CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-705 / S-008

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-705/S-008
APPLICANT:	Agouron Pharmaceuticals, Inc.
NAME OF DRUG:	Rescriptor® (Delavirdine)
INDICATION:	Treatment of HIV Infection
TYPE OF REVIEW:	Clinical
DOCUMENTS REVIEWED:	Volumes 1, 96, 102, 110, 106, 112, 126, 127, 137, 138
MEDICAL INPUT:	Linda Lewis, M.D. (HFD-530)

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-705

1. Background

1.1 Objectives in Trials

The applicant submitted two pivotal randomized, double blind, controlled clinical trials with delavirdine, trial 21, part II and trial 13C.

The primary objective of these studies was to assess the clinical and antiviral efficacy of delavirdine (DLV) as part of triple drug ART therapy in HIV infected patients with limited or no anti-retroviral experience.

In addition, the applicant submitted data from three other groups of trials. Group 2, trials ACTG 359 and 370, assessed the efficacy of DLV in combination with protease inhibitors (PI) in patients with moderate to extensive anti-retroviral experience. Group 3, trials 63, 73A, 73B, 74 and 81, assessed the efficacy of DLV in combination with PI in patients with limited to no anti-retroviral experience. Group 4, trial 13B, assessed the efficacy of DLV in combination with one NRTI in patients with no anti-retroviral experience.

1.2 Summary of Study Designs

1.2.1 Trial 21, part II:

This study was a double-blind, double-dummy, randomized, three-arm, parallel, multi-center, multinational trial using patients with no more than 6 months experience with ZDV and with no other experience with NRTI's or NNRTI's. Patients had CD4 counts of 200-500 cells/mm^3.

Subjects were randomized to one of three arms:

1) ZDV (200 mg tid) + 3TC (150 mg bid),
2) ZDV (200 mg tid) + DLV (400 mg tid), or
3) ZDV (200 mg tid) + 3TC (150 mg bid) + DLV (400 mg tid).

(The 3TC dose was 150 mg qd if the patient's mass was < 50 kg.)

1.2.2 Trial 13C:

This study was a double-blind, double-dummy, randomized, two-arm, parallel, multi-center, multinational trial using patients with no more than 6 months experience with NRTI's or PI's and with no experience with NNRTI's. Patients had CD4 counts < 350 cells/mm^3.

Subjects were randomized to one of two arms:
1) ZDV (200 mg tid) + ddX
2) ZDV (200 mg tid) + ddX + DLV (400 mg tid).
Here ddX was one of
a) ddI at 200 mg bid (125 mg bid if patient's mass was < 60 kg),
b) ddC at .75 mg tid, or
c) 3TC at 150 mg bid (150 mg qd if patient's mass was < 50 kg).

Randomization was stratified by prior NRTI experience (yes or no) and by choice of ddX (ddI, ddC, or 3TC).

1.2.3 Trial ACTG 359:

This study was a partially double-blind, randomized, six-arm, parallel, controlled, multi-center trial comparing the clinical efficacy of DLV to adefovir (ADV) and to DLV+ADV when added to saquinavir (SQV) and another PI. It enrolled patients with at least 6 months experience with indinavir (IDV), including at least 2 weeks of stable IDV therapy prior to study entry; with less than 2 weeks experience with SQV or ritonavir (RTV) and with no experience with NNRTI's, other PI's or ADV. Patients had HIV RNA levels between 2,000 and 200,000 copies/mL.

This trial was basically a comparison of three regimens when added to concomitant protease inhibitors:
1) DLV 600 mg bid, 2) ADV 120 mg qd, and 3) DLV 600 mg bid + ADV 120 mg qd.
There were two choices of concomitant PI regimens:
1) SQV 400 mg bid + RTV 400 mg bid and 2) SQV 800 mg tid + NFV 750 mg tid.
Subjects were randomized to one of the six arms obtained by combining the three choices for comparator regimens with the two

choices for concomitant PI regimens.
Randomization was stratified on baseline HIV RNA < or > 20,000 copies/mL.

1.2.4 Trial ACTG 370:

This study was a phase II open-label, randomized, three-arm, parallel trial comparing the clinical efficacy of DLV to 3TC when added to indinavir (IDV) and ZDV. It enrolled patients from dual nucleoside trial ACTG 306 whose HIV RNA exceeded 500 copies/mL.

63 subjects who had received ddI+3TC or d4T+3TC in trial ACTG 306 were randomized to either
1) DLV 400 mg tid + IDV 600 mg tid + ZDV 300 mg bid or
2) 3TC 150 mg bid + IDV 800 mg tid + ZDV 300 mg bid.
Subjects who had received ZDV+3TC in trial ACTG 306 were assigned to 3) DLV 400 mg bid + IDV 600 mg tid + d4T 40 mg bid (30 mg if weight <60 kg). Since this third group of subjects were not randomly assigned, they are uncontrolled with respect to clinical efficacy and will not be discussed further.

1.2.5 Trials 63, 73A, 73B, 74 and 81

These were all open-label trials conducted as exploratory analyses to find the dose regimen that would be used in the two pivotal trials. They were all 24 week studies, later extended to 48 weeks. All of the trials except trial 81 enrolled subjects with HIV RNA > 20 K copies/mL, CD4 count > 50 cells/mm^3, no ART experience beyond 1 month of ZDV, and age $\geq$ 14 years.

Trial 63 enrolled 45 patients who were randomized to 3 arms as follows:
1) DLV 400 mg tid + ZDV 200 mg tid + IDV 400 mg tid
2) DLV 400 mg tid + ZDV 200 mg tid + IDV 600 mg tid
3) 3TC 150 mg bid (qd if weight < 50 kg) + ZDV 200 mg tid + IDV 800 mg tid.

Trial 73A was a dose ranging study with 22 patients randomized to either
1) DLV 600 mg tid + NFV 750 mg tid + d4T + ddI
2) DLV 400 mg tid + NFV 750 mg tid + d4T + ddI

Trial 73B enrolled 173 patients, of whom 137 were described in the summary report for 24 weeks of study. The remaining subjects had not yet reached 24 weeks of study at the time the database was closed. They were randomized to one of four arms:
1) DLV 600 mg bid + NFV 1250 mg bid + d4T 30 or 40 mg bid
2) DLV 600 mg bid + NFV 1250 mg bid + ddI 125 or 200 mg bid
3) DLV 600 mg bid + NFV 1250 mg bid + d4T + ddI
4) NFV 1250 mg bid + d4T + ddI.
The doses of d4T and ddI were varied according to patient's weight.

Trial 74 enrolled 225 patients, of whom 186 were described in the summary report for 24 weeks of study. The remaining subjects had not yet reached 24 weeks of study at the time the database was closed. The subjects were enrolled in Mexico. They were randomized to one of four arms:
1) DLV 400 mg tid + ZDV 200 mg tid + IDV 600 mg tid
2) DLV 400 mg tid + 3TC 150 mg bid or qd + IDV 600 mg tid
3) DLV 400 mg tid + 3TC 150 mg bid or qd + ZDV 200 mg tid + IDV 600 mg tid or
4) 3TC 150 mg bid or qd + ZDV 200 mg tid + IDV 600 mg tid.
As in other trials described above, the dose of 3TC was varied according to patient's weight.

Trial 81 enrolled subjects with HIV RNA > 5 K copies/mL, no ART experience, and age $\geq$ 14 years. A total of 97 subjects were enrolled, of whom 48 had reached 24 weeks on trial at the time the database was closed. The subjects were enrolled in Canada and Latin America. They were randomized to one of four arms:
1) DLV 600 mg bid + SQV 1400 mg bid + 3TC 150 mg bid
2) DLV 400 mg tid + SQV 1000 mg tid + 3TC 150 mg bid
3) DLV 600 mg bid + SQV 1400 mg bid + 3TC 150 mg bid + ZDV 300 mg bid
4) SQV 1200 mg bid + 3TC 150 mg bid + ZDV 200 mg bid

1.2.6 Trial 13 B

This trial was a stratified, randomized, double-blind, placebo-controlled, multicenter, multinational trial comparing the efficacy of DLV to placebo when added to one or two NRTI's for subjects with ARC or AIDS, CD4 count < 350 and either nucleoside naive or receiving ZDV monotherapy. Subjects were randomized to either 1) ZDV 200 mg tid with d4T or ddI at the physician's discretion or 2) DLV 400 mg tid + ZDV 200 mg tid with d4T or ddI at the physician's discretion. 597 subjects were randomized in this trial.

1.3 Subject Accounting and Baseline Characteristics

1.3.1 Trial 21, part II: Pivotal Study

373 subjects were randomized to receive treatment. The treated population was 86% male with an age range of 17 to 67 years (mean age 35 years). They were 61% white, 25% black, and 10% Hispanic. Mean CD4 count was 360 cells/mm^3 and mean log HIV RNA was 4.4 log copies/mL.

Table 1.3.1 A summarizes the subject status in trial 21, part II.

TABLE 1.3.1 A
SUBJECT STATUS IN TRIAL 21, part II

	ZDV+3TC	DLV+ZDV	DLV+3TC+ZDV
Randomized, Received Drug	123	125	124
Completed	31	19	50
Discontinued	97	109	76
Viral load criteria	39	34	17
New/recur AIDS defining ill	1	0	0
Medical Event serious	2	2	2
Medical Event non-serious	14	19	14
Other	10	15	7
Protocol noncompliance	0	4	3
Subject lost to follow-up	14	16	19
Subject's personal request	12	16	12

1.3.2 Trial 13C: Pivotal Study

345 subjects were randomized to receive treatment. The treated population was 65% male with an age range of 18 to 72 years (mean age 35 years). They were 63% white, 31% black, and 2% Asian. Mean CD4 cell count was 210 and men log HIV RNA was 4.8.

Table 1.3.2 A summarizes the subject status in trial 13C.

TABLE 1.3.2 A
SUBJECT STATUS IN TRIAL 13C

	ZDV+ddX	DLV+ZDV+ddX
Randomized, Received Drug	173	172
Completed	107	88
Discontinued	63	84
Lack of efficacy	17	6
Death, HIV-1 related	0	1
New/recur AIDS defining ill	9	8
Medical event serious	0	4
Medical event non-serious	13	24
Other	8	16
Protocol noncompliance	2	4
Subject lost to follow-up	7	8
Subject's personal request	10	13

1.3.3 Trials ACTG 359 and 370

277 subjects were randomized in the trial ACTG 359. The treated population was 83% male with a median age of 40 years. They were 49% white, 29% black and 19% Hispanic. Mean CD4 count was 225 cells/mm^3 and mean log HIV RNA was 4.5 log copies/mL.

159 subjects were randomized in the trial ACTG 370. The treated population was 80% male with a median age of 37 years. They were 60% white. Mean CD4 count was 510 cells/mm^3 and mean log HIV RNA was 3.2 log copies/mL.

The applicant did not provide data on subject status in trials ACTS 359 and 370 since they were not pivotal trials and were not conducted by the applicant.

1.3.4 Trials 63, 73A, 73B, 74 and 81

Demographic data for the third group of trials is summarized in table 1.3.4 A.

TABLE 1.3.4 A
DEMOGRAPHY FOR TRIAL 63, 73A, 73B, 74, 81

Trial	Enrolled	% Male	Mean Age	%White	CD4	Log HIV RNA
63	45	93%	36	67%	350	4.9
73A	22	81%	38	91%	373	4.8
73B	137	81%	34	56%	300	4.9
74	186	89%	46	39%	262	5.0
81	97	81%	35	35%	254	4.9

Patient status in these 5 trials are given in table 1.3.4 B.

TABLE 1.3.4 B

PATIENT DISPOSITION IN GROUP 3 TRIALS

Trial 63	DLV+ZDV +IDV400	DLV+ZDV +IDV600	3TC+ZDV +IDV800
Randomized	15	15	15
Discontinued	6	9	4

Trial 73A	DLV400+NFV+d4T+ddI	DLV600+NFV+d4T+ddI
Randomized	11	11
Discontinued	5	5

Trial 73B	d4T+ddI +NFV	DLV+d4T +NFV	DLV+ddI +NFV	DLV+d4T+ddI +NFV
Randomized	34	35	34	34
Discontinued	8	11	10	23

Trial 74	ZDV+3TC +IDV800	DLV+ZDV +IDV600	DLV+3TC +IDV600	DLV+ZDV+3TC +IDV600
Randomized	46	47	47	46
Discontinued	5	13	11	19

Trial 81	ZDV+3TC +SQV1200	DLV400+3TC +SQV1000	DLV600+3TC +SQV1400	DLV600+3TC+ZDV +SQV1400
Randomized	24	24	24	25
Discontinued	7	4	2	2

1.3.5 Trial 13B

597 subjects were randomized in the trial 13B. The treated population was 83% male with a mean age of 38 years. They were 62% white. The mean CD4 cell count was 140 cells/mm^3 and the mean log HIV RNA was 5.1.

Table 1.3.5 A summarizes the subject status in trial 13B.

TABLE 1.3.5 A
SUBJECT STATUS IN TRIAL 13B

	ZDV	DLV+ZDV
Randomized	297	300
Discontinued	218	235

1.4 Summary of Methods of Assessment

1.4.1 Schedule of Measurements

In trial 21, part II, HIV RNA was measured at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52. In trial 13C, HIV RNA was measured at weeks 4, 8, 12, 24, 36, 48, and 54.

In trial ACTG 359, HIV RNA was measured at weeks 1, 2, 4, 8, 12, 16, and 24. In trial ACTG 370, HIV RNA was measured at weeks 2, 4, 8 and every 4 weeks thereafter out to week 72.

In trials 63, 73A, 73B, and 81, HIV RNA was measured at weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, and 48

In trial 74, HIV RNA was measured at weeks 2, 4, 8, 12, 16, and 24.

All trials used the Amplicor and Ultrasensitive assays.

1.4.2 Assessment of Treatment Effects

In trials 21, part II and 13C, the primary endpoint was time to virologic failure = first of two consecutive HIV RNA measurements above limit of quantitation (LOQ) after being confirmed below limit of quantitation (BLQ). Subjects who never reached BLQ were counted as failures at time zero. In trial 13C, virologic failure was defined to include clinical progression. Percent BLQ on the Amplicor and Ultrasensitive assays at end of the trial were secondary endpoints.

In trial ACTG 359, the primary endpoint was virologic response in the first 16 weeks in 359. In trial ACTG 370, the primary endpoint was proportion with at least one HIV RNA level above 200 copies/mL at weeks 20-24 or at weeks 44-48.

In trials 63, 73A, 73B, 74 and 81, the primary endpoints were percent of subjects BLQ on Amplicor and Ultrasensitive assays.

In all these trials except the ACTG trials, the applicant also listed change in baseline HIV RNA as a primary endpoint. The FDA statistical reviewer considers this to be a secondary endpoint.

In trial 13B, the primary endpoint was time to death or new AIDS defining illness.

1.5 Summary of Statistical Analysis

The primary endpoint of time to virologic failure was analyzed by log-rank test. The endpoint of percent BLQ was analyzed using non-completers as failures. Analyses were stratified by the randomization factors within each trial.

In trial 13B, log rank tests and proportional hazards regression were used to test for treatment differences in time to clinical progression.

The methods of statistical analyses in the two ACTG studies are unclear and were not conducted by the applicant.

2. Summary of Applicant's Results

2.1 Trial 21, part II: Pivotal Study

There was a statistically significant increase in time to virologic failure in the triple therapy arm, DLV+ZDV+3TC, compared to the placebo control arm, ZDV+3TC. This difference was significant at p-values of .0001 whether virologic failure was defined using 400 copies/mL or 50 copies/mL as limit of quantitation (LOQ). The median time to failure with an LOQ of 400 was 40 weeks on triple therapy and <20 weeks on the dual therapy control. Using an LOQ of 50, the median time to failure was about 20 weeks with triple therapy and 0 weeks with dual therapy control. I.e., fewer than 50% of subjects on the control arm ever achieved HIV RNA levels that were BLQ.

The dual therapy with DLV+ZDV was inferior to the dual

therapy control, ZDV+3TC. The inferiority was statistically significant.

The triple therapy arm was also superior to the dual therapy control with respect to percent still BLQ at weeks 24, 32, 40, and 52, all with p-values < .0001. At week 40, the observed percent < 400 was 48% vs 13%; the observed percent < 50 was 41% vs 4%. The DLV+ZDV arm had only 3% < 400 at week 40.

2.2 Trial 13C: Pivotal Study

There was a statistically significant increase in time to virologic failure in the triple therapy arm, DLV+ZDV+ddX, compared to the placebo control arm, ZDV+ddX. This difference was significant at p-values of .0001 whether virologic failure was defined using 400 copies/mL or 50 copies/mL as limit of quantitation (LOQ). The median time to failure with an LOQ of 400 was about 16 weeks on triple therapy was 0 weeks on the dual therapy control. The Kaplan-Meier curve for the triple therapy was 20-25% higher than the curve for the control until the study ended at week 54.

Fewer than 50% of subjects on either arm ever achieved HIV RNA < 50 copies/mL, so both arms had median times to failure equal to 0 weeks. However, the Kaplan-Meier estimate of the percent with HIV RNA sustained < 50 was 20-30% higher for the DLV triple therapy than for the dual therapy control until the end of the study at week 54.

The triple therapy arm was also superior to the dual therapy control with respect to percent still BLQ at weeks 24, 36, 48, and 54, all with p-values < .0001. At week 48, the observed percent < 400 was 24% vs 8%; the observed percent < 50 was 20% vs 4%.

2.3 Trial ACTG 359

The results on percent of subjects with HIV RNA < 500 copies/mL at week 24 are summarized in tables 2.3 A.

TABLE 2.3 A
PERCENT OF SUBJECTS < 500 C/ML AT WK 24

	Comparator Arm		
Concomitant Arm	ADV_120	DLV_600	DLV-600 + ADV-120
SQV_400 + RTV_400	7/35 (20%)	11/37 (30%)	11/36 (31%)[1]
	7/47 (15%)	11/47 (23%)	11/45 (24%)[2]
SQV_800 + NFV_750	8/40 (20%)	15/37 (40%)	8/36 (22%)[1]
	8/45 (18%)	15/48 (31%)	8/45 (18%)[2]

[1] Denominator = subjects with data
[2] Denominator = subjects enrolled

No comments were made about the statistical significance of results. The pattern suggests that delavirdine as a third component added more to the virologic response than did adefovir.

2.4 Trial ACTG 370

The ACTG report on this trial indicated that there was a statistically significant superiority at week 44-48 for DLV+ZDV+IDV relative to 3TC+ZDV+IDV. The percentages of subjects with HIV RNA < 200 copies/mL were 83% vs 48% (p=.001) and with HIV RNA < 50 copies/mL were 77% vs 39% (p=.005).

2.5 Trials 63, 73A, 73B, 74 and 81

Results on percent of subjects BLQ at week 24 for trials 63, 73A, 73B, and 74 are given in table 2.5 A below. Results for trial 81 were not reported. In these analyses, non-completers were failures.

TABLE 2.5 A
PERCENT WITH HIV RNA BLQ AT WK 24
IN GROUP 3 TRIALS

Trial 63	3TC+ZDV +IDV800	DLV+ZDV +IDV400	DLV+ZDV +IDV600
BLQ = 400	7/15 (47%)	4/15 (33%)	5/15 (27%)
BLQ = 50	6/15 (40%)	2/15 (13%)	2/15 (13%)

Trial 73A	DLV400+NFV+d4T+ddI	DLV600+NFV+d4T+ddI
BLQ = 400	6/11 (55%)	6/11 (55%)
BLQ = 50	4/11 (36%)	5/11 (45%)

Trial 73B	d4T+ddI +NFV	DLV+d4T +NFV	DLV+ddI +NFV	DLV+d4T+ddI +NFV
BLQ = 400	23/34 (68%)	20/35 (57%)	22/34 (65%)	9/34 (27%)
BLQ = 50	16/34 (47%)	10/35 (29%)	15/34 (44%)	6/34 (18%)

Trial 74	ZDV+3TC +IDV800	DLV+ZDV +IDV600	DLV+3TC +IDV600	DLV+ZDV+3TC +IDV600
BLQ = 400	30/46 (65%)	22/47 (47%)	32/47 (68%)	25/46 (54%)
BLQ = 50	23/46 (50%)	13/47 (28%)	25/47 (53%)	23/46 (50%)

The sample sizes in these trials are too small and the duration of follow-up is too short to warrant formal statistical testing. The overall pattern of results is not particularly favorable to delavirdine.

In trial 63, the DLV arms are 15-20% inferior to the 3TC control, although that arm had a higher dose of IDV. This trial had the smallest samples. The inferiority was only 3-4 subjects.

In trial 73A, there was no real difference between 600 mg and 400 mg DLV.

In trial 73B, the quadruple therapy performed much worse. This reflects a higher drop-out rate. Recall from table 1.3.4 B that 23 out of 34 subjects discontinued in the quadruple therapy arm compared to 8-11 discontinuations in the other arms. The three triple therapy arms all had approximately the same success rates.

In trial 74, the arm with DLV substituting for ZDV in the triple therapy had the same success rate as the control but substituting DLV for 3TC gave results which were 20% worse than

control. (20% worse meant 8-10 subjects worse.) The quadruple therapy was no better than the two best triple therapies.

For trial 81, the applicant only reported mean change from baseline in log HIV RNA. The results for the last two observations are given in table 2.5 B. All four arms give comparable results but with enough missing data to make any conclusions impossible. Results on mean changes in HIV RNA are not reproduced here for the other trials because they all suffer from comparable missing data problems.

TABLE 2.5 B
MEAN CHANGE FROM BASELINE IN LOG HIV RNA
AT WEEKS 20 AND 24, TRIAL 81

Trial 81	ZDV+3TC +SQV1200	DLV400+3TC +SQV1000	DLV600+3TC +SQV1400	DLV600+3TC+ZDV +SQV1400
Randomized	24	24	24	25
Week 20	-1.9 (N=15)	-2.1 (N=11)	-2.1 (N=17)	-2.2 (N=18)
Week 24	-2.2 (N=9)	-1.6 (N=8)	-2.2 (N=12)	-2.0 (N=12)

2.6 Trial 13B

There was no difference in the rates of clinical progression between the ZDV (plus optional ddX) and the DLV+ZDV (plus optional ddX).

3. Summary of Applicant's Conclusions

The applicant concluded that use of 400 mg tid delavirdine resulted in significant improvement in anti-retroviral efficacy when used in combination with two NRTI's. Time to virologic failure and percent of subjects with HIV RNA BLQ at end of study were both increased on arms with delavirdine, relative to placebos. These effects were seen both in large applicant pivotal studies with relatively naive populations and in smaller ACTG studies with relatively experienced populations.

The applicant observed that the group III studies all had sample sizes too small to provide any proof of benefit of delavirdine. The applicant did not remark that these studies have point estimates which were unfavorable to delavirdine, although changes in responses of as few as 3-10 subjects would have eliminated these unfavorable responses.

4. Statistical Reviewer's Comments and Analyses

The FDA statistical reviewer has recalculated the proportion of subjects without disease progression and with viral load maintained below limit of quantitation out to week 48 while still on assigned therapy for the two pivotal trials, trial 21 part 2 and trial 13 C. The proportions obtained in these recalculations are somewhat different than those reported above by the applicant. The overall conclusion is not substantively different.

There was a statistically significant and clinically meaningful superiority in percent below 400 copies/mL and in percent below 50 copies/mL for DLV compared to placebo when added to ZDV+3TC in trial 21, part 2. In this same trial, the dual therapy of DLV+ZDV was slightly inferior to ZDV+3TC. The statistical significance of the triple therapy to the ZDV+3TC control remained even after adjusting for the two possible comparisons.

There was a statistically significant and clinically meaningful superiority in percent below 400 copies/mL and in percent below 50 copies/mL for DLV compared to placebo when added to ZDV+ddX in trial 13 C.

The small group 3 pilot studies combining DLV_400 mg tid with a PI and an NRTI showed small inferiorities (3-10 subjects) to same combination with 3TC but these are not large enough to cast doubt on the two large studies.

4.1 Re-analysis of Trial 21, part 2

The results of the re-analysis in trial 21, part 2, are given in table 4.1 A. In this table, the counts and percents BLQ are given for each of the two strata defined by level of prior ZDV experience at baseline. Four p-values are also given: the p-values for the comparison of DLV+ZDV+3TC vs ZDV+3TC in each stratum and in both strata pooled (labelled Separ(ate) in the table) and the p-value for the stratified Cochran-Mantel-Haenszel test (labelled Strat(ified) in the table). In the less experienced stratum and overall, the triple therapy is significantly superior to the dual therapy control. The success rates on both arms are lower in the more experienced stratum but remain higher for the triple therapy than for the control; sample sizes in this stratum are too small to permit determination of statistical significance. Results using log-rank tests on time to failure instead of Cochran-Mantel-Haenszel tests on percent failed by week 48 produce the same findings of statistical significance.

In both strata, the dual therapy of DLV+ZDV was slightly inferior to the ZDV+3TC control. This confirms the results of trial 17 in the accelerated approval package that delavirdine is ineffective when used with only one NRTI.

TABLE 4.1 A
PROPORTIONS BLQ THROUGH WEEK 48, TRIAL 21, PART 2
STRATIFIED BY PRIOR ZDV EXPERIENCE
Using Amplicor Assay, LOQ = 400 copies/mL

	Percent BLQ			P-values Triple vs Z+3	
Prior ZDV	Triple	ZDV+3TC	DLV+ZDV	Separ	Strat
Low	51/99 = 52%	12/109 = 11%	1/105 = 1%	<.001	—
High	6/25 = 24%	1/14 = 7%	1/20 = 5%	.19	<.001
Both	57/124 = 46%	13/123 = 11%	2/125 = 2%	<.001	
Using Ultrasensitive Assay, LOQ = 50 copies/mL					
Low	44/99 = 44%	3/109 = 3%	0/105 = 0%	<.001	
High	4/25 = 16%	1/14 = 7%	1/20 = 5%	.43	<.001
Both	48/124 = 39%	4/123 = 3%	1/125 = 1%	<.001	

The FDA reviewer has also computed Kaplan-Meier curves for time to failure, where failure is defined as the earliest of confirmed viral rebound, death or disease progression, discontinuation of assigned therapy, or loss to follow-up. These curves (not reproduced here) confirm that the observed superiority of DLV triple therapy over dual therapy control appears early and persists to the end: the percent of subjects never confirmed BLQ is about 20% (if LOQ = 400) or 30% (if LOQ = 50) and the difference in percent still not rebounded, progressed, died, or discontinued grows larger out to week 48.

Table 4.1 B gives the status of subjects at week 48 with reasons for failure broken down into confirmed viral load above LOQ, death, disease progression, or toxicity.

TABLE 4.1 B
STATUS AT WEEK 48, TRIAL 21, PART 2

Status at Week 48	DLV+ZDV+3TC	ZDV+3TC	DLV+ZDV
SUCCESS AT WEEK 48	57	13	2
FAILED AT WEEK 48			
Above 400 copies/mL	42	95	89
Medical Event(s)	12	10	18
Other	13	5	16

Although most patients who discontinued before the end of the study had viral loads above 400 copies/mL at the time of discontinuation, the listed reasons for discontinuation were not always viral failure. Patients who never achieved BLQ viral loads but discontinued for other reasons by week 24 or earlier were counted as failing for reasons other than viral load.

If one compares table 4.1 B with table 1.3.1 A above, one will notice that table 1.3.1 A has considerably more discontinuations for reasons other than viral rebound. The protocols of both this trial and trial 13 C did not originally call for real-time monitoring of viral load. Consequently, many subjects remained on their assigned treatments after loss of BLQ. Most of non-viral load reasons for discontinuation in table 1.3.1 A occurred after viral rebound.

4.2 Re-Analysis of Trial 13 C

The results of the re-analysis in trial 13 C are given in table 4.2 A. In this table, the counts and percents BLQ are given for each of the two strata defined by level of prior ZDV experience at baseline. Four p-values are also given: the p-values for the comparison of DLV+ZDV+ddX vs Placebo+ZDV+ddX in each stratum and in both strata pooled (labelled p-value in the table) and the p-value for the stratified Cochran-Mantel-Haenszel test (labelled pooled p-value in the table). In both the less experienced stratum and the more experienced stratum and overall, the triple therapy is significantly superior to the dual therapy control. Results using log-rank tests on time to failure instead of Cochran-Mantel-Haenszel tests on percent failed by week 48 produce the same findings of statistical significance.

TABLE 4.2 A
PROPORTIONS BLQ THROUGH WEEK 48, TRIAL 13 C
STRATIFIED BY PRIOR ZDV EXPERIENCE

Using Amplicor Assay, LOQ = 400 copies/mL

Prior ZDV	% on DLV	% on Placebo	P-value	Pooled P-value
Low	42/105 = 40%	13/112 = 12%	<.001	
High	9/64 = 14%	3/61 = 5%	.08	<.001
Both	51/169 = 30%	16/173 = 9%	<.001	

Using Ultrasensitive Assay, LOQ = 50 copies/mL

Prior ZDV	% on DLV	% on Placebo	P-value	Pooled P-value
Low	32/105 = 30%	5/112 = 4%	<.001	
High	7/64 = 11%	0/61 = 0%	.008	<.001
Both	39/169 = 23%	5/173 = 3%	<.001	

The FDA reviewer has also computed Kaplan-Meier curves for time to failure, where failure is defined as the earliest of confirmed viral rebound, death or disease progression, discontinuation of assigned therapy, or loss to follow-up. These curves (not reproduced here) confirm that the observed superiority of DLV triple therapy over dual therapy control appears early and persists to the end: the percent of subjects never confirmed BLQ is about 30% (if LOQ = 400) or 20% (if LOQ = 50) and the difference in percent still not rebounded, progressed, died, or discontinued declines slightly out to week

50) and the difference in percent still not rebounded, progressed, died, or discontinued declines slightly out to week 48.

Table 4.2 B gives the status of subjects at week 48 with reasons for failure broken down into confirmed viral load above LOQ, death, disease progression, or toxicity.

TABLE 4.2 B
STATUS AT WEEK 48, TRIAL 13 C

Status at Week 48	DLV+ZDV+ddx	ZDV+ddx
SUCCESS AT WEEK 48	51	16
FAILURE AT WEEK 48		
Above 400 copies/mL	88	136
Death	1	0
New AIDS event	2	2
Medical Event(s)	18	9
Other	12	10

Although most patients who discontinued before the end of the study had viral loads above 400 copies/mL at the time of discontinuation, the listed reasons for discontinuation were not always viral failure. As with table 4.2 A, patients who never had BLQ viral loads and discontinued on or before week 24 were counted as failures for reasons other than viral load.

Again, one will notice that table 4.2 B has considerably fewer discontinuations for reasons other than viral rebound than table 1.3.2 A above. As mentioned in section 4.1, this occurs because many subjects remained on their assigned treatments after loss of BLQ since there was no real-time monitoring of viral load. Most of non-viral load reasons for discontinuation in table 1.3.2 A occurred after viral rebound.

5. Statistical Reviewer's Summary

The results in these trials confirm that delavirdine at 400 mg tid is effective in maintaining viral load BLQ when used with 2 NRTI's in naive or slightly experience patients. It is not effective when used with only 1 NRTI.

The smaller trials also suggested that delavirdine at 400 mg tid and delavirdine at ——— may be effective in experienced patients in combination with either 2 PI's or a PI and an NRTI.

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Mathematical Statistician

Concur: Dr. Soon

cc:
Archival NDA #20-705

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/s/

Thomas Hammerstrom
5/8/01 02:00:22 PM
BIOMETRICS
THIS CORRECTS TABLES 4.1 B AND 4.2 B

Greg Soon
5/18/01 10:19:29 AM
BIOMETRICS