	N Con
REASON							
Complete	-07.9%	-14.0%	-01.7%	38%	46%	550	449
AE/Death	-01.6%	-08.6%	05.3%	02%	04%	44	51
LOE	00.0%	00.0%	00.0%	00%	00%	16	25
LTFU	-00.3%	-07.4%	06.7%	05%	05%	79	74
PRIOR_AIDS							
No	-05.4%	-10.7%	00.0%	31%	36%	648	560
Yes	10.7%	-09.6%	30.9%	35%	24%	40	37
Unknown	00.0%	00.0%	00.0%	00%	00%	1	2
IV_DRUG_USE							
No	-05.0%	-10.4%	00.4%	32%	37%	638	553
Yes	03.0%	-10.9%	16.8%	15%	12%	48	43
Unknown	00.0%	00.0%	00.0%	00%	00%	3	3
HEP_B_S_AG							
Negative	-05.0%	-10.6%	00.6%	31%	36%	601	510
Positive	15.7%	-09.3%	40.6%	36%	21%	22	29
Unknown	-07.6%	-23.5%	08.3%	26%	33%	66	60
HEP_C_AB							
Negative	-05.4%	-11.2%	00.4%	33%	39%	559	483
Positive	08.5%	-04.0%	21.0%	21%	12%	73	58
Unknown	-08.2%	-24.7%	08.3%	25%	33%	57	58
BMI_Quartile							
1st Q	-06.2%	-17.1%	04.7%	34%	40%	159	142
2nd Q	02.6%	-07.9%	13.1%	35%	32%	157	154
3rd Q	-09.1%	-19.6%	01.5%	29%	38%	171	141
4th Q	-04.3%	-13.7%	05.2%	27%	31%	202	162

TABLE 5 F (continued)
WEEK 48 PERCENT WITH HIV RNA < 50
TRIALS 34, 7, 8 POOLED

Covariate	Diff	95% Limit Lower	95% Limit Upper	Mean % ATV	Mean % Cont	N ATV	N Con
HT_Quartile							
1st Q	-06.0%	-15.9%	03.9%	24%	30%	160	148
2nd Q	-01.3%	-11.7%	09.0%	32%	33%	170	148
3rd Q	-08.4%	-19.1%	02.3%	31%	40%	170	139
4th Q	-02.5%	-12.7%	07.6%	37%	39%	189	164
WT_Quartile							
1st Q	-01.6%	-12.1%	08.9%	34%	35%	167	148
2nd Q	-05.6%	-16.1%	04.9%	27%	33%	148	144
3rd Q	-08.8%	-18.9%	01.3%	28%	37%	188	146
4th Q	-01.7%	-11.8%	08.4%	35%	37%	186	161
DBP_Quartile							
1st Q	-08.3%	-20.0%	03.5%	31%	40%	128	124
2nd Q	-09.5%	-32.6%	13.5%	17%	27%	23	26
3rd Q	-01.3%	-16.3%	13.8%	37%	38%	79	79
4th Q	-03.3%	-09.7%	03.1%	31%	34%	459	370
SBP_Quartile							
1st Q	-01.4%	-13.6%	10.7%	36%	37%	121	119
2nd Q	-08.5%	-21.8%	04.8%	31%	40%	99	98
3rd Q	25.0%	-33.3%	83.3%	50%	25%	6	4
4th Q	-04.3%	-10.6%	02.1%	30%	34%	463	378

6. Statistical Reviewer's Conclusions

The applicant has demonstrated in three clinical trials with ART naive patients that atazanavir, 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.

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 tested atazanavir for 24 weeks in one trial with patients who have already failed at least regimen containing a PI. In that trial, atazanavir was statistically and clinically significantly inferior to Kaletra when each was added to a background regimen of two NRTI's. Meta-analysis supports the inference that atazanavir would have been statistically significantly superior to placebo with respect to proportion of subjects whose viral load was undetectable had it been ethical to include such an arm in the trial.

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

Thomas Hammerstrom,

Ph.D.

Mathematical

Statistician

Concur: Dr. Soon
cc:
Archival NDA #21-567
HFD-530
HFD-530/Dr. Birnkrant

HFD-530/Dr. Murray
HFD-530/Dr. Kukich
HFD-530/Ms. Reddy
HFD-725/Dr. Hammerstrom
HFD-700/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Ms. Robinette
*

APPENDIX
ESTIMATION OF DIFFERENCE IN TAD, ATV-PLACEBO USING ALL NFV NDA TRIALS
TABLE APPENDIX A
COMPARISON OF ATV TO PLACEBO, USING TAD

Observed Data

Source	Arm1	Arm2	Mean1	Mean2	Difference	SEE
ATV NDA						
Trial 43	ATV	LPV/r	-1.49	-1.73	.24	.086
LPV/r NDA						
Trial 863	LPV/r	NFV	-1.798	-1.801	.003	.057
NFV NDA						
Trial 511	NFV	Placebo	-1.77	-1.40	-.37	.083
Trial 506	NFV	Placebo	-1.31	-.50	-.81	.071

Imputed

Arm1	Arm2	Difference	SEE
ATV	NFV	.24+.003 = .243	$\sqrt{.086^2+.057^2} = .103$
NFV	Plac	(-.37-.81)/2 = -.59	$\sqrt{.083^2+.071^2}/2 = .055$
ATV	Plac	.243-.59 = -.347	$\sqrt{.103^2+.055^2} = .116$