CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-183

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #:	21183
SPONSOR:	Bristol-Myers Squibb
NAME OF DRUG:	Videx EC (didanosine or ddI)
INDICATION:	Treatment of [redacted]
DOCUMENTS REVIEWED:	Vol. 3.1-16 submitted on 1/31/2000
MEDICAL INPUT:	HFD-530: Russ Fleischer, P.A.C. MPH

A: Introduction

Didanosine (ddI) is a nucleoside analogue available in tablets in strengths of 25, 50, 100, 150 and 200 mg of didanosine. The recommended dosing interval is either once [redacted] daily.

This NDA contains two pivotal, randomized, open-label, multi-center, controlled trials (AI454-152 and AI454-158) to support a new capsule formulation (EC). Both trials incorporated a non-inferiority design and were conducted in antiretroviral naïve subjects. Study AI454-152 used a double-substitution design and compared ddI EC/d4T/NFV to ZDV/3TC/NFV, Study AI454-158 used a single substitution design and compared ddI EC/d4T/NFV to ddI tablet QD/d4T/NFV. Study AI454-152 is ongoing and about two thirds of subjects was included for Week 48 efficacy analysis.

B: Study Design

Protocol AI454-152: "Evaluation Of HIV RNA Suppression Produced By A Triple Combination Regimen Containing Tan Enteric Coated Formulation Of Didanosine (DDI EC) Administered Once Daily Compared To A Reference Combination Regimen."

This is an open-label multinational trial designed to compare ddI EC/d4T/NFV vs. Combivir/NFV in HIV-infected subjects who are almost treatment naïve with screening CD4 counts of at least 200 cells/mm^3, plasma HIV RNA level of at least 2000 copies/mL. The trial will last at least 48 weeks after enrollment of the last subject.

Five hundred subjects will be equally randomized to the two treatment arms. The randomization will be stratified by the plasma HIV RNA level (<30,000 vs. ≥30,000) and investigate site using a permutated block design.

The primary endpoint is the proportion of subjects with plasma HIV RNA below 400 copies/mL at Week 48. Secondary endpoints include time to viral load response with confirmation, the magnitude and duration of changes in HIV RNA and CD4 in terms of time-averaged difference (TAD), and proportion of subjects experiencing clinical adverse events and laboratory

abnormalities. Measurements will be collected at Weeks 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter. HIV RNA levels are measured with the standard Roche Amplicor Assay. Ultrasensitive assay will be performed only for samples below detection limit of the standard assay.

Interim analyses will be conducted at Week 16 when at least 200 subjects have been treated for 16 weeks and at Week 24 when at least half of the subjects have been treated for 24 weeks. The Week 16 analysis will compare TAD through Week 16 for the two treatment groups. Week 16 interim analysis will be used for regulatory registration.

Efficacy data sets will include as-treated, which includes all blinded data for subjects who received at least one dose of any study medication, and all-randomized, which includes all data available. Safety data set will include all subjects who received at least one dose of study medication. The primary efficacy analyses will be based on as-treated population.

All analyses will be stratified by screening HIV RNA level (<30,000 vs. ≥30,000) but not on study sites.

Treatment differences for proportions below detection limit will be estimated by pooling the differences in stratums using CMH weights of each stratum, and 95% confidence interval will be computed using normal approximation. For Week 16, 24 and 48 analyses, a window of ±4, ±8 and ±12 weeks will be used respectively. Missing values will be regarded as failures unless it is surrounded by two measurements below detection limit.

TADs in Log10 (HIV RNA) and CD4 of the two regimens will be compared using the as-treated data set. An estimate of the TAD between the two regimens and a 95% CI will be computed using a repeated measures model with a compound symmetry covariance structure, stratified by the two stratums of HIV RNA. The non-parametric stochastic ordering test will be used to compute p-values for longitudinal data, censoring the missing measurements and assign them the lowest rank for the time period they occur. In addition, the generalized Wilcoxon test will be used.

Protocol AI454-158: "Comparison Of HIV RNA Suppression Produced By Triple Regimen Containing Either Didanosine Enteric Coated or Didanosine Tablets Formulation Each Administered Once daily."

This is an open-label trial designed to compare ddI EC/d4T/NFV vs. ddI tablet/d4T/NFV in HIV infected subjects who are almost treatment naïve with screening CD4 counts of at least 100 cells/mm^3, plasma HIV RNA level of at least 5000 copies/mL. The trial will last 48 weeks.

One hundred and twenty subjects will be equally randomized to the two treatment arms. The

randomization will be stratified by the plasma HIV RNA level (<30,000 vs. ≥30,000) and investigate site using a permutated block design.

The primary endpoint is the magnitude and duration of changes in HIV RNA through Week 24 in terms of time-averaged difference (TAD). Secondary endpoints include the proportions below 400 copies/mL at Week 24, time to viral load response with confirmation, the magnitude and duration of changes in CD4 in terms of time-averaged difference (TAD), and proportion of subjects experiencing clinical adverse events and laboratory abnormalities. Measurements will be collected at Weeks 4, 8, 16, 24, 36, 48. HIV RNA levels are measured with the standard Roche Amplicor Assay. Ultrasensitive assay will be performed only for samples below detection limit of the standard assay.

Interim analyses will be conducted at Week 16 when all subjects have been treated for 16 weeks. Week 16 interim analysis will be used for regulatory registration.

Efficacy data sets will include as-treated, which includes all blinded data for subjects who received at least one dose of any study medication, and all-randomized, which includes all data available. Safety data set includes all subjects who received at least one dose of study medication. The primary efficacy analyses will be based on as-treated population.

All analyses will be stratified by screening HIV RNA level (<30,000 vs. ≥30,000) but not on study sites.

Treatment differences for proportions below detection limit will be estimated by pooling the differences in stratums using CMH weights of each stratum, and 95% confidence interval will be computed using normal approximation. For Week 16 and 24 analyses, a window of ±4 and ±8 weeks will be used respectively. Missing values will be regarded as failures unless it is surrounded by two measurements below detection limit.

TADs in Log10 (HIV RNA) and CD4 between the two regimens will be compared using the as-treated data set. An estimate of the TAD between the two regimens and a 95% CI will be computed using a repeated measures model with a compound symmetry covariance structure, stratified by the two stratums of HIV RNA. The non-parametric stochastic ordering test will be used to compute p-values for longitudinal data, censoring the missing measurements and assign them the lowest rank for the time period they occur. In addition, the generalized Wilcoxon test will be used.

C: Study Population and Patient Disposition

The following table summarizes the baseline characteristics of the enrolled subjects in the two studies.

Baseline Characteristics

	AI454-152		AI454-158	
Treatment	DdI EC/d4T/NFV	Combivir/NFV	DdI EC/d4T/NFV	DdI Tab/d4T/NFV
Total Randomized	258	253	72	66
Age (mean)	34.3	35.2	35.4	34.5
Race (%)				
White	51	55	44	55
Black	24	24	29	30
Hispanic/Latino	18	15	22	11
Other	7	6	4	5
Gender (% male)	69	75	83	88
IV Drug Use (%)	10	6	6	5
Log10 HIV RNA level (mean)	4.7	4.7	4.7	4.6
HIV RNA level (% <30,000)	33	35	44	45
CD4 cell counts (mean)	411	411	382	381
CD4 distribution (%)				
<300	26	30	33	35
300 - <500	48	41	39	41
≥500	25	27	24	23
AIDS-defining diagnosis (#)	7	5	1	2

The two study populations are very similar, except Study AI454-158 had a higher percentage of males than Study AI454-152. Within each study, the baseline characteristics are generally well balanced between the two treatment arms.

The table below summarizes the reasons for discontinuation for all subjects randomized. Note about one third subjects in Study AI-454-152 did not complete 48 weeks of therapy yet, and the rates in the table will go up once the trial is completed.

Reason for Discontinuations

	Number (%)			
	AI454-152		AI454-158	
Treatment	Ddl EC/d4T/NFV	Combivir/NFV	Ddl EC/d4T/NFV	Ddl Tab/d4T/NFV
Total Randomized	258	253	72	66
All discontinued	62 (24)	67 (26)	35 (49)	32 (48)
Never treated	3 (1)	3 (1)	3 (4)	1(2)
Due to AE	23 (9)	21 (8)	5 (7)	13 (20)
Lost to follow up	14 (5)	18 (7)	12 (17)	9 (14)
Subject withdraw	6 (2)	6 (2)	6 (8)	1 (2)
Disease progression or relapse	5 (2)	9 (4)	2 (3)	4 (6)
Non-compliance	5 (2)	5 (2)	4 (6)	3 (5)
Physician's decision	3 (1)	-	1 (1)	-
Death	2 (<1)	3 (1)	1 (1)	1 (2)
Incarceration	1 (1)	-	-	-
Completed treatment	-	2 (1)	1(1)	-

The discontinuation rates were much higher in the Study AI454-158 than were in Study AI454-152, even after taking into the consideration that Study AI454-152 is still ongoing. For Study AI454-152, the rate and reasons of discontinuation are similar in the two treatment arms. For Study AI454-158, the overall rate of discontinuation was similar, but the reasons differed. 7% of subjects taking ddI EC discontinued due to AE, compared to 20% for ddI tablets (p-value=0.026), and 25% of subjects taking ddI EC lost to follow up or withdraw, compared to 15% for ddI tablets (p-value=0.144).

D: Efficacy Results

HIV RNA

The original protocol-defined primary endpoints are crude proportions at Week 48 for Study AI454-152 and TAD at Week 24 for Study AI454-158. Upon FDA request, analyses based on a modified algorithm with virologic rebounds and disease progressions carried forward as failures were provided. These analyses will be considered primary and summarized in the tables below.

AI454-152: Proportions with Treatment Response at Week 48 (LOQ [redacted])
Cohort randomized before 11/29/1999

Treatment	Ddl EC/d4T/NFV	Combivir/NFV	Difference & 95% CI
FDA definition	87/167 (52%)	93/166 (56%)	-3.8% (-14.3%, 6.9%)
Crude proportions	95/167 (57%)	91/166 (55%)	2.4% (-8.3%, 13.0%)

AI454-152: Proportions with Treatment Response at Week 48 (LOQ=[redacted])
Cohort randomized before 11/29/1999

Treatment	Ddl EC/d4T/NFV	Combivir/NFV	Difference & 95% CI
FDA definition	47/167 (28%)	56/166 (34%)	-5.3% (-15.1%, 4.6%)
Crude proportions	61/167 (37%)	61/166 (37%)	0.2% (-10.1%, 10.5%)

The applicant concluded that the two arms are similar at Week 48.

AI454-158: Treatment Response at Week 48 (LOQ= [redacted])
All Randomized Subjects

Treatment	Ddl EC/d4T/NFV	Ddl tab/d4T/NFV	Difference & 95% CI
FDA definition (LOQ= [redacted])	25/72 (35%)	28/66 (42%)	NA
FDA Definition (LOQ= [redacted])	22/72 (31%)	21/66 (32%)	NA
TAD	NA	NA	-0.19 (-0.43, 0.06)

The applicant concluded that ddI EC is similar or superior to the control arm based on TAD analysis.

CD4

CD4 over time were similar between two treatment arms in both studies. The table below summarizes the results.

CD4 Changes

Study	Treatment	TAD through Week 48	Week 48 Change from Baseline	
		Mean TAD difference & 95% CI	N	Mean Change
AI454-152	ddI EC/d4T/NFV	-7 (-26, 11)	120	156
	Combivir/NFV		119	188
AI454-158	ddI EC/d4T/NFV	-13 (-43, 17)	36	120
	ddI Tab/d4T/NFV		36	141

E: Statistical Reviewer's Comments

Primary Endpoints

As mentioned earlier, The two studies used different primary endpoints and both differ from the current FDA version of the endpoints used in anti-retroviral (ART) naïve subjects. The current practice uses proportion of responders at Week 48 as the primary endpoint, with "responder" defined as achieving confirmed below LOQ and sustained it through Week 48 without experiencing any AIDs-defining events or discontinuation of the randomized treatment. For study AI454-152, the protocol defined primary endpoint is proportion of subjects with HIV RNA below LOQ at Week 48, which does not take the subjects' history (disease progression, virologic rebound) into account. Disease progression as clinical events may indicate failure in control the damage from viral infection by the treatment, while viral rebound may indicate a permanent loss

in the ability to suppress viral load to below LOQ, i.e., the FDA definition of failure may be subject to less measurement error than a single viral measurement at Week 48. The primary endpoint for Study AI454-158 is TAD, which is more problematic. The problem is several folds, first, the viral measurements are truncated at LOQ, [redacted] When a large proportion of subjects were able to get below LOQ the truncation is likely to make the TADs of the two arms more similar and reduce the variability of the estimates, giving the false impression that the treatment difference is smaller and confidence bands are narrower than the true measurements. Secondly, it is difficult to find a clinically meaningful way to replace missing values due to discontinuations. Third, there is little knowledge on what should be an accepted equivalence limit. Giving all these issues, FDA defined primary endpoint will be regarded as primary throughout the review and the protocol defined primary endpoints will be regarded as secondary.

Handling of missing values

In the responder analysis proposed by FDA, all discontinuations or lost to follow-ups or withdraws are considered as failures. Discontinuations due to lack of efficacy (rebound, failure to achieve BLQ etc.) or tolerability or clinical events are unlikely to occur due to the lack of confidence in the treatment received, therefore regarding them as failures will unlikely produce biases. However, lost to follow-ups and withdraws can occur due to reasons related to the knowledge in the treatment assignment and produce biases in the estimates. Sensitivity will be conducted on lost to follow-ups and withdraws to evaluate the stability of the efficacy results.

Study Design

Study AI454-152 used a double substitution and it will be impossible to isolate the contribution of ddI EC in the combination. Further, both studies were open-label and vulnerable to biases produced by knowledge in treatment assignment. This is especially a problem in Study AI454-158 where lost to follow-up and withdraw rates are high. Study AI454-158 is limited also by its small sample size that was determined based on the TAD of HIV RNA instead of the current FDA defined endpoint.

Equivalence limit

The original equivalence limit of 12% for Study AI454-152 was recommended only for sample size evaluation. Due to a lack of Combivir/NFV vs. Placebo/NFV trial in a naive population, we will base the judgement on trials with combivir vs. placebo components. One such trial is Study 035. Study 035 compared indinavir vs. indinavir added to 3TC+d4T in d4T experienced subjects. 31 subjects were randomized to indinavir arm and 33 were randomized to the triple therapy arm. The response rates at Week 24 were over 80% for the triple therapy arm and less than 40% for the indinavir arm, so the observed treatment difference was over 40%. The lower bound of the 95% confidence interval was greater than 19%. Note however, due to the difference in the background therapy (indinavir vs. nelfinavir), evaluation time (24 weeks vs. 48 weeks) and study population (d4T experienced vs. naïve), we can not say for certain that Combivir/NFV vs. NFV

will have at least 19% effect size. An appropriate equivalence limit is difficult to determine in this case and 19% will be used as a maximum non-inferiority margin.

F: Statistical Reviewer's Analyses

Study AI454-152

About 2/3 of all subjects randomized completed 48 weeks of trial by the database lock date August 11, 2000. The primary analysis here will focus on this cohort of subjects. Specifically, the cohort consists of subjects randomized before September 13, 1999. Note the applicant claimed to have used a cohort consists of subjects randomized before November 29, 1999. This appears to be incorrect.

The results for the responder status are displayed below.

HIV RNA Status (LOQ= [redacted] (%)

Cohort randomized before September 13, 1999 for Week 48, before November 30, 1999 for Week 36, and all randomized subjects for Weeks 4, 8, 16 and 24

Week	Treatment	N	Responder[a]	Virologic failure[b]	Death or Disease progression	Disc due to AE[c]	Disc due to others[d]	Never treated
4	ddI EC/d4T	258	28	66	0	1	3	1
	Combivir	253	26	64	0	4	4	1
8	ddI EC/d4T	258	46	46	1	1	5	1
	Combivir	253	45	41	1	6	6	1
16	ddI EC/d4T	258	60	27	1	3	7	1
	Combivir	253	58	24	1	7	9	1
24	ddI EC/d4T	258	60	24	1	5	9	1
	Combivir	253	59	21	1	8	10	1
36	ddI EC/d4T	238	57	24	1	7	10	1
	Combivir	232	60	18	1	8	11	1
48	ddI EC/d4T	167	52	28	1	8	9	1
	Combivir	166	57	23	1	7	11	2

[a] Achieved confirmed below [redacted] and maintained it through the study week of interest without experiencing any disease progression.

[b] Virologic rebound (two consecutive measurements above LOQ or a single measurement above LOQ if last visit after achieving virologic response), or failure to achieve virologic response by the visit date or after more than 24 weeks of treatment

[c] Discontinuation due to adverse events.

[d] Lost to follow-ups, non-compliance, physician decision or withdraws

At Week 48, there was one more responder in the Combivir/NFV arm than was in the applicant's result. The response rates were 52% vs. 57% with a difference of -5% favoring Combivir/NFV

arm. The 95% confidence interval is (-15%, 6%). A sensitivity analysis where discontinuations due to other reasons are considered censored for the Combivir/NFV arm yielded a result of 52% vs. 64% with a difference of -11% favoring Combivir/NFV. The 95% confidence interval for the difference is (-22%, -1%), significantly favoring Combivir/NFV arm.

Since the computation is only based on 333 subjects instead of all 511 subjects, the confidence interval will be narrower when all subjects completes 48 weeks trial. In fact, the width of the confidence interval will shrink by a factor of sqrt(1/253+1/258)/sqrt(1/167+1/166) = 0.81. Had all 511 subjects completed 48 weeks therapy with rates similar to the current response rates (52% vs. 57%), the 95% confidence interval becomes (-13%, 4%), and the sensitivity analysis becomes (-20%, -3%).

HIV RNA Status (LOQ= [redacted] ; (%)

Cohort randomized before September 13, 1999 for Week 48, before November 30, 1999 for Week 36, and all randomized subjects for Weeks 4, 8, 16 and 24

Week	Treatment	N	Responder[a]	Virologic failure[b]	Death or Disease progression	Disc due to AE[c]	Disc due to others[d]	Never treated
4	ddI EC/d4T	258	7	87	0	1	4	1
	Combivir	253	5	86	0	4	4	1
8	ddI EC/d4T	258	18	74	1	1	5	1
	Combivir	253	12	74	1	6	6	1
16	ddI EC/d4T	258	31	57	1	3	7	1
	Combivir	253	26	57	1	7	9	1
24	ddI EC/d4T	258	35	49	1	5	9	1
	Combivir	253	32	48	1	8	10	1
36	ddI EC/d4T	238	33	49	1	7	9	1
	Combivir	232	36	43	1	8	11	1
48	ddI EC/d4T	167	29	51	1	8	10	1
	Combivir	166	34	46	1	7	10	2

[a] Achieved confirmed below [redacted] and maintained it through the study week of interest without experiencing any disease progression.

[b] Virologic rebound (two consecutive measurements above LOQ or a single measurement above LOQ if last visit after achieving virologic response), or failure to achieve virologic response by the visit date or after more than 24 weeks of treatment

[c] Discontinuation due to adverse events.

[d] Lost to follow-ups, non-compliance, physician decision or withdraws

The Estimated treatment difference was 5% with 95% confidence interval (-15%, 5%), the sensitivity analysis yielded a 95% confidence interval (-19%, 2%).

Both tables indicated a slight trend in the separation of the responder and virologic failure rates. Other rates are similar between the two arms.

Homogeneity of response rates at Week 48 were examined with respect to baseline HIV RNA (<30,000 vs. >=30,000 copies), age (<33 vs. >33), gender, and race (white vs. nonwhite). None of them showed interaction with treatments. Therefore there are no need to consider using the two treatments differently in any of the subgroups defined by these four variables.

CD4 results are the same as the applicant's and will be omitted here.

Study AI454-158

The efficacy results over time and failure reasons are summarized in the table below.

HIV RNA Status (LOQ= [redacted]) (%)

Week	Treatment	Responder[a]	Virologic failure[b]	Death or Disease progression	Disc due to AE[c]	Disc due to others[d]	Never treated
4	ddI EC	18	67	1	0	10	4
	ddI Tab	26	71	0	0	0	2
8	ddI EC	39	40	1	1	14	4
	ddI Tab	44	39	0	5	11	2
16	ddI EC	44	26	3	3	19	4
	ddI Tab	55	23	0	8	14	2
24	ddI EC	47	18	3	4	24	4
	ddI Tab	45	15	2	18	18	2
36	ddI EC	42	24	3	4	24	4
	ddI Tab	47	14	2	18	18	2
48	ddI EC	35	28	3	6	25	4
	ddI Tab	42	17	2	20	18	2

[a] Achieved confirmed below [redacted] and maintained it through the study week of interest without experiencing any disease progression.

[b] Virologic rebound (two consecutive measurements above LOQ or a single measurement above LOQ if last visit after achieving virologic response), or failure to achieve virologic response by the visit date or after more than 24 weeks of treatment

[c] Discontinuation due to adverse events.

[d] Lost to follow-ups, non-compliance, physician decision or withdraws

Note the sample sizes are fixed at 72 for the ddI EC arm and 66 for the ddI tablets arm.

The responder rates at Week 48 are identical to the applicant's results, but the two results differed by two subjects in the categories "virologic failure" and "discontinued due to AE" for

the ddI tablets arm. However, this will not make a difference for the overall interpretation of the results.

When all categories other than "responders" are considered failures, the treatment difference at Week 48 is 8% and the 95% confidence interval is (-24%, 8%). The lower bound is far from 10%, which is typically used for equivalence evaluations. Note also that a high percentage of subjects fall into the category "Discontinued due to others", which consists primarily subjects lost to follow-up or withdraw (25% vs. 18%). Any unfavorable interpretation of these subjects will make the results look even worse. Overall the result at Week 48 did not provide sufficient evidence to support equivalence claim. At Week 24 the observed treatment difference is smaller at 0.1%, the 95% confidence interval is (-17%, 17%). Considering that the high rates of discontinuation due to others, the results are still not sufficient to support equivalence claim.

The difference in response rates came mainly from virologic failures and discontinuations due to AEs. Subjects treated with ddI EC became virologic failures more often than subjects treated with ddI tablets (28% vs. 17% at Week 48 with p-value=0.17 using Fisher's Exact Test) and this gap increased over time. On the other hand, fewer subjects discontinued due to AEs in the ddI EC than in the ddI tablets arm (6% vs. 20% at Week 48 with p-value=0.02 using Fisher's Exact Test) and the gap also increased over time.

HIV RNA Status (LOQ= [redacted] (%)

Week	Treatment	Responder[a]	Virologic failure[b]	Death or Disease progression	Disc due to AE[c]	Disc due to others[d]	Never treated
4	ddI EC	1	83	1	0	10	4
	ddI Tab	3	94	0	0	2	2
8	ddI EC	8	71	1	1	14	4
	ddI Tab	11	73	0	5	11	2
16	ddI EC	26	44	3	3	19	4
	ddI Tab	27	50	0	8	14	2
24	ddI EC	32	32	3	4	25	4
	ddI Tab	36	24	2	18	18	2
36	ddI EC	36	28	3	4	25	4
	ddI Tab	33	27	2	18	18	2
48	ddI EC	31	31	3	6	26	4
	ddI Tab	33	27	2	18	18	2

[a] Achieved confirmed below [redacted] and maintained it through the study week of interest without experiencing any disease progression.

[b] Virologic rebound (two consecutive measurements above LOQ or a single measurement above LOQ if last visit after achieving virologic response), or failure to achieve virologic response by the visit date or after more than 24 weeks of treatment

[c] Discontinuation due to adverse events.

[d] Lost to follow-ups, non-compliance, physician decision or withdraws

The results at Week 48 differed by 1 subject in the category "responder" for the ddI tablets arm. The difference is due to a subject discontinued on Day 52*7. Day 52*7 was not considered to be in the Week 48 evaluation window and therefore the subject should not be considered a discontinuation for Week 48 evaluation.

Even though the treatment differences are more favorable for ddI EC here than in the table using LOQ= [redacted] the lower bounds of the 95% confidence intervals are still greater than 14%. This, together with high rates of discontinuations due to other reasons, lead us to conclude that the evidence in this trial is insufficient to conclude equivalence of the two treatment arms.

Applicant's results on CD4 are reproducible and will not be repeated here.

Subgroup analyses will be omitted here because the high discontinuation rates make any such analysis results uninterpretable.

G: Statistical Reviewer's Conclusion

Both Study AI454-152 and AI454-158 were open-label studies, which may lead to discontinuations due to unwilling to continue on the randomized treatment.

Study AI454-152 was further hampered by the double substitution design that makes it impossible to isolate the contribution of ddI EC in the combination. When all discontinuations are regarded as failures, the ddI EC/d4T/NFV arm could be as much as 15% worse than the control arm based on lower bound for the 95% confidence. Sensitivity analysis indicates that ddI Ec/d4T/NFV arm could be 22% worse than the control arm. Overall, this trial showed marginal evidence for equivalence.

Study AI454-158 was limited by its small sample size and high discontinuation rates, which makes it impossible to reach any conclusion on equivalence of the two treatment arms.

/S/

Greg Soon, Ph.D.
Mathematical Statistician

APPEARS THIS WAY
ON ORIGINAL

/S/

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